口演

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O-01-1

抗ganglionic AChR抗体陽性自己免疫性自律神経障害における臨床的特徴の解析

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【背景】抗ganglionicアセチルコリン受容体（gAChR）抗体は自律神経節に存在するgAChRを標的とし，自己免疫性自律神経節障害（AAG）の約50%で検出されることが報告されている．【対象・方法】全国の施設より送付された血清検体（572症例752検体）を対象とした．血清検体は2012年1月27日から2015年5月31日までの期間に集積した．抗gAChR抗体（α3及びβ4サブユニット）をルシフェラーゼ免疫沈降法で測定し，陽性と判明した53例（α3単独陽性が29例，β4単独陽性が8例，double positiveが16例）を抽出した．抗体陽性53症例において送付された臨床情報を元に年齢，性別，発症様式，先行感染，初発自律神経症状，各種自律神経症状（瞳孔異常，起立性低血圧・起立不耐，乾燥症状，発汗障害，上／下部消化管症状，排尿障害）の頻度，併発する疾患及び症状（合併症，内分泌障害，感覚障害，中枢神経症状）の頻度，自律神経機能検査（MIBG心筋シンチ，CVRR），髄液蛋白細胞解離について解析した．【結果】年齢は57.1±20歳，男性29人，女性24人であった．急性・亜急性34.0%，慢性66.0%であった．初発自律神経症状は起立性低血圧・起立不耐が78.8%と最も多く認めた．起立性低血圧・起立不耐が94.2%と最多，下部消化管症状が86.5%，発汗障害と排尿障害が59.6%，とこれに続いた．膠原病の合併が17.3%と多く，内分泌障害の併発は17.3%，感覚症状の出現は50.0%，中枢神経症状を認める症例は25.0%であった．【考察】抗gAChR抗体陽性AAGにおいて自律神経症状のうち，起立性低血圧・起立不耐が高率であった．今後は自律神経機能検査解析や複合免疫療法の有効性，中枢神経症状や感覚障害と抗gAChR抗体との関連性など更なる検討を行っていく．

O-01-2

疼痛関連誘発電位を用いたPOEMS症候群における神経障害性疼痛の病態解析

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【目的】POEMS症候群，慢性炎症性脱髄性多発神経炎（CIDP）はいずれも後天性の脱髄性末梢神経疾患であるが，POEMS症候群ではCIDPと比較し疼痛を呈する頻度が多いことが知られている．小径有髄・無髄線維（Aδ・C線維）を選択的に刺激できる表皮内電気刺激法（IES）を用いて疼痛関連誘発電位を評価し，POEMS症候群における神経障害性疼痛の病態について検討する．【方法】POEMS症候群34例，CIDP24例，正常対照17例を対象とした．IESにより手首でAδ及びC線維の選択的刺激を行った．記録電極をCz，基準電極を両耳朶に配置し，各線維刺激による疼痛関連誘発電位の振幅・潜時を測定した．臨床評価はVisual analogue scale（VAS）を用いて行った．【結果】POEMS群，CIDP群間で，年齢，性別，罹病期間に有意な差はなく，神経伝導検査で評価される脱髄の程度についても有意差はなかった．一方，POEMS群はCIDP群と比べ，有意に疼痛を呈する頻度が高かった．Aδ刺激では，誘発電位の潜時はPOEMS群・CIDP群とも正常群と比較し延長し，振幅はPOEMS群でCIDP群・正常群と比較し低下する傾向を認めた．C刺激では，誘発電位の潜時・振幅とも，POEMS群・CIDP群・正常群間での有意な差は認めなかった．また，C/Aδ振幅比は，POEMS群において正常群・CIDP群と比べ有意に増大し，その傾向は疼痛が強い例でより大きかった．以上より，POEMS群ではCIDP群と比較し，Aδ線維の障害が強く，その程度が疼痛の程度と関連する可能性が推察された．【結論】POEMS症候群ではCIDPと比較し，小径有髄線維が強く障害され，神経障害性疼痛の発現に関連している可能性が示唆された．IESによる疼痛関連誘発電位の評価は，小径線維の障害の程度や神経障害性疼痛の病態解析・客観的評価において有用な手法になりうると考えられた．

O-01-3

Recapitulation of ML-induced reprogramming of Schwann cells by artificial methods

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[Purpose] Previously we reported that M.leprae（ML）reprogram adult mouse Schwann cells and induced mesenchymal stem cell（MSC）- like cells. During the reprogramming, epithelial mesenchymal transition（EMT）seemed to play an important role. This time, we tried to recapitulate the ML-induced reprogramming process by introducing Snai1 gene, a master regulator of EMT, into mouse immortalized Schwann cell（IMS32）.[Materials and methods] Snai1 gene was introduced into IMS32 using lentivirus or plasmid along with TGF- b stimulation of IMS32. Then, the cells were put into sphere-forming media. When spheres were formed, they were moved into stem cell media for proliferation.[Results] Sphere-forming efficiency by IMS32 was significantly increased by Snai1 ectopic expression and TGF-b. When the spheres were moved into stem cell media, the MSC-like cells vigorously proliferated, and also small number of cells with numerous intracellular small droplets spontaneously appeared. The droplets were positively stained with Oil red O, suggesting that those cells are preadipocytes.[Discussion] The results suggested that combination of ectopic expression of Snai1 and activation of TGF- b signaling pathway induced reprogramming of IMS32, and induced MSC-like cells with differentiation potential to adipocyte lineage. Overall we believe that we made a partial success in recapitulating the ML-induced reprogramming process by these artificial methods.

O-01-4

家族性アミロイドポリニューロパチーにおける血液神経関門の定量的検討

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［目的］家族性アミロイドポリニューロパチー（FAP *ATTR* Val30Met）における神経内鞘の小血管の形態変化を定量的に検討する．［方法］対象は遺伝子診断で確定したFAP *ATTR* Val30Met 43例．5例は集積地の若年発症（50歳未満）例であり，37例は非集積地の高齢発症例（50歳以上）例であった．腓腹神経生検で得られた検体をグルタールアルデヒド固定・エポン包埋した後，超薄切片を作成して電子顕微鏡にて各症例30本の神経内鞘に存在する小血管の横断像について，形態変化と内皮細胞間に存在するtight junctionの有無を定量的に評価した．対照としてFAPと同様の軸索障害をきたした栄養欠乏性ニューロパチー（NN）30例を検討した．［結果］FAP群で1290本，NN群で900本の小血管を評価した．各小血管のあたりの横断面における内皮細胞の核数と内皮細胞数は，FAP群で1.7±0.3と7.0±0.9であり，栄養欠乏性ニューロパチー群と比較して優位に増加していた（1.4±0.3と6.3±0.8，$p < 0.01$と$p < 0.001$）．小血管の閉塞像はFAP群で1.0±1.2%，栄養欠乏性ニューロパチー群で0.3±0.7%にみられた（$p < 0.01$）．FAP群ではNN群と比較して，小血管内皮細胞の形態変化に伴う血管内腔から血管外への開窓（0.5%±1.2 vs 0.1±0.3%）やtight junctionの消失（0.2±0.5% vs 0.01±0.03%）が目立った（$p < 0.05$）．全体としては血液神経関門の破綻はFAP群で18例にみられたのに対し，NN群では3例のみにみられた（$p < 0.01$）．［結論］FAPでは神経内鞘の小血管の形態異常がみられた．血液神経関門の破綻によって血管内の有害物質の神経への到達が容易になることが推測され，FAPにおける神経障害への関与が今後の検討課題であると考えられた．

O-01-5

TTR型アミロイドーシスの神経障害発生機序の研究：シュワン細胞の関与について

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【目的】これまで我々はトランスサイレチン（TTR）型アミロイドーシスの神経変性機序を明らかにするため，家族性アミロイドポリニューロパチー（FAP）モデルマウスからヒト異型TTR遺伝子を発現する自発的不死化シュワン培養細胞TgS1を確立し，その培養上清が初代後根神経節（DRG）培養細胞の神経突起成長を抑制することを明らかにした．また高齢FAPマウスDRGの免疫染色で，シュワン細胞や衛星細胞の細胞質にTTR陽性顆粒が観察されることを報告した．今回はこれらの機序について検討した．【方法】①正常マウスシュワン細胞株IMS32に正常TTRと異型TTR（Met30TTR）発現プラスミドをトランスフェクションしstable transformantsを作成し，それらを無血清培地で培養し，24時間後の培養上清を初代DRG培養細胞に加え神経突起数や伸展度合いを観察し神経突起成長抑制効果を見る．②IMS32の培養上清に正常TTR組み替え蛋白と異型TTR組み替え蛋白を添加し，初代DRG培養細胞に加え神経突起成長抑制効果を調べる．③TgS1細胞にプロテオソーム阻害剤MG132を添加し，免疫染色を施行し，共焦点顕微鏡で観察する．また透過型電子顕微鏡で検討する．【結果】①異型TTRが発現しているstable transformantの培養上清で神経突起成長抑制効果が観察された．②また異型TTR蛋白を添加した培養上清でも神経突起成長が有意に抑制された．③TgS1細胞をプロテオソーム阻害剤で処理するとアグリソームの部位にTTR凝集が観察された．また電子顕微鏡ではautolysosomeが見られた．【結論】シュワン細胞由来の異型TTRは感覚神経細胞突起の成長に抑制性の効果を及ぼし，感覚神経障害発症に関与しているかもしれない．またシュワン細胞の蛋白品質管理システムの低下は細胞内TTR凝集に関連していることが示唆された．

O-02-1

POEMS症候群の新規診断基準の提唱

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【目的】POEMS症候群はplasma cell dyscrasiaとvascular endotherial growth factor（VEGF）上昇を基盤として，多発ニューロパチーを始め，臓器腫大，内分泌異常など多彩な症状を呈する稀少疾患である．本症候群の診断基準は類似のものがこれまで複数報告されている．しかし，基準作成の根拠，感度・特異度等は示されてこなかった．統計学的解析に基づいたPOEMS症候群の診断基準を作成し，その感度・特異度を検討する．【方法】当院で診療を行い，治療経過等を含め，POEMS症候群と確定診断した79例を対象とした．また，慢性炎症性脱髄性多発神経炎（CIDP）・多発性骨髄腫・単クローン性ガンマグロブリン血症・ALアミロイドーシスを含む63例を疾患対照とした．現在，国際的に使用されている診断基準から大基準および小基準の各項目の頻度から，ロジスティック回帰分析で変数選択を実施し，ROC曲線から感度及び特異度が最大になる組み合わせを選択し，診断基準を作成した．同基準の感度・特異度を検討した．【結果】大基準は，多発ニューロパチー，M蛋白，VEGF上昇（必須）の3項目を選択し，そのうち2項目以上，小基準は，皮膚異常，血小板増多，骨硬化性病変，浮腫・胸腹水の4項目を選択し，そのうち1項目以上を満たすとする組み合わせで，AUCが最大となり，優れた基準と考えられた．この基準の感度は100%，特異度は100%であった．【結論】統計学的解析に基づきPOEMS症候群の診断基準を作成した．単施設での検討であり，本基準の検証が引き続き必要である．

O-02-2

経口ステロイド治療が有効であった重症筋無力症217例の臨床像

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【目的】血液浄化療法やIVIgを併用せずにプレドニゾロン（prednisolone, PSL）を中心とした経口薬物治療のみでMM以上に臨床症状が改善した重症筋無力症（myasthenia gravis, MG）の臨床像を国内多施設共同研究によって明らかにした．【方法】調査参加施設に通院中の既診断MG連続症例（2015年4-7月）のうち，診療録から経口ステロイド使用経過と臨床経過について詳細に調査し得た全身型MG711例のうち，血液浄化療法やIVIgを併用せずにPSLを中心とした経口薬物のみで治療を受けた313例を主な解析対象とした．【結果】313例のうち一度でもMMに到達したことがあるのは217例であった（69.3%）．PSLのピーク値はMM達成群（29.4 ± 17.6 mg/日）と非達成群（27.3 ± 17.9 mg/日）で有意差はなく，PSLのピーク時にMMを達成できないとその後もMMは達成できなかった．最初にMMを達成した時期は投与開始後13.6 ± 31.0か月（最大276か月：23年）であり，1年以内にMMを達成した症例は125例（57.6%），1年以内に5mgMM（PSL5mg/日でMM）を達成した症例は59例（27.2%）であった．MMを達成したかどうかと発症年齢，罹病期間，自己抗体の有無とは関連はなく，投与期間，重症度，PSLピーク値，カルシニューリン阻害薬（calcineurin inhibitors, CNIs）の併用，PSL投与法の違いを変量とした多変量解析では，少なくとも一度は経過中にMMに到達できる経口ステロイド療法のpredictive factorは2つのみで，発症からPSL投与開始までの期間が短いことと最重症時QMG合計点が低いことであった．【結論】MGにはsteroid responderとnon-responderの存在が示唆されるが，発症早期で比較的軽症だと経口ステロイド療法によってMMを達成する確率が上がると思われる．

O-02-3

重症筋無力症における胸腺外悪性腫瘍発生頻度と免疫療法との関連

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【目的】重症筋無力症（MG）における胸腺外悪性腫瘍の発生頻度とその内容，および免疫療法との関連を明らかにする．【方法】日本MGレジストリー多施設研究に登録された1090人中，悪性腫瘍合併の有無が判明している925人を対象として，悪性腫瘍の合併頻度，腫瘍の発生時期，腫瘍合併群と非合併群の臨床的特徴，悪性腫瘍の内訳を調査した．また，ステロイド投与量やカルシニューリン阻害薬（CNI）投与の有無と悪性腫瘍発生頻度との関連を検討した．【結果】MG患者925人中，悪性腫瘍を合併したのは83人（9.0%）であった．腫瘍合併群は非合併群と比較して早期発症MGが少なく，後期発症MGが多く，発症年齢が高かった（56.3 vs 46.5）．MGの重症度（最重症時QMGスコア）や眼筋型の割合，胸腺腫合併率に差はなかった．悪性腫瘍の内訳は乳癌17（20.5%），大腸癌11（13.3%）が最多で，次いで胃癌，子宮癌，前立腺癌，肺癌，甲状腺癌など一般的に頻度の高い腫瘍が多かった．重複癌が7人にみられた．腫瘍の発生時期は，MG発症前が31.5%，ほぼ同時が12.3%，MG発症後が56.2%であった．MG発症後の悪性腫瘍の発生頻度は，ステロイド高用量群（30mg/日以上）で7.3%，中等用量群（10-30mg/日）で3.6%，低容量群（10mg/日以下）で3.8%，ステロイド非使用群で3.3%であった．また，CNI使用群では4.0%，非使用群では4.9%であった．【結論】MGにおける胸腺外悪性腫瘍の発生頻度は比較的高く，MG発症後の腫瘍発生頻度はステロイド高用量群において高かった．一方，CNIは腫瘍発生率を高めることはないと考えられた．

O-02-4

抗MuSK抗体陽性重症筋無力症および抗LRP4抗体陽性重症筋無力症における胸腺異常

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【目的】重症筋無力症（MG）では抗AChR抗体，抗MuSK抗体あるいは抗LRP4抗体が病因となる自己抗体として知られている．これまでに抗AChR抗体陽性MGでは，高率に胸腺異常（胸腺腫または胸腺過形成）を認めることがわかっているが，抗MuSK抗体や抗LRP4抗体陽性MGにおける胸腺異常については十分な検討がなされていない．今回，抗体測定依頼のあったMG患者の臨床情報をもとに，各自己抗体と胸腺異常の関連性について検討した．【方法】日本国内の医療機関より抗MuSK抗体あるいは抗LRP4抗体測定を目的に当院に送付された205例のMG症例について，抗MuSK抗体および抗LRP4抗体測定し，添付された臨床情報から抗AChR抗体と胸腺異常の状況について検討した．【結果】205例のうち抗AChR抗体陽性例は15例，抗MuSK抗体陽性 15例（5例で抗LRP4陽性），抗LRP4抗体陽性は56例（抗AChR陽性8例，抗MuSK陽性5例を含む）で，このうちの1例では3種の自己抗体がすべて陽性例であった．胸腺異常は抗MuSK陽性例では1例，抗LRP4陽性例では7例（12.5%）であった．胸腺異常を認めた抗LRP4陽性MGでは4例が抗AChR陽性で，このうちの2例は胸腺腫であった．【結論】抗MuSK抗体陽性MGおける胸腺異常は稀であるが，抗LRP4陽性MGでは抗AChRも陽性の場合があり，胸腺異常も稀ではないことに注意が必要である．

O-02-5

重症筋無力症と炎症関連サイトカイン

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【目的】重症筋無力症（MG）では抗アセチルコリン受容体（AChR）抗体がCD4陽性T細胞依存性にB細胞から産生され，補体の活性化を介して，神経筋接合部の後シナプス側に炎症を来たす．サイトカインもこの炎症病態に重要な働きをしていると考えられており，本研究では，抗AChR抗体陽性MG患者において炎症関連サイトカインの解析を行い，MGの免疫病態に迫ることを目的とした．【方法】免疫治療導入前の抗AChR抗体陽性 MG 患者43例（男：女＝17：26，平均年齢 56.0歳，平均罹病期間12.8ヶ月，眼筋型：全身型＝13：30，ELT分類＝14：18：11），正常対照（NC）25例（男：女＝9：16，平均年齢 52.4歳）を対象として，バイオプレックスサスペンションビーズアレイシステムを用いて血清中の24種類のサイトカインを同時に測定した（Human Inflammation Panel 1）．また一部のMG患者で治療による変化も検討した．【結果】MG患者ではNCと比較してIL-10ファミリーであるIL-19（p＝0.013），IL-20（p＝0.031），IL-28A（p＝0.008），IL-12ファミリーであるIL-35（p＝0.042）及びTNFファミリーであるAPRIL（p＝0.002）が有意に上昇していた．ELT分類別では，IL-20，APRILが後期発症MGで高値，IL-28Aが胸腺腫関連MGで有意に高値であった．治療前後の比較ではIL-20，IL-28A，IL-35が治療後に有意に上昇していた（p＜0.05）．【結論】IL-10ファミリー（IL-19，IL-20，IL-28A），IL-35，APRILは抗AChR抗体陽性MGの免疫病態に関与していることが示唆された．一部のサイトカインは炎症抑制的に働き，病態保護的に機能している可能性がある．

O-03-1

A new in vitro blood-brain barrier (BBB) model incorporating tri-culturing system of BBB components

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Background At the blood-brain barrier (BBB), pericytes and end-feet of astrocytes (EFA) form close contact with the endothelium and regulate the BBB. But these regulations still remain unknown because of the lack of the *in vitro* models that are specialized to mimic endothelium-interaction of pericytes and EFA. ***Aim*** We construct a new BBB model incorporating tri-culture of conditionally immortalized human endothelial (EC), pericyte (PCT) and astrocyte (AST) cell line by the Nunc UpCell technology. Next, we evaluate whether barrier function is influenced by pericytes and EFA. ***Method*** AST were co-cultured on abluminal side of insert (3 μm pore) with PCT on luminal side. Sheet-like detachment of confluent EC cultured on the UpCell plate, which achieves detachment of cell layer by changes of temperature, was transferred onto the PCT (EC/PCT/AST). As controls, we prepared other cultured inserts with (EC/PCT-AST) or without (EC/PCT) AST-culture on the lower well. Solute permeability with 10k dextran was measured. ***Result*** Confocal 3D analysis showed that tri-cultured insert constituted a three-layer structure and that astrocyte processes protruded through the pores, terminating in proximity to the EC. The values of permeability were significantly low in the order EC/PCT/AST, EC/PCT-AST, EC/PCT, EC. ***Conclusion*** Our model is the first BBB tri-cultured model in which pericytes and EFA can directly contact with endothelium. These results suggested the EFA- and pericyte-endothelial interactions as well as astrocytes- and pericytes-secreted biomolecules in the medium could increase BBB function.

O-03-2

Generation of ventral and dorsal telencephalic tissues from human embryonic stem cells

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[Objective] In this study, using three-dimensional (3D) culture of human embryonic stem (ES) cells, we aimed to generate ventral and dorsal telencephalic tissues in vitro. **[Methods]** To induce neuroectodermal tissues from human ES cells, we used an efficient 3D culture method, called serum-free floating culture of embryoid body-like aggregates with quick reaggregation (SFEBq). First we induced neocortical tissues, then, we tried to ventralize and dorsalize the neocortical tissues by addition of signaling factors such as SAG, CHIR99021, and Bone Morphogenetic Protein (BMP) 4. **[Results]** By culturing the aggregates under the medium that was suitable for neocortical tissue induction, human ES cell-derived aggregates differentiated into multilayered neocortical tissues, and we found that these neocortical tissues were ventralized by hedgehog signal in dose-dependent manner. By contrast, when the neocortical tissues were cultured under the dorsalizing factors, BMP4 and CHIR99021, the most dorsomedial telencephalic region, choroid plexus was sufficiently induced. Lastly, we found titrating BMP4 and CHIR exposure allowed the self-organization of medial pallium, which produced hippocampal pyramidal and granule neurons. **[Conclusions]** Ventral and dorsal telencephalic tissues were sufficiently induced under the medium that was suitable for each tissue differentiation. Generation of telencephalic tissues from human pluripotent stem cells will provide a new experimental platform for medical researches, such as disease modeling, drug screening, and cell-based transplantation therapy.

O-03-3

The role of β1-integrin controlling neuronal migration in injured mouse brain

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[Introduction]Adult neurogenesis occurs in the brain of various species including humans. New neurons generated in the ventricular-subventricular zone (V-SVZ) form chain-like aggregates and migrate toward the olfactory bulb. After brain injury, some of the new neurons move within the striatum toward the injured area, formming chains and frequently along the blood vessels. Though such migration patterns appear to determine the efficiency of neuronal migration toward the injured area, its mechanism is largely unknown. **[Objective]**We investigated the role of β1-integrin in controlling chain formation and vessel associated migration of the new neurons in the post-stroke striatum. **[Methods]**New neuron-specific and tamoxifen-inducible β1-integrin knockout(KO) mice were subjected to transient middle cerebral artery occlusion. After tamoxifen treatment, distribution and migration mode of the new neurons toward the injured area were examined at 18 days post-stroke. **[Results]**In the KO mice, the percentage of individually migrating new neurons was significantly increased, whereas those forming large chain was decreased. Morphology of the chains and association with the vessels were also affected in the KO mice. The migration distance of the new neurons from the V-SVZ toward the injured area in KO mice was significantly shorter than that in control mice. **[Conclusions]**β1-integrin supports new neurons to form chain and move efficiently toward the injured area. These findings provide an insight into the promising strategy for efficient regeneration by endogenous system.

O-03-4

Analysis of MSA patient iPSC-derived neural cells with COQ2 mutation

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[Purpose] We previously identified that functionally impaired variants of *COQ2*, which encodes COQ2 protein, an essential enzyme for the biosynthesis of coenzyme Q10 (CoQ10), were associated with an increased risk of multiple system atrophy (MSA), providing evidence of a role of impaired COQ2 activities in the pathogenesis of this disease. The purpose of this research is to elucidate COQ2 dysfunction in MSA patient-derived cells with *COQ2* mutations. [Methods] We generated induced pluripotent stem cells (iPSCs) from two MSA patients carrying *COQ2* mutations (MSA1 [c.1159C→T, c. 1178T→C] and MSA2 [c. 1178T →C]) and two MSA patients without the mutations (MSA4 and MSA-KA), and differentiated them into neural cells *in vitro*. [Results] Following quality check, we finally selected three iPSC clones each of the samples for further analyses. Moreover, the mutations in *COQ2* gene were confirmed in all of the selected iPSC clones via pyrosequencing analysis. No significant differences were detected in either MSA iPSCs or controls with regard to neural cell differentiation efficiency. [Conclusion] We generated iPSCs from MSA patients carrying *COQ2* mutations and differentiated them into neural cells. In further study, we will measure CoQ10 levels in MSA iPSCs, expression of mitochondrial markers and apoptotic markers of MSA iPSC-derived neural cells. We will also evaluate the effects of supplementation of CoQ10 in MSA iPSC-derived neural cells and the potential of COQ10 administration as a therapy for MSA.

O-03-5

Systematic Analysis of Fly Models Elucidates Sleep disturbance in Huntington's Disease

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[Objective]Huntington's Disease (HD) is a neurodegenerative disorder which exhibit non-motor symptoms include sleep disturbances. We newly designed multiple HD model flies to elucidate the molecular and neural mechanism of the sleep disturbance.[Methods]We mated UAS-Htt exon1-103Q and -20Q flies with elav, 1407, cha, ple, repo or gcm-Gal4 flies to develop a new models which express Htt in remote neurons. We analyzed Zeitgeber rhythms of the resultant flies for 7 days by Drosophila Activity Monitor (n = 5-10 for each genotype). [Results] Cholinergic, dopaminergic or glial expression of Htt exon1-103Q attenuated the sharpness of daily activity peaks without changing total daily activity. [Conclusions] Our results suggest that a specific type of neuron or glia is responsible for the sleep disturbance in HD. Recent research supposed PKA/CREB pathway underlies the sleep disturbance. The kind of neuron which is responsible for PKA/CREB dependent sleep disturbance is still unknown. We will be able to understand the cell type specific mechanism of neurodegeneration from our new model flies.

O-04-1

Identifying freezing of gait and falls in Parkinson's disease patients using a body-worn sensor

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OBJECTIVE: The aim of the present study is to objectively detect and quantify freezing of gait (FOG) and falls in Parkinson's disease (PD) patients during everyday activities.METHODS: Patients were selected from among 36 patients who participated in our previous prospective study on falls. We developed a motion recorder (body-fixed 3D accelerometer) with a long-lasting battery. Movements of recurrent PD fallers with severe FOG were recorded using the waist mounted device in the outpatient clinic and during their everyday activities. A newly developed freezing index (cross correlation calculation based on pattern matching) was calculated and compared with the validated index (ratio of power spectrum, 3-8 Hz/0.5-3Hz) .RESULTS: Characteristic patterns of acceleration signals were recorded for freezing and falls. Knee trembling was recorded as a rapid oscillation of acceleration, and the freezing index increased during knee trembling. In PD patients, actual falls in everyday life were also detected as abrupt trunk angle changes, and knee trembling was recorded when patients reported FOG-induced falls. The freezing index increased during the start and turning hesitations, similarly to the index calculated using previously validated method. In the previous method, the largest value of freezing index varied according to the directions analyzed.CONCLUSIONS: Motion recording using our wearable sensor is useful for detecting FOG and falls in everyday life in PD freezers, and calculating the freezing index may improve the quantification of FOG.

O-04-2

A study of relation between change of L-dopa response of gait ability and cognitive function in PD

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【目的】パーキンソン病(PD)患者の歩行機能の経過と認知機能の関連を検討する．【方法】入院時精査として認知機能評価（ミニメンタルテスト（MMSE），改訂長谷川式簡易知能評価スケール（HDS-R），前頭葉機能検査（FAB）），L-dopa infusion test（前後でUPDRS part III(UP3)および歩行関連評価としてParkinson gait score(PGS)を記録））を2回以上行った9症例（女4，男5，初回精査時平均66.0歳，精査から再精査まで平均38.1月）についてUP3及びPGSのL-dopa反応性の変化と認知機能の関連を検討した．【結果】UP3の悪化とMMSE，HDS，FABとの関連については決定係数が各々0.2581，0.0849，0.1189であった．PGSの悪化との関連については各々0.0976，0.0715，0.3660であった．【結論】本研究において，PDの運動症状全体のL-dopa反応性の経過に伴う変化は認知機能の変化との間に明らかな関連は認められなかった．歩行機能のL-dopa反応性の経過に伴う悪化とFABの低下の間に弱い相関が認められ，歩行障害の進行と前頭葉機能の低下に何らかの関連がある事が示唆された．

O-04-3

Acrocyanosis in Parkinson's disease correlates with diurnal fluctuation

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Objective To elucidate the characterics of Parkinson's disease (PD) patients with acrocyanosis. **Methods** Subjects were 103 PD patients aged from 40 to 90 year-old (mean age was 72.7). We defined patients who experienced acrocyanosis in cold season as acrocyanosis group. Intellectual activity was evaluated by MMSE. Subjective walking difficulty was measured by freezing of gait questionnaire (FOG). Severity of motor symptoms of PD was evaluated by UPDRS. Diurnal fluctuation of Parkinsonian symptoms was evaluated by symptom diaries. We asked all subjects whether they had lower back pain or not, and whether they experienced hallucination in one year or not. We extracted duration of PD as potential risk factors of diurnal fluctuation. **Results** Acrocyanosis was experienced by 22 patients (21%). Comparing with no-acrocyanosis group by univariate analysis, acrocyanosis group had higher FOG (7.0 vs 3.7), and higher UPDRS part 3 (23.0 vs 15.3), significantly. Acrocyanosis group also experienced lower back pain (77.2% vs 48.0%) and hallucinations (54.5% vs 18.6%) more frequently than no-acrocyanosis group did.Furthermore, acrocyanosis group experienced diurnal fluctuation of symptoms (68.2% vs 38.7%) and falling (77.3% vs 48.0%) more frequently than non-acrocyanosis group. In additon, logistic regression analysis revealed that independent factor associated with diurnal fluctuation were patient's body weight, duration of PD and acrocyanosis. **Conclusions** Results of this study suggest that acrocyanosis in PD patients may be one of the surrogate markers of diurnal fluctuation.

O-04-4

Depression is associated with abnormal nocturnal blood pressure fall in de novo Parkinson's disease

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【目的】パーキンソン病（PD）患者では血圧日内変動の異常がしばしば認められ，心血管系の自律神経機能障害との関連が指摘されている．今回我々は，PD患者の血圧日内変動と，抑うつ，睡眠，疲労，QOLとの関連を，質問紙法を用いて検討した．【方法】De novo PD患者37例を対象に，24時間血圧測定による血圧日内変動の評価を行った．血圧日内変動の評価では，昼間収縮期血圧に対する夜間収縮期血圧の下降度を指標としてdipper型（10％以上），non-dipper型（10％未満）に分けた．質問紙法として，Zung self-rating depression scale（SDS），Parkinson's Disease Sleep Scale（PDSS），Parkinson Fatigue Scale-16（PFS-16），Parkinson's Disease Questionnaire-39（PDQ-39）の評価を行った．抑うつの評価では，SDSの合計得点が50点以上の場合，抑うつありとした．【結果】PD患者の血圧日内変動の評価では，dipper型13例（70.5±8.1歳），non-dipper型24例（73.6±8.3歳）であった．SDSを行った27例のうち，抑うつありの患者は7例，抑うつなしの患者は20例であった．SDSの合計得点はdipper型では39.5±6.7点，non-dipper型では45.6±11.1点であり，non-dipper型ではdipper型と比べ，抑うつのある患者が多かった（Fisherの正確確率検定：p=0.048）．PDSS，PFS-16，PDQ-39の点数はdipper型とnon-dipper型で有意差はなかった．【結論】De novo PD患者では，non-dipper型では，dipper型に比べ，抑うつのある患者が多かった．PD患者において，心血管系の自律神経機能障害と気分障害は関連している可能性がある．

O-04-5

Autonomic function after STN-DBS in patients with Parkinson's disease (second report)

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【目的】視床下核脳深部刺激術(STN-DBS)は，パーキンソン病(PD)患者の起立時の血圧調節機能に影響を与える可能性について我々は過去に本学会で報告した．今回は対象患者数を増やし，STN-DBSが自律神経機能に与えるより長期的影響を評価する．【方法】対象はPD 19例(年齢64±7歳，罹病期間12±4年)．R-R間隔変動係数(CV_{R-R})，head-up tilt試験，手掌部交感神経性発汗反応(SSwR)，皮膚血管運動反射(SkVR)をSTN-DBS施行前および術後3ヶ月と1年で施行した．【結果】off時UPDRS3rdはDBS後に改善し(術前44±15，術後3カ月18±7，術後1年28±20)，levodopa equivalent doseも減量できた(823±175，564±183，552±216 mg/日)．STN-DBS前，3カ月後，1年後の各指標については，不整脈例を除く16例のCV_{R-R}値はそれぞれ2.2±1.8，2.2±1.1，1.7±1.0%と変化しなかった．Head-up tilt試験での収縮期血圧変化(-16±14，-14±19，-10±18 mmHg)，拡張期血圧変化(-5.2±7.7，-5.4±8.7g，-4.5±8.0 mmHg)，脈拍変化(12±5.4，11±7.6，10±6.9/分)に有意な変化はなかった．起立時収縮期血圧20 mmHg以上または拡張期血圧10 mmHg以上の低下を起立性低血圧(OH)と定義すると，術前で8例，術後3ヶ月で7例，術後1年で7例にOHを認めた．術前にOHを認めた8例のうち6例で術後にOHが消失した一方で，5例で新たにOHが出現した．全観察期間に渡りOHがみられたのは1例のみであった．SSwR振幅とSkvR減少率に有意な変化はなかった．【結語】STN-DBS術後に自律神経機能の一定した変化はなかったが，術後にOHが新たに出現・消失した例が存在した．このようなOHの変化には術後の抗パーキンソン病薬の減量，電極刺入によるmicro lesioning effect，刺激電圧の変更等が関与した可能性がある．

O-05-1

筋萎縮性側索硬化症における低周波帯域の安静時脳機能MRI信号変化とFA値の関係

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【目的】近年機能画像であるresting state functional magnetic resonance imaging（RSfMRI）やdiffusion weighted imaging（DWI）から再構成される構造的結合性を反映するfractional anisotropy（FA）を用いてamyotrophic lateral sclerosis（ALS）に関する研究が多く行われてきたが，この二つの方法を統合し，機能的・構造的両面から解析した報告は限られている．RSfMRIから計算されるamplitude of low frequency fluctuation（ALFF）とFAを同時に解析することにより，ALSにおける機能的・構造的異常の関連性を明らかにすることを目的とし，本研究を行った．【方法】改訂El Escorial診断基準でpossible以上を満たすALS患者10人と四肢の筋力低下を来しうる疾患対照11人のRSfMRIとDWIを用いて解析を行った．RSfMRIに関しては0.1Hz未満でのバンドパスフィルタリング含む前処理後にStatistical Parametric Mapping（SPM）を用いて，ALSと対照群で差を認める脳部位を同定した．Pearson product-moment correlation coefficientを用いて同部位のALFF値と内包後脚のFA値との相関を解析した．【結果】疾患対照群に比し，ALS群でALFF値が低下する部位として右Brodmann area（BA）4，左BA6と右BA24が同定された．右BA4と左BA6におけるALFF値と左右それぞれの内包後脚のFA値との相関関係を解析したが，右BA4と右内包後脚との間で有意な負の相関を見出した（$r = -0.696, p = 0.025$）．【結論】右BA4，左BA6と右BA24におけるALFF値の低下を見出した．特に，ALSの運動野における神経の活動性を反映するALFF値は錐体路の構造的結合性を表すFA値と負の相関があり，今後この二つを組み合わせることにより，さらに信頼性の高い診断法の開発につながる可能性がある．

O-05-2

前頭側頭葉変性症9例における[11C]PBB3 PETを用いた脳内タウ集積の検討

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【目的】前頭側頭葉変性症（fronto-temporal lobar degeneration：FTLD）は背景病理が多様であり，さらに臨床診断と病理診断が必ずしも一意対応しないことが知られている．本研究の目的は，FTLD患者にpositron emission tomography（PET）を用いた脳内タウならびにアミロイド病理の評価を行い，イメージングの脳内集積パターンと臨床症状の関連を検討することである．【方法】対象は臨床的にFTLDと診断された54～87歳（平均69.7歳）の9例で，behavioral variant fronto-temporal dementia（bvFTD）7例，progressive non-fluent aphasia（PNFA）1例，semantic dementia（SD）1例であった．頭部画像検査としてMRI，アミロイドPET（[11C]PiB），タウPET（[11C]PBB3）を施行し，PETでは小脳皮質を参照領域として後期standardized uptake value ratioの画像を作成した．PiB PETではアミロイド集積の有無を視覚的に判定し，PBB3 PETでは定量画像に基づく解析を用いて若年健常者10例を対照群とする脳内タウ蓄積部位の評価も行なった．【結果】PiB PETでは，bvFTDの3例（33％）が集積陽性であり，他はいずれも陰性であった．PBB3 PETでは，PiB陽性の3例を含むbvFTDの4例とPNFAの1例で，側頭葉内側から外側にかけてを中心に高い集積を認めた．SDでは側頭葉に軽度の集積の可能性が考えられた．PiB陰性のbvFTDの1例では中脳や線条体周辺に特徴的な集積を認めたが，本症例は神経学的に垂直性眼球運動障害や姿勢反射障害が前景に立つParkinson症状を認め，臨床的には進行性核上性麻痺としても診断可能であった．他の2例では明らかなPBB3集積を認めなかった．【結論】表現型はFTLDであってもそれぞれ多彩な臨床症状と混合病理を背景に有する．アミロイド・タウイメージングはこうした多様性を病理学的側面から説明し得ると考えられた．

O-05-3

アルツハイマー型認知症と健常加齢のタウPETトレーサー[18F]THK5351所見

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（目的）アルツハイマー型認知症(AD)の二大脳病理像は，アミロイドβ蛋白質を主成分とする老人斑とタウ蛋白質を主成分とする神経原線維変化である．診断，病態解明，および治療法開発のために，これらの凝集化した蛋白質に対する非侵襲的計測が求められてきていた．今回，我々はPiBPETにてアミロイドβの蓄積が確認されたADの症例で，東北大学で開発されたTHK5351を投与し，蓄積のパターンとこれまで病理学的に示されてきたタウ病変の分布と比較，検討した．（方法）NINCDS-ADRDA の診断基準でProbable AD を満たし，ACE-Rは82点以下，MMSE 23点以下，CD-R 0.5点以上，さらに論理的記憶検査およびPiB PETを用いて評価したAD10例，ACE-R 88点以上，MMSE24点以上，CD-R 0点，論理的記憶検査にて有意な異常を認めない健常者(NC)10例に対して，THK5351PETを施行した．当院にて作製したTHK5351 約185MBqを静脈内に投与し，40分後より20分間，PET-CTでダイナミックスキャンにて撮像を行なった．（結果）THK5351は，全例で良好な画像を得ることが可能だった．AD群では，側頭葉内側面と外側面皮質，前頭葉内側面，頭頂葉皮質や帯状回後方に集積を認めた．一次運動野や一次感覚野への集積は乏しかった．臨床スコアが悪いほど，また高齢なほど，トレーサーの集積範囲が広く，高密度に分布していた．NC群では海馬から内側側頭葉に集積を認め，帯状回後方や海馬周辺以外の大脳にも集積がみられたが，その程度はAD群に比べて全般に軽度であった．（結論）THK5351の集積は，Braakらによる病理学的検討で知られている神経原線維変化の好発部位に一致してみられ，タウ蛋白質の蓄積範囲を反映していると考えられた．また，臨床的に健常者である被験者でも，側頭葉の内側面にタウ蛋白が蓄積している例を認め，これも従来報告されている病理学的所見と一致した．THK5351は，AD群やNC群におけるタウ病理の程度と分布を良く反映したマーカーである．

O-05-4

パーキンソン病患者での[11C]BF-227 PETによるα-シヌクレイン蛋白凝集体の画像化

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【目的】パーキンソン病(PD)の病理学的特徴はレビー小体であり，その主たる構成成分はα-シヌクレイン(αS)蛋白凝集体である．しかしながら，PDの生体脳内αS蛋白凝集体については，可視化・画像化ができておらず，その病態は不明のままである．今回，我々はPD患者に[11C]BF-227 PETを施行し，正常群と比較することにより生体脳内αS蛋白凝集体を可視化・画像化ができるかどうか検討するとともに，PD患者の一部に[11C]BF-227 PETを繰り返し施行し，生体脳内αS蛋白凝集体の経時的変化について検討する．**【方法】**PD患者17人に[11C]BF-227 PET撮影を施行した．そのうち，9人に平均約2.5年の間隔をおいて，2回目のPET撮影を施行した．1回目と2回目の撮像条件は同様で[11C]BF-227 投与後60分間のダイナミック撮像で行った．認知機能，嗅覚機能の指標として，MMSE，OSIT-Jを用いた．解析にはPMOD ver3.6 (PNEURO)を用いて，各個人のMRI画像をテンプレートにして前頭葉，側頭葉，頭頂葉，後頭葉，中心前回，補足運動野，帯状回，尾状核，被殻，淡蒼球，視床，扁桃体，嗅皮質，尾状核，中脳，小脳領域にROIを設定した．小脳を参照領域とし，各領域と小脳との比（SUVR）を用いて，15人の正常群と比較した．**【結果】**PD患者群は正常コントロール群と比較して，前頭葉，側頭葉，中心前回，補足運動野，帯状回，被殻，淡蒼球において有意差をもって[11C]BF-227の集積亢進を認めた（$p<0.05$）．経時的には，前頭葉と補足運動野で集積の増加を認めた（$p<0.05$）．この補足運動野領域のSUVR値とOSIT-JならびにMMSEのスコアとに相関を認めた（$p<0.05$）．**【結論】**集積亢進を示した領域はPDの病理でレビー小体が比較的多い領域と一致しており，[11C]BF-227 PETによってPDの生体脳内αS蛋白凝集体を可視化・画像化が可能と考えられた．また，経時的変化における補足運動野での[11C]BF-227集積の増加は認知機能悪化との関連が示唆された．

O-05-5

大脳皮質基底核症候群の線条体ドパミン神経活動は同側背外側前頭前野の血流と関連する

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【目的】大脳皮質基底核症候群（CBS）は，皮質と基底核がともに障害される変性疾患であるが，大脳皮質機能とドパミン神経障害との関係を明らかにした報告はない．本研究の目的は，CBSでの線条体ドパミン神経活動と全脳における脳血流の関係を明らかにすることである．【方法】メイヨー基準および改訂ケンブリッチ基準でCBSと診断された10症例を対象として，後ろ向きに検討した．[^{123}I] FP-CIT SPECT（DAT-SCAN）および [^{123}I] IMP SPECTの2検査を，検査間隔が1年未満で施行した症例を検討した．DAT-SCANの線条体ドパミントランスポーター活性は，Bolt法を用いて左右の線条体それぞれの特異的結合能／非特異的結合能比（SBR）を算出した．左右のSBRを独立変数として，[^{123}I] IMP SPECT画像をSPM8によって解剖学的標準化を行い，全脳を対象に回帰分析にて調査した．【結果】CBS症例の平均年齢は73.3歳，女性4名，罹病期間は3.54年で，症状の強い罹患側は8例が左で，2例が右であった．回帰分析の結果，右側のSBRは，右背外側前頭前野（DLPFC，ブロードマン8野）と相関を認めた（uncorrected $p < 0.001$, voxel > 150）．左側のSBRは，左背外側前頭前野（DLPFC，ブロードマン8野）と右前頭葉内側（ブロードマン8野，9野，前部帯状回）と相関を認めた（uncorrected $p < 0.001$,voxle > 150）．【結論】大脳皮質基底核症候群における線条体ドパミン神経活動は，同側の背外側前頭前野の血流と相関する．

O-06-1

日本人dysferlinopathyで最も高頻度のc.2997G>T変異のスプライス異常の有無の検討

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[目的] Dysferlin遺伝子の変異は常染色体劣性遺伝形式で三好型遠位型筋ジストロフィー（MMD）および肢帯型筋ジストロフィー2B型（LGMD2B）を主な表現型とし，dysferlinopathyという概念が確立した．日本人ではexon 28のc.2997G＞T変異が最も頻度が高く，またこの変異を有すると発症が遅くなることが知られている．この変異はコード上ではp.Trp999Cysのミスセンス変異と予想されるが，コード上でミスセンスと予想される変異のかなりの割合がスプライス異常をきたすという報告もある．そのためこの変異がスプライス異常をきたすかを検討した．[方法]ゲノムDNAを直接塩基配列決定しdysferlin遺伝子診断した日本人180家系でのc.2997G＞T変異の頻度を確認した．スプライス異常の有無はc.2997G＞T変異を複合ヘテロ型で有するdysferlinopathy患者1例の生検筋からmRNAを抽出し，RT-PCRして得られたcDNAのexon 26から31をふくむ領域にプライマーを設定しPCR産物の大きさをアガロースゲル電気泳動で観察した．[結果]c.2997G＞T変異は日本人ではアレル単位で22.2％に認められ最も高頻度だった．mRNAの解析ではプライマー設計での予想通りの大きさのPCR産物のみが得られた．そのためC.2997G＞T変異はスプライス異常をきたさないと考えられた．[結論]c.2997G＞T変異はミスセンス変異である．日本人で最も多く，発症の遅くなる変異がミスセンス変異であることが確認されたことは今後病態や治療研究を進める上で大きな意義をもつ．

O-06-2

Clinical and pathological characterization of patients with FHL1 myopathy

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[Objective] Mutations in the four and a half domains 1（*FHL1*）gene on chromosome Xq26.3 are known to cause quite variable types of myopathies including reducing body myopathy, scapuloperoneal myopathy, X-linked myopathy with postural muscle atrophy, rigid spine syndrome, and Emery-Dreifuss muscular dystrophy（EDMD）. Presence of reducing bodies in muscle fibers is a characteristic pathological feature of FHL1-myophty. The objective of this study is to characterize clinical and pathological features of FHL1 myopathy. **[Methods]** We found a total of 15 patients from 10 families with *FHL1* mutations, and clinical and pathological features were analyzed.**[Results]** All *FHL1* mutations caused substitution/deletion of the Cysteine residues in the second LIM domain of FHL1. Clinical symptoms of the patients with FHL1 myopathy were quite variable from early infantile severe form to adult onset milder form. Nine of 15（60％）patients showed asymmetrical muscle involvement and some had been diagnosed to have facioscapulohumeral muscular dystrophy. Pathological changes of the skeletal muscles were also variable, but all muscle specimens examined contained reducing bodies that are strongly stained by MAG stain without substrate. Some muscles showed nearly normal with only a few reducing bodies, but others had numerous atrophic fibers with abundant reducing bodies.**[Conclusions]** FHL1 myopathy can show quite variable clinical and pathological features. MAG stain without substrate is quite useful for the diagnosis of FHL1 myopathy.

O-06-3

Isolated inclusion body myopathy caused by a multisystem proteinopathy-linked hnRNPA1 mutation

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[Objective] To identify the genetic cause of two families manifesting isolated inclusion body myopathy（IBM）with autosomal dominant inheritance.[Methods] Genetic investigations were performed using whole exome and Sanger sequencing of the heterogeneous nuclear ribonucleoprotein A1 gene（*hnRNPA1*）. The clinical and pathological features of patients in the two families were evaluated with neurological examinations, muscle imaging, and muscle biopsy. [Results] We identified a missense p.D314N mutation in *hnRNPA1* in the two families. The affected individuals developed muscle weakness in their 40s, which slowly progressed toward a limb-girdle pattern. They revealed no apparent motor neuron dysfunction, cognitive impairment, or bone abnormality. The muscle pathology was compatible with IBM, lacking apparent neurogenic change and inflammation. Multiple immunohistochemical analyses revealed the cytoplasmic aggregation of hnRNPA1 in close association with autophagosomes and myonuclei. This accumulation was characterized by coaggregation with ubiquitin, sequestome-1/p62, valosin-containing protein/p97, and a variety of RNA-binding proteins. [Conclusions] We found the p.D314N mutation in *hnRNPA1* in two families manifesting IBM with pure muscular phenotype. The present study expands the clinical phenotype of *hnRNPA1*-linked multisystem proteinopathy. Although the mechanisms underlying the selective skeletal muscle involvement remains to be elucidated, the immunohistochemical results suggest a broad sequestration of RNA-binding proteins by the mutated *hnRNPA1*.

O-06-4

VCPDMモデルマウスの作成および筋病理学的解析

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【目的】声帯および咽頭麻痺を伴う遠位型ミオパチー（VCPDM）は筋病理学的に縁取り空胞を特徴とし，これまでに本邦，北米，ブルガリア，ドイツでのみ報告されている希少性筋疾患である．近年，核マトリックス構成蛋白であるMatrin-3（MATR3）のミスセンス変異によりVCPDMならびに筋萎縮性側索硬化症（ALS）を生じることが報告された．しかしMATR3の変異が筋変性を生じるメカニズムについては明らかにされていない．今回我々は変異MATR3トランスジェニックマウスの作成を行い，VCPDMモデルマウスとして有用であるか検討することを目的とした．【方法】CAGプロモーターを用いてC57BL6マウスに変異MATR3（S85C）を導入したトランスジェニックマウスを作成し，HE染色，mGT染色，抗MATR3抗体，抗TDP-43抗体を用いた免疫染色を行い，筋病理学的に野生型マウスと比較した．【結果】変異MATR3トランスジェニックマウスの骨格筋では縁取り空胞を認め，筋線維萎縮，内在核を有する線維の増加を認めた．またMATR3の核での染色性が失われ，筋形質内にMATR3の凝集を認めた．【結論】変異MATR3トランスジェニックマウスはVCPDMのモデルマウスとして有用であり，VCPDMの病態には核変性や蛋白分解経路の異常が関与していることが示唆された．

O-06-5

マイオスタチン阻害活性中心ペプチドによる筋萎縮治療法

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【目的】マイオスタチンは骨格筋量を負に体脂肪量を正に制御するTGF-βファミリー分子で，血中ではN末端プロドメインがC末端の活性をもつアクティブドメイン（リガンド）を非共有結合で包含し，その活性を抑制する不活性型複合体を形成している．プロドメイン全長239アミノ酸残基から阻害活性中心(IC)を同定し，この領域のペプチドによる筋萎縮治療法を開発する．【方法と結果】①マイオスタチンのエフェクターであるSmad感受性配列（$CAGA)_{12}$を上流に組み込んだレポーター遺伝子とプロドメインの各部分のFc融合蛋白質をHEK293胎児腎細胞に共発現．上清にリコンビナントマイオスタチンを添加し転写活性を阻害する領域を同定した．②ICとリガンド・受容体（タイプI，タイプII）を強制発現させ相互作用を検討した．③ICに相当する合成ペプチドを肢帯型筋ジストロフィー（LGMD）1Cおよびデュシェンヌ型筋ジストロフィーモデルマウスに投与した．【結果】①29アミノ酸残基からなるICを同定．②IC強制発現では，リガンドばかりでなく，タイプII膜受容体およびタイプI膜受容体と共染色・共沈降した．一方，マイオスタチン全長からこの領域を欠損させると，阻害活性は消失した．③筋ジスモデルマウスの前脛骨筋への局所投与で筋萎縮は軽減した．【結論】マイオスタチンN-末端を構成するプロドメインの阻害活性中心は，これまで知られていなかった細胞表面でのリガンド-受容体結合を阻害する機構がある．ペプチド最適化による，筋ジストロフィーおよび筋萎縮治療法開発への取り組みと今後の展望について紹介する．

O-07-1
withdrawn

O-07-2
The appearance frequency of the pericranial tenderness is related to the completeness as migraine

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【目的】頭痛発作時の頭蓋周囲圧痛点と片頭痛の診断基準上のC，Dの8項目の各項目との相関関係を検証した．【対象・方法】2007年4月から2007年12月までの頭痛外来来院患者100名（男性29名，女性71名，平均年齢43.8歳）を対象とした．頭痛の診断は基本的にはICHD-3βに基づいたが，めまいと強い関連のある緊張型頭痛様の頭痛は別項目とした．疑い例を含まない片頭痛と緊張型頭痛は各46例，14例であった．また，片頭痛の診断基準のC，D項目の8項目（片側性，拍動性，運動増悪，頭痛強度中等度から重度，悪心，嘔吐，光過敏，音過敏）のうち何項目に該当したかをスコア化し，0点から8点の9群に分類した．スコアが高い程典型的片頭痛の病像に近いと考えた．【結果】頭蓋周囲圧痛点の陽性率は片頭痛が74%，緊張型頭痛が50%，その他の頭痛が84%で，緊張型頭痛で有意に低下していた．8項目中では片側性と拍動性のみに頭蓋周囲圧痛点と有意な関連が認められた．なお，8項目への該当が多い程有意に頭蓋周囲圧痛点陽性率が上昇していた．緊張型頭痛は当然片頭痛の診断基準の該当項目が少なくなるが，今回の検討では，片頭痛と緊張型頭痛を合わせてスコアを検討しても有意に関連性が認められた．【考察】片頭痛診断基準の8項目への該当数をスコア化すると，確定診断された緊張型頭痛と片頭痛はそれぞれ0-4点，3-8点をとる．頭蓋周囲圧痛点は片頭痛の典型的な病像に近づく程出現率が高くなった．緊張型頭痛は診断基準上片頭痛の対立概念的な意味合いを持つため頭蓋周囲の圧痛点の出現率が低くなる事が合理的に説明できた．【結論】頭蓋周囲圧痛点は片側性，拍動性と有意な関連があり，典型的な片頭痛に近づく程陽性率が高くなり，緊張型頭痛では陽性率が低下した．

O-07-3
Morphological evaluation in patients with chronic migraine using Voxel-based morphometry

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【目的】片頭痛慢性化の病態を検討するため，高磁場MRI装置で得られた高空間・コントラスト分解能を有する形態画像を，自動形態解析ツールSPM12を用いVoxel-based morphometry（VBM）で脳形態を評価した．【方法】対象は慢性片頭痛患者7例（平均年齢37歳，男性1例・女性6例），非慢性片頭痛患者23例（平均年齢40歳，男性6例・女性17例）．VBMは3T MRI装置（General Electric社製Discovery）で撮影した画像を，SPM12で前処理として分割化・解剖学的標準化・平滑化を行い，年齢・性別・全脳容量で多重比較補正し解析し，cluster-level およびpeak-levelがp＜0.01のボクセル群を有意な変動部位と判定した．【結果】慢性片頭痛患者は非慢性片頭痛患者に比べ，右下頭頂小葉に高ボクセル群を，左下頭頂小葉・左下前頭回・左側頭極・右前帯状皮質・右視床・右海馬に低ボクセル群を認めた．【結論】今回の検討からは，慢性片頭痛では右前帯状皮質・右視床の灰白質の体積低下が生じていることより慢性化にPain Matrixの異常が関与していることが示唆された．また体積増加を認めた右下頭頂小葉は，反応抑制の遂行機能に関連する部位と推測されており，片頭痛慢性化に反応抑制の遂行機能の過剰な反応が関与している可能性が示唆された．

O-07-4
Retrospective study of omega-3 fatty acid treatment for migraine patients with dyslipidemia

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【目的】慢性片頭痛に対して，脂肪酸に関する食事介入により頭痛が改善したとする報告はあるが，脂肪酸製剤の投与効果に関する報告は限られている．脂質異常を伴い，かつ難治性の片頭痛にω3系脂肪酸製剤が有効か検討する．【方法】国際頭痛分類第3β版に基づき，前兆を伴う片頭痛（MA），前兆を伴わない片頭痛（MO），慢性片頭痛（CM）と診断し，2015年1月から同年10月まで診療した症例が対象．脂肪酸4分画を測定し，EPA/AA比＜0.4を脂質異常と定義した．以下の条件を満たす症例に患者の同意を得てEPA 1800mg/dayを投与した．(1)従来の予防薬が奏効しない，もしくは副作用のために従来の予防薬を使用できない，(3) EPA/AA比＜0.4．他の予防薬の変更や追加は行った症例は除外した．NSAIDsやトリプタンは適宜使用した．頭痛ダイアリーを参照し，治療開始前，1か月後，2ヶ月後で次の項目を比較した．(1)4週間あたりの頭痛日数，(2)平均visual analogue scale（VAS）．【結果】EPA/AA比を測定した片頭痛症例は67人で，EPA/AA比 0.21 ± 0.12であった．このうちEPAを投与したのは26人（男性7人，女性19人，年齢 34.0 ± 8.2歳，MA 1人，MO 16人，CM 9人，頭痛日数16.7 ± 9.5日，平均VAS 60.0 ± 16.0，EPA/AA比 0.19 ± 0.09であった．投与2ヶ月後には頭痛日数 12.2 ± 9.6日，平均VAS 44.2 ± 24.7でともに有意に減少した（P＜0.05）．Episodic migraine（MA+MO）とCMに分けて解析すると，前者では頭痛日数，平均VASともに有意に改善したが，後者では減少傾向を示したものの有意ではなかった．【考察】EPAは難治性または従来の予防薬薬剤が使用できない片頭痛患者に有効であった．ω3系脂肪酸であるEPAは代謝により炎症抑制性エイコサノイドを生じる．EPA投与により，神経原性炎症の際に硬膜肥満細胞から放出される炎症促進性プロスタグランジンが減少することが片頭痛に対する作用機序と推測される．

O-07-5
The influence of telmisartan to cortical spreading depression on Zucker fatty rat

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(Objectives) To examine the effect of telmisartan on cortical susceptibility to spreading depression.(Backgrounds) Migraine and obesity represent two major public health problems. Obesity is a risk factor for migraine chronification. We recently reported an increased cortical susceptibility to cortical spreading depression (CSD) in Zucker fatty (ZF) rat, which is an obesity model and harbors a missense mutation in the leptin receptor gene with hyperleptinemia. It is suggested that this ZF rat CSD-induction model may be used as an obesity migraine model. While recent study demonstrated migraine prophylactic effect of candesartan, a first generation of angiotensin II receptor blocker (ARB), we did not confirm its CSD inhibitory effect in our ZF rat model. Then, we hypothesized that telmisartan, a second generation of ARB, might have more potent inhibitory effect on CSD than the first generation.(Methods) Using a ZF rat, telmisartan (1mg/kg, n=5) or saline (control, n=5) was administered orally once a day for 28 days, and CSD was induced on day 29. We measured % changes in CBF, % changes in DC potential, the number of CSDs and the duration of CSDs.(Results) The number of CSDs was significantly decreased in ZF rats pretreated with telmisartan than vehicle (p=0.017), but no significant changes were seen in the other parameters.(Conclusion) The results of this preliminary study deserve migraine prophylactic trial with telmisartan in refractory migraine. The second generation of ARB, such as telmisartan, may provide additional prophylactic effect in patients with migraine aura.

O-08-1
The effectiveness and safety of MR guided focused ultrasound (MRgFUS) for essential tremor

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【目的】薬物治療抵抗性で中等度以上の本態性振戦例に対する経頭蓋MRガイド下集束超音波治療（以下FUS）の臨床試験は2015年11月末現在，本邦で25例程が施行され，進行中である．従来の外科的治療である深部脳刺激療法や視床破壊術に比し，侵襲が少ないことが利点とされるが，その有効性や安全性については，まだよく知られていない．当院におけるFUSの有効性評価とともに，軽微なものも含めたadverse eventsを併せて報告する．【方法】対象は2015年3月～10月の7ヶ月間に当院にてInSightec社製ExAblate Neuroを用いてFUSを施行され，術後1ヶ月の評価が終了している8例（平均72.4歳，男性7例女性1例）．術前と術後1ヶ月時点における姿勢振戦，企図振戦，書字振戦のそれぞれの程度を「振戦の臨床的評価尺度CRST（0～4）」を用いて評価するとともに，社会生活面における障害の程度の変化についても検討した．【結果】全例左視床腹側中間（Vim）核に対してFUSが完遂された．治療側の平均CRSTは，姿勢2.4から0.1，企図1.6から0.3，合計4.0が0.4と著明に改善（改善度90%，p＜0.05）し，書字時の振戦3項目の総スコア（0-12）も8.8が1.5と有意に改善した（p＜0.05）．また，社会生活面における障害の程度のスコアは有意に全例改善（12.4→3.1，p＜0.05）し，高い患者満足度が得られた．一方，adverse eventsは軽微なものを含め8例中7例計12件認めたが，術中の嘔気嘔吐や頭皮関連のものがほとんどで，永続するものや重篤なものはなかった．【結論】本態性振戦に対するMRgFUSは現在，本邦での臨床試験中であるが，症状を劇的に改善させ得る，ほぼ安全で有用な治療と考えられる．

O-08-2

The outcome of Parkinson's disease cases who received multiple neuromodulation therapy

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【目的】脳深部刺激療法(DBS)をはじめ機能外科手術はパーキンソン病の運動合併症，難治性の振戦などに対する確立した治療法である．症状にあわせ視床下核，淡蒼球，視床など標的部位を選択する．運動症状に対する長期予後の知見は確立しているが，効果が不十分で症状制御に難渋する症例も存在する．複数回の機能外科手術を必要とした症例に関して背景，経過，手術適応等について検討した．【方法】対象はパーキンソン病の症状制御のため機能外科手術施行後，再手術を必要とした4例で，先行した手術はSTN-DBS3例，視床凝固術1例であった．再手術を必要とした症状はジスキネジア4例，ジストニア2例，ウェアリングオフ1例で，手術後経過，症状変化，追加手術内容について検討した．【結果】平均発症時年齢は38歳，初回手術までの平均罹患期間は14.5年，再手術までの期間は11.3年であった．STN-DBSを先行した症例ではジスキネジア，ウェアリングオフとも改善傾向であったが，長期経過中にジスキネジアの制御が困難になった．主な理由として刺激を強める際に周囲への刺激波及が起こり，十分な刺激が行えなかったことがあげられた．いずれもGPi-DBSを追加施行し，症状は改善した．視床凝固術を先行した症例では当初は振戦優位で，他の運動症状は軽度であったが，症状進行に伴い，ウェアリングオフやジスキネジアが顕在化したため，年齢や精神症状の存在を考えGPi-DBSを追加施行し運動症状は改善した．DBSを2回施行した症例では，STN刺激をGPiで肩代わりさせ，併用することで運動症状改善のみならず，STN刺激の周囲への波及と考えられる発声障害，嚥下障害，バランス，感覚症状なども改善した．【結論】機能外科手術により，進行期パーキンソン病の症状は改善するが，長期的には刺激調整などを図っても症状の制御に難渋することがある．その際，外科治療を追加施行することで改善しうる症状があれば，ADLを高められると考えた．

O-08-3

Efficacy of istradefylline on urinary tract symptoms in Parkinson's disease

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Background: In addition to motor symptoms, bladder dysfunction is a major clinical issue in patients with Parkinson's disease (PD). Istradefylline, a non-dopaminergic selective adenosine A2A receptor antagonist, has been reported to improve motor function in PD patients. However, the efficacy of istradefylline for lower urinary tract symptoms (LUTS) has not yet been clarified. The aim of this study was to determine the effects of istradefylline on LUTS in PD patients.**Methods:** We enrolled 21 PD patients with male/female prevalence of 13/8. The mean of age of patients was 73 (61-77) years old, the Hoehn-Yahr stage was 2 (2-3), and disease duration was 9 (3-28) years. The effects of istradefylline (20 mg/day) on LUTS in PD patients with motor complications after 4, 8, and 12 weeks of therapy were evaluated based on the International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS) before and after its administration.**Results:** Motor symptoms significantly improved after 12 weeks (MDS-UPDRS Part III: 26.0 ± 11.6 vs. 10.0 ± 7.0; P＜0.01). Significant improvements were also observed in the answers provided on urinary questionnaires after 4 weeks (IPSS: 12.5 ± 7.3 vs. 8.9 ± 6.3, OABSS: 7.1 ± 3.4 vs. 5.9 ± 3.4; P＜0.01). Nighttime urinary frequency (2.5 ± 1.4 vs. 1.7 ±0.9; P＜0.01) and the percentage of the nocturnal urine volume also improved significantly (46.9 ±10.5 vs. 37.9 ± 9.6%; P＜0.01). Adverse urological effects did not develop in any patient.**Conclusion:** Istradefylline effectively improved not only motor symptoms, but also LUTS in patients with PD.

O-08-4

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, reduces OFF time in Parkinson Disease

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[Objective] Duloxetine is an antidepressant that inhibits serotonin and noradrenaline reuptake. We have demonstrated that both serotonin and noradrenaline transporters play major roles in uptake of L-dopa-derived dopamine in the rat striatum with dopaminergic denervation by 6-hydroxydopamine. Furthermore, we have shown that duloxetine enhances L-DOPA-induced motor behaviors in the rat model of Parkinson Disease (PD). The study aim was to examine efficacy of duloxetine in PD patients with wearing-off in an open label study. [Methods] Permission for the study was given by Ethical Committee of our hospital. Written informed consents to participate in the clinical trial were obtained from 13 PD patients (8 women and 5 men) with depressive complaints and wearing-off at least for 2 hours a day. A stable regimen of all antiparkinsonian drugs had been kept for 4 weeks prior to and during the study. Duloxetine 20 mg/day was given during the first week and then increased to 40 mg/day. Patients' diary and clinical evaluations were made at 0, 2, 4 and 8 weeks. [Results] Eleven patients completed the study. When compared to 0 week, UPDRS part II score during ON (-0.64, P＜0.05) and OFF (-2.8, P＜0.05) and UPDRS part III score during ON (-4.43, P＜0.01) significantly improved at 8 weeks. Daily OFF time became significantly shortened (-4.9 hours, P＜0.01) at 8 weeks. However, 4 patients complained of aggravation of troublesome dyskinesias. [Conclusions] Duloxetine enhances the effects of L-DOPA and shortens daily OFF time, but may worsen L-DOPA-induced dyskinesias.

O-08-5

Zonisamide enhances effects of levodopa in a rat model of Parkinson's disease

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Objectives: To examine the effects of zonisamide, the antiparkinsonian mechanisms are not clearly understood yet, on motor symptoms in a rat model of Parkinson's disease when co-administered with levodopa or apomorphine.Method: We used 24 Wistar rats. 6-hydroxydopamine was injected into the right medial forebrain bundle to create dopaminergic denervation. Seven weeks after the surgery, the rats were randomly allocated to one of five groups. Eight rats received levodopa only (6 mg/kg); eight rats received levodopa plus zonisamide (50 mg/kg); six rats received apomorphine only (0.05mg/kg); six rats received apomorphine plus zonisamide; six rats received zonisamide only. The drugs were administered once daily for 15 days. We evaluated abnormal involuntary movement (AIM) score every 20 min during the three-hour period following the injection of drugs, on the treatment Day 1, 8, 15.Results: Scores of AIMs were significantly higher in the levodopa plus zonisamide group when compared with the levodopa only group on day 15 of the treatment. On the other hand, zonisamide treatment has no impact on apomorphine-induced AIMs. Zonisamide monotherapy brought no AIMs.Conclusions: Zonisamide appears to enhance the motor effects of levodopa but not that of a dopamine agonist, apomorphine. These results suggest that zonisamide represents its antiparkinsonian effects by modulating levodopa-dopamine metabolism.

O-09-1

Evaluation of cerebral oxidative stress in patients with ALS using ^{62}Cu-ATSM PET

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[Objective] To investigate cerebral oxidative stress caused by mitochondrial dysfunction and its relationship to disease severity in patients with amyotrophic lateral sclerosis (ALS) using PET with ^{62}Cu-ATSM. [Methods] Twelve patients with ALS and 9 age-matched healthy controls underwent a 20-minute dynamic brain PET scan after ^{62}Cu-ATSM injection. The standardized uptake value (SUV) images obtained from the last 10 minutes of frames were normalized by the global mean (nSUV). Regional ^{62}Cu-ATSM retention in the nSUV images was compared between groups using statistical parametric mapping (SPM) and region of interest (ROI) analysis. Secondary analyses evaluated the correlations between regional nSUVs and the clinical characteristics of the participants. [Results] In SPM mapping, patients with ALS showed a significantly greater accumulation of ^{62}Cu-ATSM compared to controls in the bilateral cortices around the central sulcus, including the motor cortex, and the right superior parietal lobule. ROI analysis also revealed significantly greater nSUVs in patients than controls in these regions. Increases in nSUV for these regions were associated with decreases in the revised ALS Functional Rating Scale score, suggesting a good correlation with the severity of ALS. [Conclusions] ^{62}Cu-ATSM PET imaging demonstrated increased oxidative stress based on an over-reductive state, primarily in the motor cortex, in patients with ALS. The magnitude of oxidative stress correlated well with clinical severity, indicating that it may be associated with neurodegenerative changes in ALS.

O-09-2

Underlying pathomechanisms of motor neuronal hyperexcitability in amyotrophic lateral sclerosis

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[Objective] While motor neuronal hyperexcitability potentially contributes to motor neuron death in amyotrophic lateral sclerosis (ALS), pathomechanisms of motor neuron hyperexcitability have not yet been revealed.[Methods] Threshold tracking transcranial magnetic stimulation and multiple excitability measurements were performed in 150 healthy controls (HC), 83 sporadic ALS (sALS) patients, 12 patients with *superoxide dismutase-1* (*SOD-1*) mutations, 16 *C9orf72* hexanucleotide repeat expansions and 2 *FUS* mutations.[Results] Compared to HC, in peripheral nerve excitability sALS had greater strength-duration time constant ($p < 0.05$), depolarizing threshold electrotonus ($p < 0.0001$) and superexcitability ($p < 0.05$) and smaller late subexcitability ($p < 0.05$). In cortical excitability, sALS had reduced short interval intracortical inhibition ($p < 0.0001$). These indices were not significantly different in *SOD-1* and *C9orf72*, compared to sALS. These findings suggest both sALS and familial ALS have increased sodium and decreased potassium currents, leading to peripheral nerve hyperexcitability. In addition, ALS patients across the spectrum demonstrated decreased intracortical inhibition. [Conclusions] Cortical and peripheral motor neuronal hyperexcitability may be common features in both sporadic and familial ALS, associated with different pathological bases, and suggesting the presence of common therapeutic effector sites.

O-09-3

The efficacy of combined bone marrow transplantation plus G-CSF treatment in ALS mice

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Objective: Bone marrow (BM) transplantation (BMT) using wild type (WT)-BM cells or granulocyte-colony stimulating factor (GCSF) treatment has clinical neuroprotective effects in amyotrophic lateral sclerosis (ALS) model mice. Furthermore, the combined BMT plus GCSF therapy shows neuroprotective and neuroregenerative effects compared with only BMT therapy in ischemic model mice. Therefore, we investigated the clinical benefit of combination therapy using BMT with WT-BM cells plus GCSF after disease onset in ALS mice.Methods: 91-day-old G93A transgenic (Tg) mice were treated with vehicle, BMT only, GCSF only, or BMT plus GCSF. The survival of G93A Tg mice were recorded. Lumbar spinal cord sections were analyzed by immunohistochemistry.Results: Combined BMT plus GCSF treatment prolonged the survival of G93A Tg mice compared with single BMT or GCSF treatment. Furthermore, combined BMT plus GCSF treatment ameliorated motor neuron loss, increased the expression of neurotrophic factors and activated angiogenesis compared with single BMT or GCSF treatment.Conclusions: These results suggest that combined treatment with BMT plus GCSF has potential neuroprotective and angiogenic effects in ALS mice.

O-09-4

The effect of exercise in a mouse model of spinal and bulbar muscular atrophy

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Objective: Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disease caused by the expansion of a CAG repeat in the androgen receptor (AR) gene. Several studies indicate that physical exercise is likely to be protective in neuromuscular disease. It is also reported that excessive exercise related to risk of the onset in motor neuron disease. Whether physical exercise is beneficial or harmful is still under debate. We aimed to investigate the effect of exercise in SBMA model mice.**Methods:** To investigate the effect of exercise on different stages of disease, exercise was started from the pre or post-onset stage (5 or 9 weeks of age) in a transgenic mouse model of SBMA (AR-97Q). Exercise was loaded by forced wheel running cages for 1 hours a day, 5 days a week, and maintained for 4 weeks. We then performed behavioral and biochemical analysis on these mice and compared the results with sedentary mice.**Results:** The motor function and life span of the AR-97Q mice that started exercise at the post-onset stage were similar to those of sedentary control mice. On the other hand, the exercise from the pre-onset stage improved behavioral and histopathological findings, and extends the life span in AR-97Q mice. In biochemical analysis, we found that the exercise from the pre-onset stage inhibits mutant AR aggregation in the skeletal muscles of AR-97Q mice.**Conclusion:** The present study showed that the exercise from the pre-onset stage mitigated symptoms and increased life span of SBMA model mice via reducing AR aggregation in skeletal muscle.

O-09-5

Modeling spinocerebellar ataxia type 36 using patient induced pluripotent stem cells

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(**Purpose**) Spinocerebellar ataxia type 36 (SCA36) is an untreatable neurodegenerative disease that causes not only spinocerebellar ataxia but also motor neuron (MN) disease. In 2011, the causative mutation of SCA36 was found to be the GGCCTG repeat expansion of nucleolar protein 56 intron1. However, SCA36 MN pathology remain unclear even today. In order to analyze the SCA36 MN pathology, we generated iPSCs from SCA36 patients. (**Method**) We generated iPSCs from four SCA36 patients and three control individuals. Then we differentiated iPSCs into spinal MNs, and performed immunocytochemistry and fluorescence in situ hybridization. (**Results**) All iPSC lines expressed the pluripotency markers along with a normal karyotype. SCA36 iPSCs exhibited the GGCCTG repeat with the repeat primed polymerase chain reaction. There was no significant difference of the differentiation propensity of spinal MNs from iPSCs between SCA36 and control. However, RNA foci were detected in several SCA36 iPSCs and MNs. (**Conclusions**) We have succeeded in modeling SCA36 using patient iPSCs.

O-10-1

THERAPEUTIC HYPOTHERMIA AFTER CARDIOPULMONARY ARREST: 5 YEAR CLINICAL EXPERIENCE

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BACKGROUND Therapeutic hypothermia is a standard of care for post-arrest patients. Despite its implementation, it was observed that majority would still result in poor outcomes.**OBJECTIVE**: We aim to describe our 5-year clinical experience in the use of Therapeutic Hypothermia and the factors affecting clinical outcome after three months.**METHODOLOGY**: A descriptive analytical study was done on all post-arrest patients who had undergone therapeutic hypothermia admitted from June 2011 to January 2015.**RESULTS:** Among the 88 consecutive patients who were included in the study, 23% were discharged alive but only 11% had good functional outcome. Majority of the population were males, about 60 years old, cases of out-of-hospital arrest, none of which were provided basic life support. Patients above 60 years old have poor outcome. Statistically significant risk factors associated with poor outcome were > 5 minutes duration of CPR ,and an initial rhythm of asystole and pulseless electrical activity. The absence of corneal reflex and motor response 72 hours post-arrest were predictive of a bad outcome.**CONCLUSION:** Our findings suggest that the survival of post cardiac arrest (23%) and good outcome of 11% are both inferior compared to published survival incidence of other countries (75% and 49-55% respectively). The following factors were associated with bad outcome: older age, increasing number of co-morbidities, increased CPR duration , initial rhythm of asystole and pulseless electrical activity, non shockable rhythm, absence of motor response and corneal reflex 72 hours post arrest.

O-10-2

The study on the characterization of the visual-illusion figure cognition in cerebellar disorders

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【目的】これまで運動機能との関連が研究されてきた小脳であるが，症例研究の蓄積や解剖学的知見，さらには健常者を対象とした脳機能画像研究から，近年では高次脳機能との関連が注目されている．一方で，Poggendroff錯視などのいくつかの錯視図形の知覚は，生活環境における視覚情報から経験的に修得されるとの仮説があり，学習に重要とされる小脳が錯視形成に関与している可能性がある．そこで我々は，小脳損傷が錯視図形の認知に与える影響について検討した．【方法】小脳のみに病巣をもつ脳卒中(Ce-S群)15例(出血2例，梗塞13例，平均75.7歳)，小脳変性症(Ce-D群)8例(SCA6 3例，SCA31 2例，CCA各3例，平均74.4歳)，非小脳性神経疾患(Non-Ce群)21例(脳卒中，Alzheimer病など，平均71.1歳)の3群を対象に，Poggendroff錯視図形を用いた視覚課題(9課題)，非錯視性図形を用いた視覚認知コントロール課題(12課題)を施行し，錯視の有無とその程度について評価を行った．全例で検査に支障をきたす視覚・認知機能障害がないことを確認し，錯視が生じた割合である錯視率(%)と，錯視の強さを表す錯視指数を算出し，各群で統計比較を行った．【結果】3群間の年齢・性別に有意差は認めなかったが，錯視率はCe-S, Ce-D, Non-Ce群それぞれ，平均55.6%，52.8%，83.1%と小脳損傷群で有意に低く，錯視指数についても平均5.07，5.26，8.14と小脳損傷群で有意に低値であった．以上より，小脳損傷群では錯覚が生じにくく，幾何学的に正しい選択肢を選ぶ傾向が明らかとなった．一方，コントロール課題の正答率は3群間で有意差はなく，通常の視知覚機能は各群で同等であった．【考察】運動学習に重要とされる小脳だが，本検討より錯視図形の知覚にも関与している可能性が示唆された．小脳と錯視の因果関係を明らかとするため，今後さらなる症例の蓄積とともに，病巣の左右差や小脳亜区域との対応，運動失調の重症度との関連を検討していく．

O-10-3

Agrammatic comprehension affected by word order in nonfluent/agrammatic primary progressive aphasia

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Purpose: Nonfluent/agrammatic variant primary progressive aphasia (naPPA) often causes agrammatic comprehension, which is characterized by impaired understanding of sentences with syntactically complex structures. It is greatest for sentences with noncanonical word order. Two possible informational cues help predict canonical word order: *grammatical-function* information (the subject precedes the object) and *thematic-role* information (an agent precedes a theme). We aimed to clarify the significance of informational cues for canonical word order in agrammatic comprehension. **Methods:** We assessed syntactic ability of four patients with naPPA and 14 healthy controls using picture-sentence matching tasks with stick figures. Four different sentence types were tested: subject/agent-initial active (SA), subject/theme-initial passive (SP), object/theme-initial active (OA), and object/agent-initial passive (OP). **Results:** While all patients showed normal comprehension of SA sentences and relatively preserved comprehension of SP and OP sentences (two-tailed binomial tests, all $Ps < 0.015$), they performed at chance level for the OA sentences (all $Ps > 0.21$). **Conclusions:** The OA sentences contain deviations in grammatical-function and thematic-role information. In contrast, OP sentences only contain deviations in grammatical-function information. The preserved ability to comprehend OP sentences indicates that the *degree* to which informational cues deviate from those that predict canonical word order affects agrammatic comprehension in naPPA.

O-10-4

The brain regions associated with ideomotor apraxia in acute ischemic stroke patients

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背景：Liepmannによる古典的概念における観念運動性失行の責任病巣として，左下頭頂小葉が重視されてきた．しかし，近年は失行概念の再構築と統計的画像解析を経て，下頭頂小葉以外の病巣の関連も主張されている．一方，実臨床では信号動作や物品使用動作のパントマイム障害である古典的概念を用いるのが主であるが，急性期脳梗塞における統計的画像解析の報告は少ない．目的：急性期脳梗塞連続例において統計的画像解析を用いて，観念運動失行の責任病巣を検出すること．方法：2007年4月から2012年3月までに当施設に発症7日以内に入院した脳梗塞連続2146例より，初回発症で右利き，発症前の認知症がない，左中大脳動脈領域限局の非ラクナ梗塞で，言語聴覚士により言語評価が行われた連続136例（平均年齢70.5±12.9歳，男性79 例）を後ろ向きに検討した．病巣解析には言語評価に最も近い日に撮像されたT2強調像もしくはFLAIR画像を用いた．観念運動失行は，口頭命令もしくは模倣による，信号動作もしくは物品使用パントマイム障害とした．観念運動失行有無による2群間でvoxel-based lesion symptom mapping（VLSM）を用いた統計解析を行った．結果：神経心理評価は発症から（中央値[四分位]）7[5-10]日で施行された． 136例中17 例（13%）が観念運動失行と診断された．解析に用いられた頭部画像は発症から中央値9 [7-12.75]日に施行されていた． VLSMを用いた解析により，左下頭頂小葉，上側頭回，中心溝下部そして中前頭回が観念運動失行と関連した．結語: パントマイムの障害である観念運動失行の神経基盤は下頭頂小葉以外の複数の病巣が関連する可能性がある．

O-10-5

EEG phase synchrony reflects the severity of left unilateral spatial neglect after stroke

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【目的】我々は安静時脳波位相同期を用いて脳卒中後の神経ネットワーク機能を評価することを試み，半球間位相同期指数や感覚運動野の位相同期指数（Phase Synchrony Index: PSI）が臨床スケールと相関を示すことを見いだした．本研究の目的は，脳卒中後の左半側空間無視（USN）と右頭頂葉を中心とするPSIの関連を検討することである．【方法】回復期リハビリ目的で当院に入院した初発脳梗塞患者のうち，右半球病変を有し書面で同意を得られた者を対象とした．臨床的なUSNの有無により，無視群（16名，平均年齢67.2歳），非無視群（17名，平均年齢63.9歳）に分けた．脳波測定後，目的電極間および各半球内全体のPSI（右半球：RH-PSI，左半球：LH-PSI）を算出した．まずRH-PSI，LH-PSIについて両群間の比較を行い，ついでPSIと行動性無視検査（BIT）の抹消課題スコア合計値との相関について検討した．抹消課題では，頭頂葉に加えて前頭葉領域（Brodmann10，45，46野）の関与が報告されており，これらの領域を解析対象とした．【結果】両群でLH-PSIはRH-PSIよりも高値であったが，無視群でLH-PSI/RH-PSI比がより高値であった．無視群では，両側頭頂葉間（P3-P4）のPSIはスコアと有意な相関を示し（ρ=0.65~0.70　p< 0.05　相関係数：Spearmanのρ），右前頭葉-頭頂葉間（P4-Fp2，P4-F8，P4-F4）PSIもスコアと相関傾向を示したが，全般的認知機能の指標であるMMSEとは相関を示さなかった．半球内PSIの比較結果は，USNの存在と半球内位相同期の左右不均衡増大が関連していることを示唆し，PSIとスコアの相関は，電極ペアと周波数依存性であり，課題選択的に病態を反映していると考えた．【結論】脳波位相同期を定量化することにより運動機能障害にとどまらず，USNのような認知機能の評価指標との関連が示されたことから，幅広い脳卒中病態の理解に有用であると考える．

O-11-1

Clioquinol decreases phosphorylation levels of tau protein via JNK inactivation

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[Objective] Bio-metals imbalance may be involved in the formation of senile plaques（SP）and neurofibrillary tangles（NFT）, thus metal modulation may be a direction for research of Alzheimer's disease（AD）treatment. One of metal-protein attenuating compounds clioquinol（CQ）has mild chelating effect for Zn^{2+} and Cu^{2+}. CQ can detach metals from SP and reduce the amyloid aggradation in cerebral cortexes. But researches about the effects of CQ on tau are still rare. We report here the effect of CQ on phosphorylation levels of tau protein. [Methods] We used a human neuroblastoma cell line, M1C cells which express wild type tau protein（4R0N）via tetracycline off induction. Phosphorylation levels of tau protein were examined before and after CQ treatment by Western blotting and immunocytochemical study. [Results] 1 to 10 μM of CQ reduces the phosphorylation levels of tau protein. The activity of JNK, one of tau kinase, was reduced by CQ treatment. Interestingly, activation of protein phosphatase 2A（PP2A）, which acts as phosphatase, was also observed. Fractionation study showed that reduction of oligomeric tau in tris insoluble, sarkosyl soluble fraction by CQ treatment. 10 μM of CQ reduced caspase cleaved tau, which accelerates aggregation of tau protein. Morphological study detected that 0.1 to 10 μM of CQ had no effects on cell viability. But 100 μM of CQ has cytotoxic effects. [Conclusions] Although further researches are needed to elucidate the mechanisms responsible for the effects of CQ on tau, CQ may shed light on the possible therapeutics of AD.

O-11-2

Downward spiral of CAA and tau pathology in Alzheimer's disease

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[Objective] The fact that more than 90% of Alzheimer's disease（AD）is pathologically concomitant with cerebral amyloid angiopathy（CAA）implies the significance of CAA in AD pathogenesis. CAA mainly results from impaired Aβ clearance. Several studies showed that crossbreeding of AD and tauopathy model mice resulted in enhanced tau degeneration, although interaction between Aβ and tau *in vivo* remains to be clarified. Here, we investigated whether and how CAA influences tau metabolism.**[Methods]** We developed double transgenic mice by crossbreeding PS19 mice carrying the MAPT gene with P301S mutation with CAA model mice expressing the APP gene with Swedish-Dutch-Iowa mutations, in which Aβ clearance was severely impaired. All the mice were analyzed at 8 months of age.**[Results]** The bigenic mice showed marked reduction of cerebral blood flow and impairment of cerebrovascular reactivity compared to the other groups of mice. The bigenic mice also displayed decreased anxiety in the elevated plus maze test and impaired spatial reference memory in the Barnes maze test. Immunohistochemical staining showed that the amount of A$\beta_{1\text{-}40}$, A$\beta_{1\text{-}16}$, total tau, 4 repeat tau, and hyperphosphorylated tau was significantly elevated in the double Tg mice compared with the other mouse groups. Astrogliosis, microgliosis, and neuronal loss were the most prominent in the bigenic mice. **[Conclusions]** There is a bidirectional influence between CAA and tau, suggesting a positive feedforward loop of toxic protein accumulation. Thus, neurovascular approach is warranted for AD and CAA.

O-11-3

Induction of phosphorylated tau in synapse by accumulation of Abeta oligomers

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[Objective] Tau is recently considered an executor of neuronal damage and cognitive dysfunction in Alzheimer's disease（AD）. Aβ oligomers are suggested to induce phosphorylated tau, however, the relationship between Aβ oligomers and tau is not obvious. Aβ oligomers, phosphorylated tau, and Fyn signaling are supposed to cause synaptic dysfunction in AD brain. We have shown that phosphorylated tau is induced in lipid rafts of Tg2576 mouse brain, and that Aβ oligomers/PrP^c complex and activated fyn-NMDA signaling are found in lipid rafts of Tg2576 mouse brain. We examined if Aβ oligomers induce phosphorylated tau and fyn-NMDA cascade in synapse. [Methods] We prepared synaptosome fraction from brains of Tg2576 mice（Tg n=33, NonTg n=33）. The lipid rafts fraction was prepared from synaptosome fraction. The samples were analyzed using western blotting. The colocalization of tau and synapse marker was examined by immunofluorescent staining of cryostat sections. [Results] Aβ oligomers, PrP^c, fyn, and phosphorylated tau were localized in synaptosomes, and also localized in lipid rafts of synaptosome. The amount of phosphorylated tau and fyn was increased in synaptosome, and also in lipid rafts of synaptosome with accumulation of Aβ oligomers. Phosphorylated tau colocalized with PSD95, a postsynaptic marker. [Conclusions] Aβ oligomers may induce phosphorylated tau and Fyn-NMDA receptor signal transduction pathways in lipid rafts of synapse.

O-11-4

Deciphering the Molecular Profile of Amyloid Pathology for Alzheimer disease by Deep Sequencing

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Purpose: The elucidation of the molecular signatures triggered by the amyloid cascade of pathological events is one of the central research questions on the etiology of Alzheimer's disease（AD）. Next-generation sequencing allows the identification of genes involved in disease progression in an unbiased manner. We here to decipher the molecular profile of amyloid pathology in transgenic mice for AD by deep sequencing. **Methods:** We applied this technique with the analysis of APP/PS1 mouse model（cases=10, controls=10）which developed early plaque formation, intraneuronal Aβ aggregation and spatial cognitive deficits. Using deep RNA sequencing, differentially expressed genes（DEGs）were identified and subsequently verified by quantitative PCR. **Results:** Analysis of the hippocampus with both the Cufflinks tool and the Deseq tool revealed 107 DEGs. Network analysis of DEGs modules revealed six hub genes（4732456N10Rik, 4933427G17Rik, A930003A15Rik, AW551984, Adra1d and Adcyap1）in hippocampus of amyloid mice. We also observed differing expression levels of five DEGs in the temporal lobe and three in the cerebellum. Gene Ontology term enrichment analysis revealed an overrepresentation of immune gene expression correlated tightly with plaques. Besides, many of the DEGs specific to the APP/PS1 model belong to neuroinflammatory processes typically associated with plaques. **Conclusions:** Our study not only provides substantial insights into the different effects of alterations in amyloid pathology but also highlights specific genes associated with plaques.

O-11-5

Genome-wide analysis of neuron specific DNA methylation in Alzheimer's disease

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[Objective] In Alzheimer's disease(AD), deposition of amyloid beta and phosphorylated tau has been shown to be the cardinal features. The purpose of our study is to elucidate how these features were related to deterioration of neuronal function and what kinds of molecules play key role in neuronal cells of AD brain. [Methods] We used inferior temporal gyrus of 30 AD and 30 age-matched healthy control brains. Neuronal and non-neuronal nuclei were separated by FACS (fluorescence activated cell sorting) with anti-NeuN antibody. Genomic DNA from neuronal cells was analyzed with Illumina's Infinium HumanMethylation450 Beadchip system and pyrosequencing. Based on these data, we performed gene expression analysis and analyzed cellular and mouse models. [Results] We found 279 differentially methylated probes (DMPs) and extracted 8 differentially methylated regions (DMRs). Three of these DMRs were in CpG islands promoters. Pyrosequencing of genomic DNA from neuronal/non-neuronal cells in AD and neuronal cells in Lewy body disease revealed these methylation changes were specific to AD and central nervous system. Immunohistochemistry and biochemical analysis revealed upregulation of the gene related to one of these DMRs and insolubilization of this gene product. Overexpression of mutant APP (APPswe: KM594/5NL) induced upregulation of this gene *in vitro* and *in vivo*. [Conclusions] We found methylation changes and expression changes of novel genes in AD. Our study showed the importance of neuron specific DNA methylation analysis to find a novel mechanism in neurodegenerative disease.

口演

5月19日(木)

O-12-1

Usefulness of Heidelberg classification for ischemic stroke patients

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【目的】急性期虚血性脳卒中の再開通療法に伴う頭蓋内出血（ICH）に対する頭部単純CTによる放射線学的分類として，ECASS分類が広く用いられてるが，2015年9月に遠隔部脳出血や血管内治療後のICHを包含するHeidelberg分類が提唱された．アルテプラーゼ0.6mg/kgによる静注血栓溶解療法時のECASS分類と比べたHeidelberg分類の有用性を検討する．【方法】静注血栓溶解療法を受けた虚血性脳卒中患者における3ヵ月後の臨床転帰を検討したSAMURAI rt-PA registry600例中，当院から登録症例を検討した．【結果】対象は129例（女性87例，73±7.4歳），治療前NIHSSの中央値は11（IQR7－16）であった．従来のECASS分類を用いるとICHは22.5%（29例），内訳hemorrhagic infarction（HI）1は3.1%（4例），HI 2は6%（4.7%），parenchymal hemorrhage（PH）1は9.3%（12%），PH 2は5.4%（7%）で，症候性ICH（sICH）は3.1%（4例）に認めた．Heidelberg分類ではICHは24.0%（31例，34血腫），内訳はHI 1は3.1%（4例），HI 2は4.7%（6例），PH 1は9.3%（12例），PH 2は5.4%（7例）で，新規項目の遠隔部脳出血は1.6%（2例），脳室内出血は0.8%（1例），くも膜下出血（SAH）は0.8%（1例），硬膜下血腫（SDH）は1.6%（2例）で，sICHは3.9%（5例）に認めた．Heidelberg分類に変更することで，新たにICH2例とsICH1例（3ヵ月後mRS3）を検出できた．ICH2例の内訳は，硬膜下血腫1例（3ヵ月後mRS4）と，遠隔部脳出血とSAH合併1例（3ヵ月後mRS0）であった．新規sICH1例ではNIHSSサブカテゴリー（右上肢）が2点以上増悪していた．【結論】Heidelberg分類を用いることで，ECASS分類では分類対象でなかったSAHやSDHを分類できるようになった．血管内治療を行う機会の増加とともにHeidelberg分類の重要性が増すであろう．

O-12-2

Detection of Atrial Fibrillation Using 7-day Holter ECG in Patients with ESUS - Interim Report-

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[Objective] It is highly relevant to detect covert atrial fibrillation（AF）in patients with a recently proposed clinical construct, "Embolic Stroke of Undetermined Source（ESUS）". However, routine short duration ECG monitoring（e.g. 24-hour Holter）may not detect AF. We conduct a study to evaluate the effectiveness of a novel wireless belt-like 7-day Holter monitor（EV-201, Parama-Tech inc.）for detecting AF in patients with recent ESUS after completion of a standard clinical work-up and report the interim results.[Methods] This is a multi-center prospective observational study（UMIN identifier : 000019170）involving 5 centers. The inclusion criteria is patients with recently diagnosed ESUS and no history of AF. All the patients receive the 7-day Holter monitoring. The primary outcome is detection of any AF on the monitoring.[Results] Between September 2014 and November 2015, a total of 25 patients（11 women ; mean age 70±11 years）were enrolled from 3 centers. During a median wear time of 167.9 hours（interquartile range 163.8 - 168.8 hours）, the 7-day Holter monitor detected AF in 3 of 25 patients（12%，95% confidential interval 2.5 - 31%）. The times from start of the examination to first detection of AF in the 3 cases were 149.0, 29.7, and 116.9 hours, respectively. Antithrombotic therapy was changed to a non-vitamin K antagonist oral anticoagulant in 2 of 3 patients with newly identified AF.[Conclusion] The 7-day Holter monitoring in patients with ESUS may increase the detection rate of AF, leading to a relevant change of antithrombotic therapy. This study is ongoing.

O-12-3

Utility of left atrial abnormality on admission electrocardiography in acute ischemic stroke

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【目的】虚血性脳卒中の約25%は原因不明の脳卒中（Cryptogenic stroke）であり，未検出の発作性心房細動（Paroxysmal Atrial Fibrillation; PAF）による未診断の心原性脳塞栓症も含まれるため，最近PAFを予測し積極的に検出することに注目が集まっている．心電図のV1誘導P波陰性成分（P-wave terminal force in lead V1; PTFV1）は，左房負荷の指標となる．今回，我々はPTFV1が虚血性脳卒中患者のPAF検出や臨床病型診断に有用であるか検討した．【方法】2014年9月から2015年10月までに虚血性脳卒中の診断で当院脳血管内科に入院していた連続108例のうち，入院時12誘導心電図で心房細動やペーシングスパイクがなく，洞調律を認めた79例（平均年齢72.8±12.9歳）を対象とした．PTFV1値（mm×sec）を計測し，入院中心電図モニターでのPAF検出の有無，虚血性脳卒中の臨床病型との関連を調べた．【結果】PTFV1値は，PAFを認めた群（n=9）で有意に高かった（0.054±0.024 vs 0.033±0.029; p<0.05）．入院後PAF検出までに要した平均日数は2.5±1.9日だった．臨床病型別のPTFV1値は，心原性脳塞栓症群（0.061±0.022）で，ラクナ梗塞群（0.018±0.019; p<0.01），アテローム血栓性脳梗塞群（0.036±0.027; p<0.05），Cryptogenic stroke群（0.032±0.031; p<0.05）より有意に高かった．PTFV1値で左房負荷（≧0.04）を認めた割合は，心原性脳塞栓症群で10/11例（90%），Cryptogenic stroke群で7/18例（39%）であった．【結論】虚血性脳卒中入院時のPTFV1は，PAFの検出や心原性脳塞栓症の診断に有用であった．Cryptogenic strokeで心電図上左房負荷を認める症例では，注意深い心電図モニター観察が必要と考えられた．

O-12-4

Diagnostic criteria for cerebral small vessel disease with HTRA1 mutation

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Objective: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy（CARASIL）is a cerebral small-vessel disease（CSVD）, accompanied by alopecia and spondylosis deformans, caused by the mutation in high-temperature requirement serine peptidase A1 gene（*HTRA1*）. Some mutations in *HTRA1* have been reported to cause CARASIL-like phenotype in a dominant manner, however the diagnostic criteria for both form of CSVD have not been established. Our purpose was to propose diagnostic criteria for the CSVD with *HTRA1* mutations. **Methods:** Our diagnostic criteria for the CSVD with *HTRA1* mutations have five major components1 the onset age of neurological symptoms ≦ 55 years-old, 2) two or more following findings, dementia, alopecia and spondylosis deformans, 3) advanced leukoraiosis classified by Fazekas scale as grade 3 with external capsule lesions　10 mm or anterior temporal lesions at the age of 60 years or less, 4) the exclusion of leukodystrophy. 'Probable' was defined to meet all major components, and 'possible' was defined to meet 3) and 4) with alopecia and/or spondylosis deformans. We recruited 56 patients with advanced leukoraiosis including 15 definite CSVD with *HTRA1* mutation and determined the sensitivity and specificity of the criteria. **Results:** The diagnostic sensitivity and specificity for 'probable' were 93.3% and 78.0%, respectively. The diagnostic sensitivity and specificity for ' possible' were 100.0% and 39.0%, respectively. **Conclusion:** The proposed criteria might be useful for selecting CSVD patients to test for *HTRA1*.

O-12-5

Clinical Characteristics of Cryptogenic Stroke Patients with Occult Cancer

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[Objective] The aim of this study is to clarify the characteristics of cryptogenic stroke with occult cancer. [Methods] Between January 2006 and October 2015, 1321 patients with acute ischemic stroke were extracted from our stroke database. Among them, 184（14%）patients, including 120 patients without diagnosed cancer and 64 patients with active caner at the time of ischemic stroke onset, were diagnosed with cryptogenic stroke etiology. We compared the characteristics between cryptogenic stroke patients with occult cancer and without cancer. All data were expressed as median and interquartile ranges or counts and percentages. [Results] Among 120 patients without diagnosed cancer in cryptogenic stroke etiology, there were 12 patients with occult cancer and 108 patients without cancer. Compared with cryptogenic stroke patients without cancer, patients with occult cancer had lower body mass index（18.6 [16.9-20.7] vs 22.5 [20.3-25.3] kg/m^2, $p < 0.001$）and albumin（3.3 [2.8-3.6] vs 4.0 [3.7-4.2] g/dl, $p < 0.001$）, higher plasma D-dimer levels（5.89 [0.77-11.41] vs 0.49 [0.30-0.94] μg/ml, $p < 0.001$）and C-reactive protein（0.45 [0.19-5.28] vs 0.15 [0.04-0.39] mg/dl, $p = 0.006$）, and more multiple vascular lesion patterns（77% vs 16%, $p < 0.001$）. Five patients with occult cancer presented with metastases at diagnosis. [Conclusion] Cryptogenic stroke with occult cancer have lower nutritional status, higher plasma D-dimer levels, and more multiple vascular lesion patterns. Patients with cryptogenic stroke having such characteristics need a detailed examination for occult cancer.

O-13-1

tPA静注療法のStroke codeが急性期脳血管障害診療にもたらす有効性と安全性

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【目的】tPA静注療法における来院から治療開始までの時間（Door-to-Needle: DTN時間）短縮を目指したStroke codeが，急性期脳血管障害診療に与える影響を検討した．【方法】2013年8月から看護師が積極的に関わる脳血管障害救急診療体制を構築し，Stroke code（NGK 48）を使って診療を開始した．pre-NGK 48 period（2010年8月から2012年7月）とNGK 48 period（2013年8月から2015年7月）に入院した発症24時間以内の脳梗塞，脳出血患者を登録した．tPA静注療法施行患者のDTN時間を比較した．tPA静注療法施行患者，全脳梗塞，脳出血患者で，背景や神経症状，画像所見，予後などを2群間で比較した．【結果】脳梗塞1119人（tPA静注療法施行患者158人），脳出血413人が登録された．Stroke codeの前後でtPA静注療法のDTN時間は56分から48分に短縮した（p=0.002）．pre-NGK 48 periodとNGK 48 periodを比較して，3か月後のmodified Rankin scale（mRS）0, 1（自立）は差がなかった（39% vs. 44%，p=0.551）．来院時虚血巣体積は差がなかったが（6 vs. 3ml, p=0.423），7日後虚血巣体積はNGK群で小さかった（26 vs. 7ml, p=0.016）．脳実質出血type 2の発生率は差がなかった（4 vs. 1%，p=0.341）．脳梗塞全体では，3か月後自立の差は両群間でなかったが（47 vs. 42%，p=0.142），脳実質出血type 2が減っていた（3.0 vs. 0.8%，p=0.025）．脳出血患者の退院時自立は両群間で差はなかったが（13 vs. 13%，p=0.986），退院時Barthel indexは改善していた（20 vs. 40, p=0.035）．【結論】救急外来で診療を急ぐことは，急性期脳血管障害患者の予後に悪影響を及ぼさない．

O-13-2

心原性脳塞栓症二次予防における発作性と慢性心房細動患者の臨床転帰比較

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【目的】現在のガイドラインでは心原性脳塞栓症二次予防の診療方針に非弁膜症性心房細動（NVAF）が発作性心房細動（PAF）であるか慢性心房細動（CAF）であるかは影響しない．本研究の目的は，脳梗塞もしくはTIA既往がありほとんどが抗凝固療法でフォローアップされているPAF患者とCAF患者で臨床転帰を比較することである．【方法】現在フォローアップ期間中の前向き多施設共同観察研究であるSAMURAI-NVAF研究に登録されたNVAFを有する急性期脳梗塞/TIA1192例をPAF群とCAF群に分けて，脳梗塞/TIA発症直後からのイベント発生率を比較検討した．【結 果】フォローアップ期間の中央値は1.8年（0.9-2.0）であった．PAF群は434例（女性191, 77.3±10.0歳），CAF群は758例（336, 77.9±9.9）であった．各々220例（50.7%）と442例（58.3%）がワルファリン，各々199例（45.9%）と276例（36.4%）が非ビタミンK阻害経口抗凝固薬（NOAC）による抗凝固療法を受けていた（p=0.004）．フォローアップ期間中に，100人年当たり全虚血イベントは各々5.63と8.99（性，年齢，登録 時の初期NIHSS，$CHADS_2$スコア，CCr，NOACで補正したHR 0.66；95% CI 0.44-0.97；p=0.032），全出血性イベントは各々3.12と3.36（補正HR 0.95，95% CI 0.55-1.71，p=0.946）であった．脳梗塞もしくはTIAは各々3.62と7.77（補正HR 0.47，95% CI 0.29-0.74，p=0.001），頭蓋内出血は各々1.23と1.46（補正HR0.91，95% CI 0.34-2.20，p=0.841），死亡は各々9.65と14.72（補正HR0.85，95% CI 0.62-1.16，p=0.313）であった．【結論】脳梗塞やTIAの既往がある患者では，PAFを有する患者に比べてCAFを有する患者で全虚血イベント，および脳梗塞もしくはTIAが多かった．PAFからCAFへの進展を防止することが脳梗塞二次予防に有益かもしれない．

O-13-3

取り下げ演題

O-13-4

アルガトロバン併用抗血小板薬2剤併用療法の安全性に関する研究

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【目的】主幹動脈高度狭窄によるアテローム血栓性梗塞（ATBI）や穿通枝領域のbranch atheromatous disease型梗塞（BAD）は急性期増悪・再発のリスクが高く，抗血小板薬2剤併用療法やさらに抗凝固薬の併用など，より積極的な抗血栓療法が行われている．当科では，このようなハイリスク例に対して，アルガトロバン，クロピドグレル，シロスタゾール，スタチンを併用した治療（MACS: multiple antiplatelet therapy combined with statin）を行っており，本研究ではその安全性について検討した．【方法】2011年10月から2015年9月までに入院した急性期虚血性脳卒中連続1456例から，入院治療開始時にMACSを行った症例を選出した．クロピドグレルとシロスタゾールの併用期間は症例毎に担当医が判断した．退院時または入院30日目までの出血性合併症，および抗血栓療法の変更を要する副作用について調査した．【結果】373例（平均72.4歳，男262例）にMACSが行われた．クロピドグレルとシロスタゾールの併用は，319例（86%）で7日以上，195例（52%）で14日以上継続された．出血性合併症は8例（0.02%）で，消化管出血による死亡が1例，輸血を要する消化管出血と皮下出血が各1例，4例に軽微な出血（肉眼的血尿の持続，紫斑，鼻出血，皮下出血）を認めた．症候性頭蓋内出血は認めなかった．抗血栓療法の変更を要する副作用は47例（12.6%）に認め，脈拍数増加（発作性心房細動を含む）が38例（10.2%）で最も多く，次いで頭痛が7例（うち1例は脈拍数増加を合併），狭心症2例，白血球減少1例であった．【結論】BADを含むハイリスクATBIに対するアルガトロバン併用抗血小板薬2剤併用療法では，症候性頭蓋内出血や重篤な出血性合併症は極めて稀である．

O-13-5

脳梗塞患者の回復期退院時の脳卒中地域連携パスにおけるバリアンスの検討

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【目的】我々の脳卒中地域連携パスでは急性期病院から転院した回復期病院で死亡した場合，および回復期病院から治療のために急性期病院に再転院した場合をバリアンスとしている．このバリアンスが発生した症例（バリアンス群）の急性期病院での初回退院時アウトカムを回復期病院から自宅・居宅系施設へ退院あるいは療養型病床群・老人保健施設・有床クリニックへ転院した症例（非バリアンス群）と比較してその特徴を知ること．【対象】熊本脳卒中地域連携パス登録症例で回復期病院に入院との記録がある脳梗塞症例4146例のうちバリアンス群416例および非バリアンス群3569例．【方法】特定できるバリアンスの発生原因のうち脳卒中再発，感染症，心疾患の頻度を算出．2群間で性別，年齢，急性期病院在院日数を比較した．【結果】バリアンスの発生原因のうち，脳卒中再発76例（18.3%），感染症63例（15.1%），心疾患55例（13.2%）で約半数（46.6%）を占めた．バリアンス群は男性54.5%，平均年齢78.9歳，急性期在院日数平均21.06日であった．非バリアンス群は男性55.8%，平均年齢75.22歳，急性期在院日数平均17.05日であった．2群間で性差はなかったが，バリアンス群で有意に年齢が高く，急性期在院期間が長かった（p<0.01）．【結論】高齢で急性期病院在院期間が長い脳梗塞患者に回復期病院退院時のバリアンスが発生しやすい．とくに脳卒中再発，心疾患，感染症に注意が必要である．

O-14-1

Neuronal intranuclear inclusion disease（NIID）の臨床症候

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【目的】孤発性および家族性Neuronal intranuclear inclusion disease（NIID）59例の臨床症候を検討する．NIIDは，H&E染色でエオジン好性に染色され，抗ユビキチン抗体を用いた免疫染色で陽性を示す核内封入体が，中枢神経系，末梢神経系の細胞，および一般臓器の細胞の核内に認められ，様々な程度で神経細胞が脱落することを特徴とする神経変性疾患である．近年，皮膚生検がNIIDの生前診断に有効であると報告されて以降，成人発症のNIID診断例が増加しておりその症候について検討した．【方法】NIIDが疑われた患者に対して皮膚生検を行った．同意が得られた症例についてはFMR1遺伝子のrepeat延長がないことを確認した．皮膚生検組織については抗ユビキチン抗体を用いた免疫染色を行った．また剖検によりNIIDと診断された症例についても検討した．【結果】孤発性NIIDのほとんどの症例で認知機能障害を認めた．体幹失調，膀胱機能障害，異常行動，痙攣発作が認められた．また，稀な症候としてはパーキンソニズム，脳炎様発作が認められた．各種検査では，髄液タンパク質の上昇，頭部MRIでの白質脳症，脳室拡大およびDWIでの皮髄境界の高信号を認めた．また，神経伝導速度検査異常も高頻度に認められた．家族性NIIDに関しては，孤発性NIIDとほぼ同じ臨床症候を示す認知症を初発症状とする群と，四肢筋力低下から発症する群の大きく2群に分けることができた．【考察】孤発性NIID症例においては，高次脳機能障害に加え，膀胱機能障害などの自律神経障害，NCV異常所見などが高頻度であった．家族性NIIDのうち，四肢筋力低下を呈する家系においても，高次脳機能検査での低下あるいは剖検脳での大脳白質の粗鬆化を認めた．【結論】頭部MRIでの白質脳症およびDWIでの皮髄境界の高信号を認める症例，家族性ニューロパチーを呈し，高次脳機能検査異常を示す症例についてはNIIDを考慮し皮膚生検を検討すべきと考える．

O-14-2

本邦における特発性基底核石灰化症（IBGC）の臨床的・遺伝学的検討（第2報）

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【目的】2014年の本学会にて，我々は本邦における特発性基底核石灰化症（idiopathic basal ganglia calcification（IBGC））のリン酸トランスポーターPiT-2をcodeする*SLC20A2*遺伝子変異につき報告した．その後さらに*PDGFRB*，*PDGFB*が原因遺伝子として報告されており，本邦におけるIBGCの臨床的，遺伝学的特徴について検討を行った．【方法】倫理委員会の承認を得て，全国の神経内科医，老年精神科医，小児科医へ臨床情報・検体提供を依頼した．提供のあったIBGC105症例（家族例16家系，孤発例70例）の遺伝子につき，*SLC20A2*，*PDGFB*，*PDGFRB*の変異について検索，さらに臨床的検討を行った．【結果】*SLC20A2*においては6つの遺伝子変異（家族例の5家系，孤発例の2例）を認め，家族例では31.3%の頻度であった．*PDGFB*では4つの新規変異，*PDGFRB*においては1つの新規変異を認めた．*PDGFB*変異は家族例の2家系，孤発例の2例で認められ，家族例の12.5%で変異がみられた．*SLC20A2*変異例，*PDGFB*変異例では脳内石灰化を確認した．両遺伝子が石灰化出現に強く関連すると考えられるが，症状，神経学的所見，頭部CT所見は，変異遺伝子群間での明らかな違いは見られなかった．一方，*PDFGRB*変異は家族例の1家系で認められたが，同一家系内で石灰化を有する例で同変異が認められない症例が存在するなど，原因遺伝子変異とは断定できなかった．【結論】本邦の家族性IBGCにおいて，*SLC20A2*，*PDGFB*は頻度の高い原因遺伝子である．臨床症候には多様性がみられた．

O-14-3

アルツハイマー病コホートにおける硬膜穿刺後頭痛の頻度と発症に関わる因子の検討

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【目的】硬膜穿刺による脳脊髄液採取は，神経内科の診療において欠くことのできない手技である．近年のバイオマーカー研究により，アルツハイマー病(AD)患者では認知症を発症する10年以上前から脳脊髄液中のAβ_{1-42}が低下していることが明らかとなり，今後は認知機能正常者を含め，メモリークリニックにおける脳脊髄液検査の重要性が増すと考えられる．硬膜穿刺に際し注意を要する合併症として硬膜穿刺後頭痛(post-dural puncture headache, PDPH)がある．ADコホートにおけるPDPHの発生頻度，および発生に影響を及ぼす因子を明らかにすることを目的とした．【方法】Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI)コホート179例（認知機能正常群54例，軽度認知機能障害群70例，AD認知症群55例）において施行された計322回の硬膜穿刺におけるPDPHを含む有害事象の発生を症例記録により確認した．さらに，メモリークリニックにおけるPDPHに関する既報を文献的にレビューし，発症に関わる因子として，年齢，認知機能，頭痛の既往，穿刺時の体位，穿刺針の形状，穿刺針の直径，脳脊髄液採取量，および穿刺後の安静を検討した．【結果】J-ADNIコホートにおいてPDPHは，認知機能正常群1例，軽度認知機能障害群4例，AD認知症群3例の計8例で発症した．発症頻度は2.5%(8/322)であった．このうち2例は入院加療を要した．既報のメモリークリニックにおけるPDPHの頻度は0.9-20.3%と報告により様々であったが，年齢が高齢になるに従い発生頻度が低下する傾向を認めた．また，cutting針とatraumatic針で発生頻度を比較した報告すべてで，atraumatic針の使用がPDPHの発症を有意に減らした．【結論】メモリークリニックにおける硬膜穿刺は，診断を目的に高齢者を対象とする場合は比較的安全に行える一方，観察研究等を目的に比較的若年者を対象とする場合は，PDPH予防としてatraumatic針の使用を考慮すべきである．

O-14-4

認知症患者における24時間自由行動下血圧と脳血管性病変との関連

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【目的】認知症患者における24時間自由行動下血圧と脳血管病変の関連を明らかにする．【方法】対象は当科を受診した認知機能低下を有する患者のうち，大脳皮質梗塞を有する患者を除外した41例（女性19例，76±7歳）である．血圧測定は，随時血圧に加えて，24時間自由行動下血圧測定（ABPM）を行った．画像診断において，頭部CTまたはMRIにて大脳白質病変（脳室周囲高信号域グレードⅢまたはⅣ，深部皮質下白質病変グレード3または4）および皮質下梗塞を有する例を脳血管障害（CVD）型，^{99m}Tc-HMPAO-SPECTにて側頭・頭頂葉および後部帯状回の血流低下を有する例をアルツハイマー病（AD）型とした．CVD型のみの患者をVaD群，AD型のみの患者をAD群，両者を伴う患者をAD+CVD群と定義した．各群における血圧測定値および夜間降圧度を検討した．【結果】AD群は9例，AD+CVD群は29例，VaD群は3例であった．AD群，AD+CVD群，VaD群の順に，随時収縮期血圧（SBP）値は134±17，141±27，145±33mmHgであった．ABPMでは，SBPの24時間平均値は137±12，139±20，147±4mmHg，昼間平均値は142±11，142±20，148±5mmHg，夜間平均値は122±19，132±24，140±2mmHgであり，夜間降圧度は14±12，7±9，5±4%であった．夜間降圧度が10%未満のNon-Dipper型はAD群がAD+CVDとVaDを併せた群と比較して少ない傾向がみられた(33対67%，P=0.082)．【結論】高血圧と血管性認知症の関連は知られているが，ADにおいても大脳白質病変や皮質下梗塞を有する例は夜間高血圧が関連する可能性が示唆された．認知症患者で特にこれらの画像所見がみられた場合には，随時血圧のみならず夜間血圧を評価することが重要である．

O-14-5

一般中高年者における軽度認知障害と糖・インスリン代謝の解析

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【目的】近年，糖尿病(DM)はアルツハイマー病(AD)発症の重要な促進因子と考えられているが，軽度認知障害(MCI)に対する糖・インスリン代謝の影響は明らかではない．一般の中高年者におけるMCIと末梢の糖・インスリン代謝との関連を検討した．【方法】当院のドック受診者で認知症の治療歴のない1,877名(男性 743名，女性 1,134名，平均年齢 65.4±9.5歳)を対象とした．認知機能はタッチパネルテスト(日本光電社製)，MCI Screen(ミレニア社製)で評価した．末梢の糖・インスリン代謝の指標として，空腹時血糖(FBS)，HbA1c(NGSP値)，空腹時インスリン値(IRI)，末梢インスリン抵抗性(HOMA-IR＝IRI×FBS÷405)，インスリン分泌能(HOMA-β＝IRI×360÷[FBS-63])を評価した．【結果】タッチパネルテスト(15点満点・cut-off 12点)での認知機能低下は131名(7.0%)に，MCI Screenで評価されたMCIは257名(19.4%)に認め，いずれも健常群と比し有意に高齢であった(p<0.0001)．またMCI群では健常群よりDM治療者が多かった(MCI群 9.3%，健常群 5.0%，p<0.0092)．DM治療歴のない1,777名で解析すると，タッチパネルテストのスコア低下は，FBS(p=0.0169)，HbA1c(p=0.0065)，HOMA-IR(p=0.0230)の上昇と有意な相関を認めた．MCI群は健常群に比し，FBS(p=0.0128)，HbA1c(p=0.0198)が有意に高値であった．さらに年齢で3群に層別化すると，若年群(62歳以下，n=619)ではHOMA-IRの上昇がタッチパネルテストのスコア低下と相関を示した(p=0.0089)が，中間群(63～70歳，n=624)及び高齢群(71歳以上，n=534)では有意な関連を認めなかった．【結論】一般の中高年者においても末梢の糖・インスリン代謝異常がMCIを促進し，特に比較的若年層において影響が大きい可能性が示唆された．さらに詳細な解析を進めている．

O-15-1

筋萎縮性側索硬化症の呼吸機能評価における横隔膜超音波検査の有用性

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【目的】筋萎縮性側索硬化症（ALS）の呼吸筋評価にはスパイロメトリーによる評価が一般的であるが，顔面筋力低下や認知症のある患者には正確に評価することが困難であった．ALSの呼吸筋力の客観的な評価のため，横隔膜超音波検査の有用性を検討する．【方法】当院通院中のALS患者26例（Spinal onset 20例，Bulbar onset 6例）を対象とした．横隔膜超音波検査は12MHzのリニアプローブを使用し，臥位にて前腋窩線正中部の第7-8，8-9肋間の高さで安静呼気時の横隔膜の厚み（Diaphragm thickness）を測定した．横隔神経伝導検査は，胸鎖乳突筋後縁で最大上電気刺激を行い，剣状突起から5cm上に陰極（G1），G1から肋骨縁に沿って16cmに陽極（G2）をおいて，横隔膜CMAP振幅 を陰性，陽性頂点間で測定した．また，呼吸機能検査にてFVC，FEV1%も測定した．【結果】ALS患者は平均年齢61.0±12.7歳，発症から25.6±8.0ヵ月で，Diaphragm thicknessはFVC（r = 0.64，p<0.001），横隔膜CMAP振幅（r = 0.67，p<0.001）といずれも相関した．また，Spinal onsetとBulbar onsetとの比較では，Diaphragm thicknessとFVC，横隔膜CMAP振幅の相関係数はいずれもSpinal onsetで高かった．26例中3例に動脈血液ガス分析にてCO_2の貯留（$PaCO_2$≥45）を認め，いずれもDiaphragm thicknessは0.9mm以下であった．【結論】ALS患者において，Diaphragm thicknessはFVC，横隔膜CMAP振幅と相関した．横隔膜超音波検査は非侵襲的で患者の協力を必要としないため，ベッドサイドで簡便に施行することが可能で，ALSの呼吸機能を把握する上で有用である．

O-15-2

筋萎縮性側索硬化症患者における舌エコー，舌圧測定，嚥下造影検査での嚥下障害の検討

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【目的】筋萎縮性側索硬化症(ALS)患者の嚥下評価における簡便かつ非侵襲的な方法として舌エコー，舌圧測定の有用性を検討する．【方法】書面同意いただいたALS患者のうち舌エコー，舌圧測定，嚥下造影(VF)を施行した18名(年齢62.5±9.9歳，女性9名)について検討した．舌エコーはフランクフルト平面に90度で両側下顎第2小臼歯遠位を通る前額面で描出し顎舌骨筋下端から舌背面表層の距離を測定しTongue thicknessとした(Nakamori et al; Clin Neurophysiology, 2015)．また線維束性収縮の評価も行った．舌圧測定はJMS舌圧測定器を用いて3回測定し最大値を舌圧値とした．VFでは時相解析を行い，Tongue thickness・舌圧値との関連性を検討した．【結果】Tongue thickness平均 41.9±4.0mm，舌圧値平均19.5±9.8kPaであった．Tongue thickness・舌圧値の低下はともに口腔準備通過時間の延長と有意な関連性がみられた．一方，咽頭相はTongue thickness低下，舌圧値低下症例でも比較的良く保たれていた．Tongue thicknessと舌圧値には相関を認めなかった．ALSFRS-R bulbar subscoreがfull score(12点)の群とnon-full score(11点以下)の群に分けると，Wilcoxonの順位和検定にて舌圧値に有意な差がみられた．Tongue thicknessはBMIとの有意な相関が認められた．またTongue thicknessは3か月ごとの評価で有意な低下を認めた．線維束性収縮はエコーで8例(44.4%)に認めた．【結論】ALSの嚥下障害は舌の筋力低下による咽頭への送り込み不良が大きな要因と考えられた．VF時相解析とTongue thickness・舌圧値に相関を認めたことより舌エコー，舌圧測定が嚥下評価に有用である可能性が示唆された．また，舌エコーは線維束性収縮の検出，舌圧は嚥下障害の早期検出の一助になりうると考えられた．ALS患者ではTongue thicknessとBMIが相関していることから，良好な栄養状態を保持することが嚥下状態の維持に重要である可能性が示唆された．

O-15-3

Electromyographic findings of progressive muscular atrophy: Comparison with ALS

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Background: Progressive muscular atrophy (PMA) is characterized by lower motor neuron syndrome, and does not meet the current diagnostic criteria of ALS due to lacking upper motor neuron signs. However, a recent large-cohort study showed that PMA should be considered a form of ALS. There has been no sufficient consideration about the difference of EMG findings between PMA and ALS. **Objectives:** To elucidate whether EMG findings of PMA are different from or same as those of ALS. **Methods:** We enrolled 53 consecutive patients who underwent needle EMG for a diagnosis of motor neuron disease in our hospital. The patients included 11 PMA patients and 42 patients with clinically definite, clinically probable, and clinically probable-laboratory supported ALS by the revised El Escorial criteria. We examined clinical features (sex, age of onset, disease duration, ALSFRS-R scores, forced vital capacity) and spontaneous EMG discharges (active denervation potentials (Fib-PSW), and fasciculation potentials (FP)) of five muscles (upper trapezius, biceps brachii, first dorsal interosseous, vastus medialis, and tibialis anterior muscles) to find any differences between PMA and ALS. For FPs, we performed a quantitative analysis for their morphology. **Results:** There were no significant differences in the clinical features and in EMG findings both for the occurrence of Fib-PSWs and the morphology of FPs between PMA and ALS patients. **Conclusion:** PMA might share a common pathophysiology to ALS regarding not only the clinical disease courses but also the EMG findings.

O-15-4

ALSの進行予測におけるカプノグラフィー（経皮的炭酸ガス連続測定装置）の有用性

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【目的】カプノグラフィー（経皮的炭酸ガス分圧(tcPCO2)測定装置）を利用してALS患者の睡眠時連続記録を行い，高CO2血症がALSの進行に及ぼす影響を調べた．【方法】ALS診断初期（発症2年以内），％FVC＞80の患者18例を対象とし，睡眠時連続記録を行った．カプノグラフィーは，Sentec 社製(SDMS)を使用した．本システムでは，経皮二酸化炭素分圧(tcPCO2)，酸素飽和度(SPO2)，脈拍(PR)の連続記録が可能である．tcPCO2＞50mmHg又はtcPCO2がベースラインから10mmHg以上上昇した症例を睡眠中の高CO2血症群と定義し，それ以外を正常群と分類した．この2つの群で，経時的にALSFRS-Rスコアを記録し，約3ヶ月毎のADL低下率（⊿ALSFRS-R/月）を比較した．【結果】tcPCO2平均値は，覚醒時，睡眠時で有意な差を示した(P＞0.001)．カプノグラフィー計測時の高CO2血症群は6例，正常群12例であり，両群間でFVC，罹病期間，ALSFRS-Rスコアに有意差は無かった．計測後3か月および6か月までのADL低下率を，高CO2血症群，正常群で比較したところ，両期間とも高CO2群で有意に進行が速かった(P＜0.05)．また，ADL低下率は，睡眠時呼吸障害項目（tcPCO2＞50mmHg，tcPCO2がベースラインから10mmHg以上上昇，SPO2＜90　5分以上）中，tcPCO2＞50mmHgと最も強い相関を示した．【結論】カプノグラフィーの終夜記録で，病初期から夜間高CO2血症を認める一群は，ALSFRS-Rの下位項目中，呼吸だけではなく項目全般において進行が速かった．カプノグラフィーで検出される夜間のみの高CO2血症は，日中に行う検査ではとらえられない呼吸筋の脆弱性を示し，ALSの進行を予測するマーカーになりうると考えられる．

O-15-5

Edaravone, a free radical scavenger, attenuates wobbler mouse motoneuron disease

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Objective: Edaravone has approved therapeutic medication of amyotrophic lateral sclerosis (ALS) in Japan. This antioxidant has benefits in mutant *superoxide dismutase 1 (SOD1)*-transgenic mice or rats. We studied whether edaravone treatment retards progression of motor dysfunction and pathological changes in wobbler mice.**Methods:** After symptomatic diagnosis of the disease onset at the age of 3-4 weeks, each wobbler mouse was assigned confidentially in numerical order into one group of two doses edaravone (1 mg/kg and 10 mg/kg) and vehicle groups. For the randomized control study, we arbitrarily determined to analyze 10 animals per group. Edaravone or vehicle was administered intraperitoneally, daily for 4 weeks. Forelimb motor deficits and body weight were evaluated weekly. After the final treatment, pathological findings were analyzed in the biceps muscle and the cervical cord. These symptomatic and neuropathological data were compared among three groups.**Results:** The weight gain did not differ among three groups. Higher dose of edaravone administration significantly attenuated muscle weakness and contracture compared to vehicle. Pathological studies also showed significant inhibition of muscle denervation atrophy, astrocyte proliferation and motor neuron degeneration compared to vehicle.**Conclusions:** The present study indicated therapeutic effects of edaravone in wobbler mice, in addition to Japanese patients and another ALS-like model of mutant *SOD1*-transgenic mice or rats. This medication could be worth performing the clinical trial for ALS patients in the USA and Europe.

O-16-1

Clinical and Genetic and histopathological features of CMT1X in 16 Chinese patients

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X-linked Charcot-Marie-Tooth disease (CMTX) is one of the commonest forms of inherited neuropathy caused by mutations in the GJB1 gene. The disease is rarely reported in China. Here we describe the clinical, pathological, and genetic features in a series of Chinese patients with GJB1 mutation.**Methods**: Sixteen patients collected from 85 genetic confirmed CMT cases were studied. They predominantly showed distal muscle weakness of low limbs with mild sensory disturbance between infantile to 42 years old. The mean onset age was 14 years old. Three cases were associated with sudden onset of cerebral symptoms including aphasia, dysphagia, quadriplegia or paralysis of low limbs. One with hand trembles, and one with constant nystagmus and ataxia. Sural nerve biopsies were performed in 16 probands. GJB1 gene was analyzed in 16 probands, 10 affected family members, 13 unaffected family members and 100 healthy women control subjects.**Results**: Sural nerve biopsies showed moderate to severe loss of myelinated fibers, with axonal regeneration, thin myelin fibers and onion bulbs. There were 16 different heterozygous mutations, including 8 novel mutations: A379T, A533G, C590T, G115T, T380A, C263A, 403_404insT, 818_819insGGGCT. There were no hot mutations nor hot localizations in Chinese patients.**Conclusions** The CNS impairment is more frequently in Chinese CMT1X patients. Sural nerve indicated severe neuropathy with both axonal and myelin lesions. There are no hot mutations nor hot localizations. The genetic findings further enlarge the variation of gene mutations of GJB1.

O-16-2

Localization of Beclin 1 in human main cerebral and carotid arteries

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[Objective]It has been reported that autophagy associate with atherosclerosis. The increase of autophagosome was seen in macrophages in atherosclerotic lesions. Becrin 1 is an essential autophagic protein. Beclin-1-interacting complex promote the formation of autophagosome. We examined the localization of Beclin 1 in human main cerebral and carotid arteries for preventing atherosclerosis and ischemic stroke. [Methods]Specimens of carotid arteries were obtained from 14 patients undergoing carotid endarterectomy. Specimens of main cerebral arteries with atherosclerotic changes were obtained from 8 autopsied human patients. We performed hematoxylin-eosin, elastica-Van Gieson and Masson trichrome staining. Immunohistochemical examination was performed by ABC method. Beclin 1 primary antibody was used. In immunofluorolabeling we incubated deparaffinized sections with a mixture of anti-Beclin 1, and either anti-human alpha-smooth muscle actin or anti-human CD68 (macrophage marker) antibodies. The fluorolabeled sections were observed under a fluorescence microscope equipped with a laser confocal system.[Results] In the main cerebral and carotid artery lesions, Beclin 1-like IR was intense in form cells. In immunofluorolabeling, Beclin 1 was colocalized both macrophages and infiltrating vascular smooth muscle cells in those atherosclerotic lesions.[Conclusions] We demonstrated the localization of Beclin 1 in human main cerebral and carotid atherosclerotic lesions. This might be contributed to the prevention of stroke.

O-16-3

Chronological change is the main cause of histopathological diversity in neuromyelitis optica

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Background: Neuromyelitis optica (NMO) have been considered as primary astrocytopathy. However, we revealed the diversity of NMO pathology which includes a pattern of demyelination predominance. It was unclear whether the variations derived from pathological or chronological differences. Objective: To clarify the influence of chronological change in NMO spectrum disorders with anti-aquaporin4 antibody (AQP4+NMOSD). Material and method: We analyzed seven autopsied materials from AQP4+NMOSD patients (Three patients in acute phase and four in chronic phase). Comparative analysis and statistical tests were performed between lesions from clinically acute phase (LCA) and chronic phase (LCC) evaluated by immunohistochemistry. Result: Sero-status were confirmed prenatally in all cases. Mean disease durations were 0.3±0.3 in acute and 15.8±5.1 in chronic phase (years). AQP4 loss lesions were seen nearly whole lesions in LCA but less common in LCC (LCA 91.2%±9.5% vs LCC 30.5%±25.5%, P<0.05). Astrocyte-lacked lesions were major pathology in LCA (LCA 82.7%±24.0% vs LCC 7.4%±13.4%) and gliosis in LCC (LCA 6.7%±11.5% vs LCC 60.8%±24.8%). Primary demyelinating lesions were rare in LCA (LCA 3.9%±6.7% vs LCC 50.0%±35.5%, P<0.05). Character of deposited complement were distinct between LCA and LCC (C9; LCA 100% vs LCC 0%, C3d; LCA 33% vs LCC 75%). Conclusion: Pathological findings from AQP4+NMOSD were similar in each phase[II] but distinct between acute and chronic phase. We concluded chronological change might be the main cause of histopathological diversity in AQP4+NMOSD.

O-16-4

Isoform-shift from 4R to 3R Tau Is Shared in Brainstem Neurofibrillary Pathology

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[Objective]Gradual shift of tau profile from 4 repeat (R) to 3R is fundamental to Alzheimer pathogenesis, as demonstrated around hippocampus. Is this fundamental shift shared with neurofibrillary changes in the brain stem? [Methods]Midbrain and pons sections from 23 brains (Braak's neurofibrillary tangle (NFT) stage I/II: 8 cases, III/IV: 8 cases and V/VI: 7 cases) were double immunofluorolabeled using 4R tau and RD3 (3R tau) antibodies. The entire sections were scanned on virtual slides and extended focused images were acquired (resolution 0.65 μm/ pixel at 10x magnification, size total approx.140 cm^2 x 5 μm) for 4R and 3R tau separately. Colocalization was also analysed. Each lesion was sorted by size (neuropil thread < 200 mm^2 < NFT), classified according to its staining profile (3+, 3/4+, 4+) and counted (total number of NFTs: 4948 at midbrain and 2911 at pons, NTs: 602839 at midbrain and 244924 at pons). [Results]3R lesions (3+ & 3/4+) exhibited predominance over 4+ lesions in both levels. Fraction of 4+ NFT and NTs were more frequent in the substantia nigra (lateral part) than the central part (periaqueductal gray and ventral tegmental area). At the midbrain, the 4 + fraction progressively decreased along progression of the NFT stages. [Conclusions]Size quantification and profile discrimination of large number of tau positive lesions were successful by thorough scanning of double stained sections for 3R and 4R tau. This powerful technique demonstrated that gradual shift of tau profile from 4R to 3R is extended to brainstem lesions as a fundamental to AD pathogenesis.

O-17-1

long-term prognosis of newly diagnosed epilepsy in a Egypt ,A retrospective cohort study

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Background: Although Epilepsy is one of the most common neurological conditions, Limited data are available on the clinical patterns of treatment response in newly diagnosed epilepsy.***Objective***: To identify the different clinical pattern of outcome of epilepsy in the newly diagnosed patients and the strong predictors of failure to achieve 2 years seizure remission.***Methodology***: In this retrospective study we collected the data of **239** patients from all ages with newly diagnosed epilepsy between the year 1994 and 2008 that were diagnosed by single senior epileptologist and followed up for at least four years at specialized epilepsy center in Egypt.***Results:*** A total of 239 patients with newly diagnosed epilepsy were included. Early remission was achieved in（**73.6**%）while（**12.1**%）entered late remission. Thirty four patients（**14.2**%）failed to achieve 2 years seizure remission. Twenty six patients（**10.9**%）have drug resistant epilepsy.Terminal remission uninterrupted by relapse was noted（**25.1**%）indicating a remitting course of epilepsy. Out of（85.5%）patients who achieved a two years remission, the events of relapse occurred in（**60.7**%）, indicating a remitting-relapsing course of epilepsy.***Conclusion:*** The prognosis of the majority of patients with newly diagnosed epilepsy is good and the clinical pattern of epilepsy during treatment is complex and dynamic.

O-17-2

Relationship between cortex and pulvinar abnormalities on DWI in status epilepticus

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[Objective] The aim of this study was to analyze the pattern of magnetic resonance diffusion-weighted imaging（DWI）findings in status epilepticus in terms of clinical characteristics. [Patients and Methods] Participants comprised 106 patients with status epilepticus who were admitted to our hospital and underwent DWI. [Results] Forty-five patients（42.5%）showed abnormal findings on DWI and were divided into 2 groups, comprising 26 patients（24.5%）with cortex lesions alone and 19 patients（17.9%）with cortex and pulvinar lesions in the same hemisphere. A long duration of status epilepticus（＞ 120 min）tended to be more prevalent among patients with cortex and pulvinar lesions（57.9%）than among patients with cortex lesions alone（30.8%）by univariate and multivariate analyses. Todd's palsy tended to be more frequent in patients with abnormalities on DWI（24/45, 53.3%）than in patients with normal DWI（21/61, 34.4%）. Six of the 26 patients with cortex lesions alone（23.1%）had taken anti-epileptic drugs before the attack compared to none of the 19 patients with both cortex and pulvinar lesions. [Discussion] The trend toward a longer duration of status epilepticus in patients with both cortex and pulvinar lesions favors a spreading pattern of seizure discharge from cortex to pulvinar via cortico-pulvinar pathways, and anti-epileptic drugs might, to some extent, prevent spreading of seizure discharge from cortex to pulvinar. In addition, existence of high-intensity areas on DWI at the onset of epilepsy may be a predictive factor for the occurrence of Todd's palsy.

O-17-3

NLRP1 inflammasome is activated in patients with medial temporal lobe epilepsy

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AbstractBackground:Recent studies have shown that the activation of NLRP1 can generate a functional caspase-1-containing inflammasome in vivo to drive the proinflammatory programmed cell death termed 'pyroptosis', which has a key role in the pathogenesis of neurological disorders. There are no reported studies that performed detailed identification and validation of NLRP1 inflammasome during the epileptogenic process.Methods: We first compared expression of NLRP1 and caspase-1 in resected hippocampus from patients with intractable mesial temporal lobe epilepsy（mTLE）with that of matched control samples. We employed a nonviral strategy to knock down the expression of NLRP1 and caspase-1 in the amygdala kindling-induced rat model. Proinflammatory cytokines levels and hippocampal neuronal loss were evaluated after 6 weeks of treatment in these NLRP1 or caspase-1 deficiency TLE rats.Results: Western blotting detected upregulated NLRP1 levels and active caspase-1 in mTLE patients, suggesting a role for this inflammasome in mTLE. Moreover, we employed direct in vivo infusion of nonviral small interfering RNA to knockdown NLRP1 or caspase-1 in the amygdala kindling-induced ratmodel, and discovered that these NLRP1 or caspase-1 silencing rats resulted in significantly reduced neuronal pyroptosis.Conclusions: Our data suggest that NLRP1/caspase-1 signaling participates in the seizure-induced degenerative process in humans and in the animal model of TLE and points to the silencing of NLRP1 inflammasome as a promising strategy for TLE therapy.

O-17-4

Wide-band Electrocorticographic（ECoG）data analysis in primary sensorimotor（SI-MI）area

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[Background] It is clinically important to identify SI-MI for epilepsy surgery. SI-MI shows characteristic electroencephalographic slow activities preceding voluntary movement, Movement-Related Cortical Potential（MRCP）, and unique pattern of HFA around the onset of voluntary movements. However, the precise comparison between MRCP and HFA originating from SI-MI remains very limited. [Objective] To elucidate the correlation between MRCP and HFA by ECoG data in SI-MI. [Methods] ECoG recorded from subdural electrodes implanted on the peri-rolandic area were analyzed in the patients who underwent epilepsy surgery. Motor tasks of the limbs were performed contralateral to the electrodes implanted in a self-paced manner every 8-10 seconds. ECoG and electromyography（EMG）were recorded with the sampling rate of 1000 or 2000 Hz. MRCP and HFA were analyzed by MATLAB software. We investigated 1）the concordance among MRCP, HFA and cortical stimulation mapping（CSM）to identify SI-MI, 2）correlation between MRCP and HFA of the SI-MI on motor tasks. [Results] In 4 patients, mean age of 43.5 years, a total of 14 kinds of motor tasks were analyzed. MI identified by MRCPs, HFAs and CSM were observed in 14, 14 and 10 out of 14 tasks. SI were observed in 10, 10 and 9 out of 14 tasks. Negative slope components in MRCPs and increased HFAs appeared respectively 0.53 and 0.47 seconds before the onset of EMG.[Conclusion] Comparing the occurrence behaviors and onset time among the 3 methodologies, it showed 1）high concordance rate, 2）HFAs may occur at latter part of pre-movement MRCP components.

O-17-5

Withdrawn

O-18-1

withdrawn

O-18-2

Clinical and immunological analysis of multiple sclerosis with a deletion type copy-number variation

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【背景】日本人多発性硬化症(MS)と視神経脊髄炎(NMO)の大規模コホートのゲノムワイドコピー数多型(CNV)関連解析から，T細胞受容体(TCR)遺伝子領域の欠失型CNVが，MSとNMOの疾患感受性を大きく高めることを報告した．NMOではTCR α 鎖領域の欠失型CNVを有する患者では，抗aquaporin-4抗体陽性率と抗体価が有意に低かった．しかし，当該欠失型CNVのMSにおける臨床的，免疫学的な意義は不明である．【目的】 日本人MSでTCR α 及び δ 鎖領域の欠失型CNVが，臨床像とT細胞サブセットに与える影響を明らかにする．【方法】TCRa及び/または δ 鎖領域の欠失型CNVを有する66名，有さない155名のMS患者で臨床像を比較した．寛解期MSで，当該CNVを有する8名と有さない24名の末梢血単核細胞の表面マーカー解析によりナイーブ($CD45RO^+CCR7^+$)，エフェクターメモリー(Tem, $CD45RO^+CCR7^-$)，セントラルメモリー($CD45RO^+CCR7^+$)，CD45陽性エフェクター($CD45RA^+CCR7^-$)，制御性T細胞($CD25^{high}CD127^{low}$)に分類した．また細胞内サイトカイン染色によりIL-17, IFN-産生CD4 T細胞とCD8 T細胞の割合を検討した．【結果】当該欠失型CNVを有するMS患者は，有意にprogression indexが高値だった(P=0.0453)．TCR α 鎖領域の欠失型CNVを有するMS患者は，有さないMS患者に比しエフェクターメモリーCD8 T細胞の割合が有意に低値だった(P=0.05)．さらに，TCR α 及び/または δ 鎖領域の欠失型CNVを有するMS患者は，有さない MS患者に比べてIFN-γ^+IL-17^+CD8 T細胞の割合が有意に高かった(P=0.0278)．【結論】TCRa及び/または γ 鎖領域の欠失型CNVを有するMS患者では，有さない患者より障害の進行が速く，特にTCR α 鎖の欠失型CNVを有する患者では，エフェクターメモリーCD8 T細胞の分化が障害され，病原性CD8 T細胞が増加していることが示唆された．

O-18-3

Sema4A as a biomarker for personalized therapy of multiple sclerosis

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【Backgrounds】 Although interferon-beta (IFN-β) is the first-line therapy for relapsing-remitting multiple sclerosis (RRMS), one-third of patients do not respond to IFN-β therapy. While other disease-modifying drugs (DMDs) such as fingolimod, natalizumab, and BG12 became available recently, there are no biomarkers for selection of suitable therapy. We previously reported that immune semaphorin Sema4A is increased in the sera of MS patients and those with high Sema4A do not respond to IFN-β therapy. We also reported Sema4A inhibited the therapeutic effect of IFN-β in experimental autoimmune encephalomyelitis (EAE). However, it remains to be elucidated whether other DMDs are effective for patients with high Sema4A or not. **【Objective】** The purpose of this study is to ascertain whether fingolimod is effective for patients with high Sema4A. **【Methods】** Fifty-two patients with MS who have been treated with fingolimod were enrolled in the this study. Serum Sema4A levels were assayed by a sandwich ELISA before and after fingolimod treatment. The association between Sema4A and clinical characteristics including the response to fingolimod were analyzed. **【Results】** The serum Sema4A titer was 3072 ± 5719 U/ml before fingolimod treatment and 3447 ± 7758 IU/ml after fingolimod treatment. Fingolimod reduced the relapse rates for patients with both low and high Sema4A. **【Conclusions】** The levels of Sema4A are not changed by fingolimod treatment. It is suggested that fingolimod is effective even for patients with high Sema4A. Sema4A can be a biomarker for the selection of IFN-β and fingolimod.

O-18-4

Systemic allergic inflammation exacerbates neuroinflammation via glial endothelin receptor type B

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[Objective]To elucidate the effect of allergic/atopic inflammation in the non-neural tissues on experimental autoimmune encephalitis (EAE).[Methods]Six weeks-old C57BL/6J mice were used (N = 4-6). Bronchial asthma (BA) model was induced by pre-administration of ovalbumin (OVA) 50 μg and aluminum hydroxide (Alum) 2 mg once per week for 3 weeks, and then OVA solution (2.5 mg/ml) were inhaled for 4 consecutive days. Thereafter, EAE was induced by immunization with MOG_{35-55} peptide emulsified in CFA at a dose of 200 μg per mouse, followed by administration of pertussis toxin (500 ng per mouse) on days 0 and 2, and clinical signs were observed for 40 days. At the onset of EAE, some of these mice were sacrificed, and lung, spinal cord, and spleen were harvested for immunohistochemical analyses. Splenocytes were also collected and subjected for flow cytometry and cell culture. [Result]BA model mice showed significantly earlier onset of EAE (BA vs. control = 12.3 vs. 16.3 days), and more severe signs. In the spinal cord, astroglial activation was more aggressively together with increased inflammatory cell infiltration. These astroglia showed up-regulation of endothelin-1 receptor (EDNRB). BQ788, a selective EDNRB receptor antagonist, successfully ameliorated the exacerbation of EAE in BA group mice.[Conclusions]Systemic allergic inflammation aggravates EAE with remarkable astroglial activation, which is successfully improved by the selective EDNRB antagonist. Astroglial EDNRB plays critical roles in atopy-induced exacerbation of neuro-inflammation.

O-18-5

Gut intraepithelial myelin responsive CD4+T cells suppress CNS autoimmunity via LAG-3

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[Objective] Multiple sclerosis (MS) is an autoimmune disease that targets the myelin of the CNS. Increasing incidence of MS in Japan let us question which components of the immune system are altered by environmental factors. Gut mucosa is by far the largest immune organ that interacts with the external environment. Since T cells are pivotal in controlling CNS inflammation, we investigated the existence of myelin responsive T cells that might be induced in the gut and their influence on CNS autoimmunity. [Methods] Gut-T cells from MOG(35-55) specific T cell receptor transgenic (2D2) mice were analyzed by flow cytometry. Sorted gut-T cells were adoptively transferred to experimental autoimmune encephalomyelitis (EAE) induced by immunization with MOG(35-55). To modulate gut microbiota, mice were orally treated with antibiotics. [Results] Here we demonstrate that the gut epithelium of 2D2 mice is abundantly inhabited by intraepithelial T-lymphocytes (IEL) that can inhibit EAE upon transfer. The regulatory IEL had the phenotype of $CD4^{+/-}$induced IEL ($CD2^+CD5^+$), exhibited T_H17-like profile and had unique ability to infiltrate the inflamed CNS tissue. The IEL constitutively expressed *Ctla4* and *Tgfb1*, and markedly upregulated *Lag3* in the CNS, thereby inhibiting the inflammation. We also demonstrated that the regulatory IEL are induced by gut microbiota. [Conclusions] Gut environment favors the generation of myelin responsive T cells that have regulatory function. Abnormality of the gut microbiota may reduce the induction of such regulatory cells, thus promoting the development of MS.

O-19-1

肩こり様症状から急性に四肢の麻痺を呈した頸椎硬膜外膿瘍の2例

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【目的】脊椎硬膜外膿瘍は稀ではあるが，診断が遅れると神経学的後遺症を残し，また1割の症例は死亡にも至る，重大な疾患である．早期診断と治療に結びつける目的で，最近経験した2例を報告する．【方法】頸椎硬膜外膿瘍2例の臨床経過をまとめ，診断や治療に関して検討した．【結果】[症例1] 60代男性．数日来の後頸部痛で整形外科を受診．ブロック注射で痛みが改善した翌朝に四肢麻痺をきたしており，搬送された．頭部MRIで椎骨動脈乖離が否定された．頸椎MRIで脊髄後方の硬膜外にSOLを認め，緊急手術を行い硬膜外膿瘍と診断した．リスク因子は飲酒のみであった．術後神経症状は中等度改善しリハビリ施設へ転院したが，半年の時点で両上肢に軽度の筋力低下と失調性歩行が残存．[症例2] 60代男性．肝細胞癌を治療中．前日からの肩こり様症状で整形外科を受診．左肩にブロック注射を受け，抗菌薬を処方された．その後数日間で左上肢の軽度の筋力低下と左上下肢の感覚障害が出現，増悪した．ペインクリニックで頸椎MRIを撮像され硬膜外膿瘍と診断され，翌日に紹介受診．来院時排尿障害も認めたが入院を拒否し帰宅．翌日歩行障害も出現し，緊急手術を行った．軽度の感覚障害を残し自宅退院した．血腫との鑑別には発症様式や，血液検査での炎症所見，造影MRIが有用であった．【結論】脊椎硬膜外膿瘍における神経症状は急性に出現し，診断時1/3の症例で既に神経症状を伴っていとされる．今回の2例は頸部痛で受診した整形外科やペインクリニックからの紹介であるが，いずれも神経症状をきたした後に紹介されている．後遺症を残さないためには神経症状出現前すなわち頸部や腰背部痛のみの時点で積極的に診断し，かつ手術介入をする事が推奨されている．脊柱に沿って広範囲に病変を認めると手術適応とならないため，全脊椎の評価が必要である．本疾患の予後改善には，頸部，腰背部痛に関わる全診療科との連携が重要である．

O-19-2

結核性髄膜炎における髄液中TNF-α測定の有用性

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【背景】結核性髄膜炎では初期治療が適切であっても，約10%の症例で臨床的に一時的な増悪がみられ，Paradoxical Reaction(PR)と呼ばれる．その機序としては炎症の改善による抗結核薬の髄液移行性が低下することや肺結核でみられる初期増悪と類似の病態が考えられているが，PRのバイオマーカーは存在しない．【目的】結核性髄膜炎に対するPRのバイオマーカーとして髄液中TNF-α の有用性について検証する．【方法】当院で経験した結核性髄膜炎3例における髄液中TNF-α の治療経過における変動を検証した．【結果】症例1は68歳男性．発症時の髄液中TNF-α :142pg/mlと高値であり抗結核薬4剤と副腎皮質ステロイド薬を併用することで症状は軽快し，髄液中TNF-α :10.0pg/mlと低下を認めた．PRもなく治療経過が良好な症例では髄液中TNF-α 値は低下傾向を示すことが示唆された．症例2は24歳男性．抗結核薬を導入するまで細菌性髄膜炎疑いとして抗結核薬以外の抗生物質と副腎皮質ステロイド薬を9日間投与され，結核腫の増大による水頭症から意識障害の悪化を来した．9日間の経過で髄液中TNF-α は260pg/mlから44.5pg/mlと低下を認めた．結核菌が増殖したことにより症状が悪化した場合には髄液中TNF-α 値は上昇しないことが示唆された．症例3は16歳女性．発症時の髄液中TNF-α ：52.5pg/mlで抗結核薬4剤と副腎皮質ステロイド薬を使用することで症状も軽快し，髄液中TNF-α ：14.1pg/mlまで低下した．しかし発症約4ヵ月目でPRと考えられる結核腫の増悪を認めた際には39.5pg/mlまで上昇を認めた．PRが生じた際には髄液中TNF-α 値が上昇することが示された．【結論】結核性髄膜炎において，髄液中TNF-α 値はPR発症の指標となりうる．

O-19-3

本邦発症の進行性多巣性白質脳症患者に対する塩酸メフロキン治療の有効性に関する検討

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【目的】本邦発症の進行性多巣性白質脳症（PML）について疫学調査し，塩酸メフロキン治療の有効性を臨床的に検証する．【方法】2010年6月以降の本邦発症のPMLについて髄液JCVPCR検査依頼時およびPML情報センターへの相談時の症例情報に基づいて匿名化して集計し，後ろ向きに調査した．【結果】本邦発症のPML症例86例と，さらに塩酸メフロキン治療症例26例の臨床情報が収集された．塩酸メフロキン治療症例26例はHIV-PML11例（すべて男性，平均年齢49.9歳），とnon HIV-PML15例（男性8例，女性7例，平均年齢61.9歳）であり，一方塩酸メフロキン非投与症例は14例確認され，HIV-PML6例（男性5例，女性1例，平均年齢36.5歳）とnon HIV-PML8例（男性4例，女性4例，平均年齢73.1歳）であった．塩酸メフロキン治療は連続3日間塩酸メフロキン275mg内服後第8投与日より塩酸メフロキン275mgを1週間ごとに内服し，6か月間継続した．塩酸メフロキン治療をした26症例のうちnon HIV-PML1例で肝障害のため塩酸メフロキン投与中止となった．HIV-PML11例でART療法を施行し，このうち3例でIRISを合併してステロイド併用療法を施行した．HIV-PMLでは臨床症状の改善を5症例で示し，臨床症状の進行停止が2症例，髄液中JCV低下が1例であり，3症例で無効（2例死亡）であった．一方non HIV-PMLでは　膠原病・自己免疫疾患が8例，リンパ腫など悪性腫瘍・血液疾患が5例，基礎疾患なしが2例であり，うち6例で臨床症状の改善，1例で臨床症状の進行停止，1例で緩徐進行となった．無効が6例で，うち4例が死亡であった．【結論】塩酸メフロキン非投与PML症例と比較解析が重要であるものの，塩酸メフロキン治療にて有効性を示すPML症例が多数含まれており，本検証にてPMLに対する塩酸メフロキン治療の有効性を示す可能性が示唆された．

O-19-4

異常型プリオン蛋白試験管内増幅法によるプリオン病患者の生体材料の定量系の確立

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（目的）現在まで異常プリオン蛋白の検出法はウェスタンブロット法やプリオン感染モデルマウスを利用した方法であった．2011年我々は異常型プリオンタンパク試験管内増幅法（RT-QUIC法）を開発し，微量の異常プリオン蛋白を検出することに成功した．このRT-QUIC法による異常プリオン蛋白の検出法は定性的あり，定量的ではなかった．今回我々はプリオン病患者の生体材料（脳・髄液・各臓器）を利用し，RT-QUIC法を定量的に評価する方法を検討した．（方法）1）プリオン病患者の10症例脳組織にて段階的に希釈してその希釈した脳組織をRT-QUIC法にて解析した．解析にはSpearman-Kärber法を利用し，SD50にて10症例の脳組織の異常プリオン蛋白を評価した．又同サンプルをdot blot法にて異常プリオン蛋白を評価し，SD50とdot blot法による異常プリオン蛋白の相関関係をみた．2）プリオン病患者20症例の髄液についてSpearman-Kärber法を利用してSD50を検討した．3）プリオン病患者4症例の各臓器についてSpearman-Kärber法を利用してSD50を検討した．（結果）1）プリオン病患者の10症例脳組織は$10^{8.79\text{-}10.63}$/gであり，dot blot法にて異常プリオン蛋白は0.6-5.4 μg/gであり，RT-QUIC法によるSD50とdot blot法による異常プリオン蛋白の相関関係は$R^2 = 0.7192$であった．2）プリオン病患者20症例の髄液中の$10^{3.0\text{-}4.3}$/mlはあった．3）プリオン病患者4症例の各臓器のSD50では脾臓では検出できない症例もあったが，log SD50で5.5-6.0，腎臓ではlog SD50で5.5-6.75，肝臓では検出できない症例が2例であった．肺ではlog SD50で5.25－6.0 であった．（消化管については施行していない）（考察）我々はプリオン病患者の生体材料に対する，RT-QUIC法による定量法を確立した．

O-19-5

医療行為でプリオン病と同時にAlzheimer型病理変化が伝播する可能性についての検討

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[目的]硬膜移植でAlzheimer型病理変化が伝播する可能性を検討する．[方法]硬膜移植後Creutzfeldt-Jakob病（CJD）（16例）および孤発性CJD（21例）の剖検脳をアミロイドβ蛋白（Aβ），リン酸化タウ，リン酸化α-シヌクレイン，リン酸化TDP-43に対する抗体を用いて免疫染色を行った．硬膜移植後CJD群と孤発性CJD群の脳Aβ沈着面積率，Aβの軟膜下沈着の程度，脳アミロイドアンギオパチー（CAA）の程度を比較した．それぞれの評価は，症例の背景を隠した状態で行った．リン酸化タウの蓄積については，Braak AT8 stageで評価を行った．[結果]検討した症例の死亡時年齢は，硬膜移植後CJD63.1±14.1歳（35-81歳），孤発性CJD63.4±10.8歳（35-80歳）で，統計学的に有意な差を認めなかった．硬膜移植後CJD群と孤発性CJD群の比較では，脳Aβ沈着面積率は有意差を認めなかったが，髄膜CAAや軟膜下沈着の程度は硬膜移植後CJD群で有意に高かった．Aβ沈着率，CAA score，軟膜下沈着scoreは，死亡時年齢，CJD罹病期間には有意な相関を認めなかったが，硬膜移植から死亡までの潜伏期間は，髄膜CAAの程度と軟膜下沈着の程度と有意な正の相関を認めた．リン酸化タウ，リン酸化α-シヌクレイン，リン酸化TDP-43の沈着は，硬膜移植後CJDおよび孤発性CJDの間で差を認めなかった．[結論]硬膜移植で脳Bアミロイドーシスが促進される可能性がある．その機序として，脳Aアミロイドーシスの個体間伝播，手術侵襲の影響，異常プリオン蛋白暴露の影響，の可能性が考えられた．

O-20-1

Analysis of GCH1 in Japanese patients with Parkinson's disease

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[Objective] *GCH1* encodes GTP cyclohydrorase I, it is the biosynthesis enzyme of tetrahydrobiopterin which is the essential cofactor for the activity of tyrosine hydroxylase. Mutations in *GCH1* are the most common cause of DOPA-response-dystonia (DRD). Recently, *GCH1* muattions were identified in Parkinson's disease (PD) patients with family history of DRD, suggesting that rare *GCH1* variants are associated with an increased risk for PD. To evaluate the features of *GCH1*-associated parkinsonism, we screened mutations of *GCH1* in PD patients.[Methods]We sequenced all protein cording exons and exon/intron boundaries of *GCH1* by Sanger method and analyzed copy number variation by Multiple ligation-dependent probe amplification (MLPA) method in 156 patients with dystonia-parkinsonism.[Results]We detected three heterozygous splice site mutations (c.344-5T＞A, c.509+2_3insT, c.626+2T＞G) in 3 sporadic PD patients and one heterozygous nonsense mutation (p.R216X) in one autosomal dominant PD patient. These mutations were not listed in ExAC Browser (http://exac.broadinstitute.org/). All mutation positive patients had no family history of DRD. One of them developed at 52 years old, but the others developed under 20 years old and progressed very slowly. A good response to levodopa was seen in all patients. [Conclusions]Our data suggest that abnormal GTP cyclohydrorase I resulting from *GCH1* mutations involves in pathogenic mechanism both of PD and DRD. Whether there is family history of DRD or not, *GCH1* genetic testing should be considered in patients with dystonia-parkinsonism.

O-20-2

A new type of double-stranded structure improved potency of antisense oligonucleotide for FAP

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Objective: Development of antisense oligonucleotide (ASO) therapy for Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) has been progressing. The effective delivery to target organs and toxicity of ASO remained challenging. We developed a new type of structure for therapeutic oligonucleotides with gapmer type ASOs: Hetero-Chimera-Duplex-Oligonucleotide (HCDO). It has a double stranded structure: DNA strand and the complementary RNA strand integrated into parent ASO. These studies revealed the potency and adverse effect of HCDO compared to the original single-stranded ASO. ***Materials and Methods***: We administered intravenously HCDOs or the original ASOs targeting several types of mRNA into wild type mice and those targeting hTTR mRNA into V30M TTR transgenic mice. We collected liver and blood sample and estimated the gene silencing effect and adverse effect by qRT-PCR and Western blot. We also evaluated the delivery-effect to liver using qRT-PCR and fluorescence detection. ***Results***: HCDOs demonstrated approximately eight-fold higher potency of silencing mRNA compared to the original ASO in sequence-specific and dose-dependent manner. HCDO showed more potent in protein level than the original ASO and no toxicity in TTR transgenic mice. The efficiency of delivery to liver by HCDO was about two-fold higher and could contribute its higher potency. ***Conclusion***: Our novel concept of HCDO is useful for the development of therapies for TTR-FAP.

O-20-3

Taurine for prevention of stroke-like episodes of MELAS: a first-ever tRNA modification disorder

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In 1966, Francis Crick predicted that the first anticodon ("wobble") nucleotide recognizes the third codon nucleotide through non-canonical Watson-Crick geometry. We discovered taurine modification at the wobble nucleotide is deficient in the mutant mitochondrial (mt) $tRNA^{Leu(UUR)}$ in MELAS patients harboring the A3243G-mutant mt DNA. Because the taurine modification defect in the mutant mt $tRNA^{Leu(UUR)}$ causes a deficiency in deciphering codons, we regard MELAS as a first-ever tRNA-modification disorder. Indeed, high-dose taurine supplementation ameliorates impaired mt dysfunction in patient-derived cells and prevents stroke-like episodes in two MELAS patients for more than nine years. Here we performed a multi-center, open, phase III investigator trial to approve the efficiencies of taurine on preventing stroke-like episodes in patients with MELAS. We enrolled 10 patients suffering from repeated stroke-like episodes in the trial. One-year oral taurine administration completely prevents stroke-like episodes in 6 patients and significantly decreased annual relapsing rates in the other 4 patients. During the trial, taurine modification ratio in the mt $tRNA^{Leu(UUR)}$ derived from white blood cells in peripheral blood were significantly increased in 5 patients. These findings provide a new insight into our understanding that supplementation with oral taurine prevents stroke-like episodes by reversing impaired taurine modification in mt $tRNA^{Leu(UUR)}$. Long-term administration study is on-going with biomarker analyses.

O-20-4

The 2nd clinical study of AADC Gene Therapy for Parkinson Disease

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Objective: We have developed gene therapy for Parkinson's disease using an adeno-associated virus (AAV) vector to deliver the aromatic L-amino acid decarboxylase (AADC) gene into the putamen. In our previous study, we demonstrated that motor symptoms were ameliorated along with increased dopaminergic activity on PET after gene therapy. For the second clinical study, a new batch of AAV-AADC vectors was produced. A specific infusion cannula was also developed.**Method:** GMP grade vectors were generated at the Center for Gene and Cell Processing of Takara Bio. To examine if the loss of vectors might occur in the infusion cannula, both genomic and biological titers of the vectors were determined on the flow through aliquots of the cannula after the surgery. Thus far, two patients have received AAV-AADC vectors infusion via stereotaxic surgery. A total dose of 3×10^{11} vector genomes was administered into the putamen bilaterally.**Results:** The titers of the vectors in the flow through of the cannula were not reduced even after the 5 hours of surgery, suggesting the stability of the AAV-AADC vectors and little absorption of the vectors in the cannula. One month after gene therapy, one patient showed less off state with an improvement of motor functions. The other patient died while taking a bath, however, the death was judged to be unrelated to gene therapy.**Conclusion:** A phase I/II clinical study on gene therapy for Parkinson's disease is currently underway using newly produced AAV-AADC vectors. Clinical benefits are anticipated along with the efficient delivery of the vectors.

O-20-5

A novel platform technology to regulate the blood-brain barrier in vivo

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Background: The blood-brain barrier (BBB) is a pathologic site in many neurological diseases such as multiple sclerosis, brain ischemia, and neurodegenerative disorders. Gene silencing in the brain microvascular endothelial cells (BMECs), the central component of the BBB, can be a new strategy of molecular targeted therapy for these diseases.**Methods:** We designed antisense oligonucleotides (ASOs) to target mouse *organic anion transporter 3 (OAT3)* which is exclusively expressed at BMECs in brain, and screened effective sequences by transfection studies *in vitro* (n=4). Next, we prepared *OAT3*-targeting heteroduplex oligonucleotide composed of each ASO and its α-tocopherol conjugated complementary RNA (Toc-HDO). We intravenously injected Toc-HDO to C57BL/6 mice and examined its distribution, silencing effect, and side effect (n=3).**Results:** We selected highly effective three sequences *in vitro*. Immunohistochemical studies after the injection of fluorescence-labelled Toc-HDO revealed that it was extensively distributed into the BMECs. Quantitative reverse transcriptase-PCR performed three days after the Toc-HDO injection showed the silencing of *OAT3* mRNA by 90% at the maximum in a dose-dependent manner. Moreover, we found a safe sequence of *OAT3*-targeting Toc-HDO causing no liver or renal toxicity.**Conclusion:** We have established a proof-of concept of effective and safe gene silencing in BMECs *in vivo* by an intravenous injection of Toc-HDO. Our technology opens a new therapeutic field of regulating the BBB function for treating a variety of intractable neurological diseases.

O-21-1

PR prolongation of electrocardiography in Parkinson's disease

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[Objective] Cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy previously demonstrated an uptake reduction in patients with PD. On the other hand, epidemiologic research showed that electrocardiography (ECG) abnormalities occurred prior to motor signs in PD. Another study reported rate-corrected QT prolongation in PD. Here we investigated whether the electrical conduction system of the heart was impaired in PD and compared the ECG findings with the abnormalities of MIBG scintigraphy. [Methods] Clinical features, ECG, coefficient of variation of R-R intervals and MIBG scintigraphy parameters were analyzed in 191 patients with PD, 42 with multiple system atrophy (MSA) and 124 normal controls (NL). [Results] The PR interval of ECG was significantly longer in patients with PD than in NL. The PR interval was significantly negatively correlated with early and delayed heart-to-mediastinum ratios in MIBG scintigraphy in PD and MSA patients. The coefficient of variation of R-R intervals was significantly positively correlated with early and delayed heart-to-mediastinum ratios but was not correlated with PR interval. [Conclusions] This study is the first to demonstrate the prolongation of the PR interval in PD and its correlation with MIBG scintigraphy parameters. The PR prolongation must show some sympathetic system abnormality since it is mainly controlled by sympathetic nervous system. PR prolongation may be considered a supportive finding in the diagnosis of PD.

O-21-2

The trunk flexion angle affected by vertical position sense in Parkinson's disease

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【目的】PD患者の体幹前屈角度に，患者が垂直位と認識する立位（VRS）の前屈角度が影響するかについて検討する．**【方法】**対象は，当院でリハビリテーション（リハ）を受けたPD患者99名のうち体幹伸展の関節可動域制限がなく，Mini mental State Examinationが24点以上の者とした．姿勢評価は，立位の体幹前屈角度と側屈角度（前屈角度，側屈角度）およびVRSの前屈角度を，運動機能評価は1）Hohen&Yahr（HY）Stage，2）Unified Parkinson's Disease Rating Scale（UPDRS）partⅢ，3）Time up and go test，4）Functional Reach Testを測定した．VRSの前屈角度は，45度の体幹前屈位から他動的に体幹を伸展し，垂直位と判断し検者に報告した角度の3回の平均値とした．前屈角度に影響を与える因子の検討は，上記の評価項目に年齢，罹病期間，VRSの標準偏差を加え，前屈角度を従属変数とした単回帰分析および重回帰分析を行った．**【結果】**選択基準に合致した患者は39名であった（71.9±10.1歳 男性17名 女性22名 HY Stage2.6±0.7）．前屈角度は10.2±14.7度であり，VRSの前屈角度は5.2±10.1度であった．単回帰分析では，VRSの前屈角度が関与する因子として認められた（β=0.74 P<0.001）．一方，HY StageやUPDRS partⅢを含むその他の評価項目は関与する因子でなかった．重回帰分析では，VRSの前屈角度（β=0.70 P<0.001）とVRSの標準偏差（β=0.40 P<0.001）が関与する因子であった．**【結論】**PD患者の前屈角度にはVRSが影響しており，前屈角度が大きい患者ほどVRSのばらつきが大きかった．前屈姿勢の改善にはVRSを改善するリハプログラムが必要である．

O-21-3

Treatment of antecollis increases the blood concentration level of levodopa

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Objective - Antecollis is one of the abnormal postures associated with Parkinson's disease (PD) and related disorders. Excessive neck flexion can affect the drug delivery through the cervix. The purpose of our study is to investigate whether antecollis affects the pharmacokinetics of levodopa in patients with PD and related disorders.Methods - The subjects were 9 patients with PD and related disorders, concomitant with antecollis. We examined the blood concentration level of levodopa before and after the administration until 240 minutes (L-dopa test). We performed the L-dopa test before and after the treatment of antecollis to evaluate its effect on the pharmacokinetics of levodopa.Results - After the treatment of antecollis, the Cmax of levodopa became higher than that before the treatment in 8 patients. Furthermore, in 6 patients, their blood concentrations of levodopa showed two peaks, and the treatment of antecollis changed the biphasic into monophasic pattern, resulting in the increase of the Cmax of levodopa. Interestingly, in a PD patient, the higher Cmax ameliorated the motor symptoms after the treatment of antecollis.Conclusions - Our study indicates that antecollis affects the pharmacokinetics of levodopa, decreasing its concentration. Therefore, the treatment of antecollis would increase the Cmax of levodopa, resulting in the amelioration of the motor symptoms, especially in PD patients.

O-21-4

Features and exacerbating factors of low back pain in Parkinson's disease

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Background: The aim of the present study was to determine the exacerbating factors of chronic low back pain (LBP) in Parkinson's disease (PD).Methods: Forty-four consecutive PD patients who developed LBP were included. The clinical characteristics of PD and LBP, spinal and musculoskeletal conditions, and clinical health status were evaluated.Results: The onset age of PD and LBP were contiguous, and a time period of LBP was mainly described as constant, or time of waking up. Exacerbating factors of LBP included modified Hoehn and Yahr stage, motor complications of PD, such as the wearing-off phenomenon and dyskinesia. Bone quality demonstrated osteopenia due to elevated bone resorption, with vitamins K and D insufficiencies. Spinal alignment demonstrated an increased sagittal vertical axis (120.2 ± 65.4 mm) with decreased lumbar lordosis (-24.0 ± 20.6°) and lumbar range of motion (28.7 ± 10.2°), which were significantly related to the severity of LBP and quality of life assessments.Conclusion: This study demonstrated that exacerbating factors of LBP include stage of motor function and motor complications of PD, stooped posture with decreased lumbar lordosis, and range of lumbar movement. Therefore, treatment of motor symptoms of PD, treatment for osteoporosis, and therapeutic exercise are important for the treatment of chronic LBP in PD.

O-21-5

A Japanese Multicenter Survey Characterizing Pain in Parkinson's Disease

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[Objective] Pain is a frequent, troublesome symptom of Parkinson's disease (PD), which despite its frequency and impact on quality of life is under-recognized and its pathophysiology poorly understood. We characterized pain clinical profiles in PD, including its prevalence, severity and location, to better understand its pathophysiology and improve diagnosis and treatment. [Methods] A multicenter, cross-sectional controlled study was conducted at 19 centers in Japan. Patients with PD, whose score on MMSE was 24 or greater, and control subjects were included. Demographic and clinical data were collected, and pain was assessed using questionnaires, the SF-36v2 bodily pain scale and a body illustration for patients to indicate the location of pain in over 45 anatomical areas. [Results] A total of 386 subjects were enrolled, 324 patients (181 women) with PD and 62 controls (28 women). Gender and mean age did not differ between the two groups. The prevalence of pain in the PD group was 79.7%, significantly higher than in controls (55.2%), as was its severity. There was no correlation between SF-36v2 score and motor scores, such as UPDRS III or Hoehn and Yahr scores. The distribution of pain was similar between groups with the lower back being the most frequent site. The PD group had a higher frequency of pain in the gluteal region. [Conclusions] Pain is a significant clinical problem in the Japanese PD population and we discuss its possible pathophysiology in this group.

O-22-1

The significance of serial D-dimer measurements on Trousseau's syndrome patients

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【目的】悪性腫瘍を成因とする急性期多発性脳塞栓症はTrousseau症候群として知られている．我々は昨年の本学会で本症候群の診断上，D-dimer2.0μg/ml以上が有力なマーカーとなり，抗凝固療法中もD-dimerが上昇する例があることを報告した．今回はD-dimer値を追跡し治療マーカーとしての意義を検討した．【方法】SCUに入院した脳梗塞1283例中，MRI拡散強調画像で急性期多発性脳梗塞を認め，かつ脳動脈主幹部狭窄を有しない145例のうち，悪性腫瘍を伴う34例（M群:男性20例，女性14例，年齢74.4±10.4歳）につき解析した．1）原発巣，2）癌の病期，3）癌の治療，4）D-dimer値．4）については心房細動のみを成因とする50例（Af単独例:男性35例，女性15例，年齢75.7±8.24歳）と比較した．【結果】1）M群34例中，主な原発巣は大腸癌8例，膵癌・肺腺癌5例，胃癌・子宮癌3例．2）M群34例中，stageⅢ以上の進行癌23例．うち脳梗塞発症を契機に検索・診断されたものが13例，発症後90日以内の死亡9例．3）M群34例中，手術14例，化学・放射線療法11例，緩和医療のみ13例．4）脳梗塞発症時のD-dimer（μg/ml）はM群34例 8.15±1.73で，Af単独例50例 1.20±0.14に比し有意に高値（p<0.0001），ROC曲線解析によるcut-off値は2.0（AUC=0.851，感度76.4%，特異度80.0%）．抗凝固療法中の再検を行った例では，M群26例 14.41±3.59，Af単独例24例 0.41±0.08で，cut-off値は1.1（AUC=0.967，感度76.4%，特異度80.0%）．M群26例では12例でD-dimerが上昇し，2.0以下に低下したのは6例のみであった．6例では一時的に低下した後再上昇し，癌の再発・増悪を伴った．【結論】Trousseau症候群の診断においてはD-dimerが発症時2.0μg/ml以上で，抗凝固療法中1.1μg/ml以下に低下しないことが，Af単独例との鑑別上有力な根拠となる．進行癌が多く，癌自体の治療のみならず抗凝固療法にも抵抗性を示すことが多い．治療効果判定や予後予測においてもD-dimer値の追跡が重要である．

O-22-2

Factors associated with leptomeningeal collateral development in Middle Cerebral Artery Occlusion

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【目的】中大脳動脈（MCA）閉塞では脳軟膜動脈を介した側副血行路が拡張し，MRI FLAIR画像のHyperintense Vessel sign（HVs）やMRAで後大脳動脈が長く描出されるPCA Laterality sign（PCALs）が認められる．側副血行路が良好に機能することは急性期再開通療法後の予後良好因子の一つと知られているが，その程度は個人差が大きい．本研究では急性期脳梗塞の側副血行路発達に関連する因子を検討した．【方法】2012年4月から2015年10月に当院へ入院した脳梗塞888例のうち，最終未発症確認時刻から24時間以内にMRIを撮影したM1閉塞の心原性脳塞栓症を対象とし，後方視的に臨床情報，画像情報を収集した．FLAIR画像のM1水平部断面より上方7 sliceのうち，HVsを認めたslice数でHV score（0-7）を定量し，HV score≧6もしくはPCALsのいずれかを認めるものを良好な側副血行路と定義した．対象を側副血行路発達良好群と不良群の2群に分け，調査項目を比較検討した．【結果】対象は45例（良好群30例，不良群15例）．NIHSSは発症時（良好群 vs. 不良群：中央値 [IQR]，18 [11-21] vs. 19 [17-25], p=0.10），1day（12 [4.5-18] vs. 22 [16-27], p=0.0012），7day（8 [3.25-12.75] vs. 19 [10.25-23.75], p=0.0058），良好群が1day, 7dayで有意に低かった．良好群は発症前の抗凝固薬内服率が有意に高く（9 / 30 vs. 0 / 15, p=0.020），患側の頸動脈内膜中膜複合体厚（IMT）が有意に小さかった（0.74±0.12mm vs. 0.84±0.19mm, p=0.028）．良好群は脳卒中既往を有する（7 / 30 vs. 0 / 15, p=0.077），体温が低い（36.1℃ [35.4-36.7] vs. 36.4℃ [36.0-36.9], p=0.070）傾向にあった．【結論】血栓溶解療法の有無に関わらず，側副血行路が良好に機能した症例群では神経学的予後が良好であった．発症前の抗凝固薬内服，IMTのコントロールによって，脳梗塞発症時に側副血行路を良好に機能させ得る可能性が示唆された．

O-22-3

Left atrial diameter and cardiovascular events in stroke patients with NVAF: Fukuoka Stroke Registry

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Purposes: We investigated whether left atrial diameter (LAD) is associated with outcomes in ischemic stroke patients with non-valvular atrial fibrillation (NVAF).Methods: Among 9, 674 patients registered in the Fukuoka Stroke Registry (FSR) between 2007 and 2014, we chose 1, 784 ischemic stroke patients with NVAF where LAD was measured by transthoratic echocardiography. Of these, 1,750 were followed up for the median of 741 days after discharge. The patients were divided into 4 groups according to the quartile of indexed-LAD adjusted by physical size. The outcomes were defined as recurrent ischemic stroke, death, and a composite of recurrent ischemic stroke, intracerebral hemorrhage, and death. The association of the indexed-LAD with these outcomes was analyzed using cox proportional hazard model. We also performed the same analyses for 1,526 patients who received anticoagulation therapy at discharge.Results: After adjustment of age, sex, stroke risk factors, stroke severity, treatment at discharge, the indexed-LAD was significantly associated with recurrent ischemic stroke (hazard ratio (HR): 1.94, P＜0.001, top vs bottom quartile), death (HR: 1.54, P=0.004, top vs bottom quartile), and the composite (HR: 1.53, P=0.001, top vs bottom quartile). The similar results were obtained in the patients with anticoagulation therapy at discharge.Conclusion: LAD may be associated with recurrent ischemic stroke and death in ischemic stroke patients with NVAF.

O-22-4

Upregulation and distribution of sphingosine-1-phosphate receptor 1 in acute ischemic stroke

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[Backgrounds]In the setting of acute ischemic stroke, enhanced collateral circulation via the leptomeningeal arteries lead to decreased infarction volume and better neurological outcome. We have reported that sphingosine-1-phosphate receptor 1 (S1PR1) on the endothelial cell senses shear stress caused by cerebral hypoperfusion and enhances collateral flows. We analyzed S1PR1 expression on acute ischemic model mice to seek the possible treatment of ischemic stroke by S1PR1 modulation.[Methods]C57Bl/6 mice（n = 30）underwent left middle cerebral artery occlusion. Leptomeningeal arteries were labeled with latex perfusion. Ischemic cortex was collected for the quantification of S1PR1 mRNA and immunohistochemical analysis at 6, 24, and 48 hours after the surgery.[Results] Infarction area was observed on the left cortex after the surgery（infarction area 25 ± 4.5%），and leptomeningeal arteries on middle cerebral artery perfusion area dilated in time-dependent manner. S1PR1 mRNA expression was increased peaking at 24 hours（6 hours; 1.15 ± 0.20 times, p = 0.60, 24 hours; 18 ± 7.6 times, p ＜ 0.05, 48 hours; 3.7 ± 1.8 times, p ＜ 0.1）compared to that in sham mice. On immunohistochemical analysis, S1PR1 expression was seen in neurons and endothelial cells of leptomeningeal arteries on ischemic cortex.[Conclusion]In ischemic stroke, S1PR1 upregulation was seen on ischemic cortex, especially in neurons and endothelial cells. We need to explore its effect on collateral growth and neuroprotection, and modulating S1PR1 can be the potential therapeutics for ischemic stroke insults.

O-22-5

Pentraxin 3 supports blood-brain barrier integrity under acute phase of stroke

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Objective: Pentraxin 3 (PTX3) is released upon inflammatory responses in many organs, including brain. However, roles of PTX3 in brain are mostly unknown. Here we asked whether and how PTX3 contributes to blood-brain barrier (BBB) function during acute phase of ischemic stroke.**Methods**: In vivo, white matter stroke was induced in C57/BL6 mice by injection of endothelin-1 (ET-1). At day 3, brains were analyzed to evaluate PTX3 expression. In vitro, rat primary astrocytes and rat brain endothelial RBE.4 cells were cultured separately. Astrocyte conditioned media (ACM) were added to RBE.4 cells to measure endothelial permeability. To confirm this result, mice were administered PTX3 siRNA by intracerebroventricular injection. BBB breakdown was assessed by injection of FITC-dextran.**Results**: During the acute phase of stroke, reactive astrocytes in the peri-infarct area expressed PTX3. Media transfer experiments in cell culture system showed that ACM reduced the in vitro endothelial permeability with increasing the expression levels of tight junction proteins. But after removing PTX3 from ACM, the PTX3-depleted ACM no longer supported the endothelial tightness, suggesting that PTX3 is directly involved in enhancing endothelial barrier function. Importantly, knockdown of PTX3 induced severe leakage of FITC-dextran.**Conclusions**: Astrocytes in the peri-infarct area tend to produce/secrete PTX3 after ischemic stroke, which may support BBB integrity. This response in reactive astrocytes may be a compensatory mechanism, and PTX3 can be an effective therapeutic target for stroke.

O-23-1

Suppression of regulatory T cells by exosomes in multiple sclerosis

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Background: Exosomes are extracellular vesicles which are involved in intercellular communication by delivering a variety of molecules such as miRNAs. **Objective**: To determine a role of exosomes and their contents including miRNAs in multiple sclerosis (MS). **Methods**: Exosomes were collected from plasma of MS patients and healthy controls (HC). Disease-related miRNAs contained in exosomes were determined by microarray analysis and RT-qPCR. The function of exosomes was examined by co-culture with T cells. **Results**: Microarray analysis and RT-qPCR confirmed four miRNAs which were significantly increased in exosomes from MS patients (n=19) compared to those from HC (n=6) (26.3±14.0 vs 11.2±4.6, 122±56.2 vs 55.1±32.8, 38.1±17.4 vs 15.7±7.3, 334±174 vs 138±81.9 [AU], respectively, $p<0.05$). T cell function after co-culture with exosomes from MS patients and HC was examined by intracellular staining of cytokines and transcription factors. There was significantly decreased frequency of $Foxp3^+$ regulatory T cells (Treg cells) in MS-exosome group (15.1±1.2%, n=9) compared to HC-exosome group (16.8±1.1%, n=5) ($p<0.05$). Furthermore, the frequency of Treg cells was inversely correlated with the amount of three miRNAs out of the four miRNAs described above ($p<0.05$). The frequency of inflammatory T cells did not differ between the groups. **Conclusion**: This study indicated that miRNAs in exosomes can be new diagnostic markers. Furthermore, it was shown that exosomes can function as a novel player in the pathogenesis of MS thorough modifying T cell function.

O-23-2

Functional analysis of astroglial Cx30 in experimental autoimmune encephalomyelitis

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Objective: To clarify the roles of astroglial Cx30 in experimental autoimmune encephalomyelitis (EAE). **Methods:** C57BL/6J and Cx30 knockout mice ＞ 12 weeks of age were used in this study (N>3 in each group). EAE was induced by immunization of mice with MOG_{35-55} peptide emulsified in CFA at a dose of 200 μg per mouse, followed by the administration of pertussis toxin (500 ng per mouse) on days 0 and 2. Mice were sacrificed and brain, spinal cord, spleen, and optic nerves were harvested for immunohistochemical analyses at the acute phase and chronic phase of EAE. Mice with EAE were scored as follows: 0, no disease; 1, limp tail; 2, abnormal gait and hind limb weakness (shaking); 2.5, paralysis of one hind limb; 3, paralysis of two hind limb; 3.5, ascending paralysis (able to move around); 4, tetraplegia; and 5, moribund (death). **Results:** EAE was significantly ameliorated in the Cx30 knockout mice rather than the control group at chronic inflammatory phase. Immunohistochemical analyses of the fourth lumbar segment, brain and optic nerves revealed enhanced activation of microglia in the Cx30 knockout mice. **Conclusion:** Lack of astroglial Cx30 induces widespread activation of microglia in the central nervous system, which ameliorates EAE possibly through neuroprotective actions.

O-23-3

Experimental autoimmune encephalomyelitis in mice with induced conditional connexin 43 knock-out

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[Objective]Multiple sclerosis (MS)is an inflammatory demyelinating disease of the central nervous system of unknown cause. We previously reported extensive loss of astrocytic connexin 43 (Cx43)in acute lesions in autopsied cases with MS. We thus aimed to clarify how astrocytic Cx43 loss affects the pathomechanisms of MS.For this purpose we developed GLAST positive cell specific inducible conditionalCx43 knock-out (cKO) mice and induced experimental autoimmune encephalomyelitis (EAE) with myelin oligodendrocyte glycoprotein (MOG).[Methods]We developed C57BL6/J background $Cx43^{F/F}$;GLAST-CreER(T2)$^{KI/+}$ mice,and then administered tamoxifen in corn oil at 8-10 week of age by intraperitoneal injection to induce acute cKO of Cx43 in GLAST positive cells. Ten days after tamoxifen injection, we induced MOG-EAE.We used $Cx43^{F/F}$ mice as controls. We also administered tamoxifen to the controls to check the effect of tamoxifen itself on MOG-EAE by comparing corn oil administration alone. [Results]EAE was significantly milder in $Cx43^{F/F}$;GLAST-CreER(T2)$^{KI/+}$ mice induced after tamoxifen injection from acute phase to chronic phase, as compared with $Cx43^{F/F}$ mice administered Tamoxifen, although Tamoxifen itself lessened EAE severity than orn oil alone.[Conclusion] Acute knock-out of Cx43 in the GLAST positive cells before induction of EAE reduce the disease severity, suggesting that loss of Cx43 before induction of EAE may have beneficial effects.

O-23-4

Stem cells from human exfoliated deciduous teeth-conditioned media (SHED-CM) ameliorate EAE

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[Objectives] The current treatments for multiple sclerosis (MS) by immunomodulators and immunosuppressants have not achieved complete remission yet. Stem cells from human exfoliated deciduous teeth (SHED) are mesenchymal stem cells that have a therapeutic potential for various diseases. SHED-conditioned media (SHED-CM) also exert immunomodulating and regenerative activities. In this study, we investigated the efficacy of SHED-CM in experimental autoimmune encephalomyelitis (EAE) as mouse models of MS. [Methods] MOG_{35-55}-EAE mice received single intravenous injection of 500 μl SHED-CM or DMEM from the tail vein at the disease peak. Mice were assessed daily according to EAE clinical score. Mice were sacrificed for histologic and biochemical assessments at the post-immunized day 16 or 28. As the *ex vivo* study, splenic $CD4^+$ Th cells were cultured in SHED-CM or DMEM for 72 h. Cell proliferation and cytokine production were examined using specific ELISAs. [Results] Single injection of SHED-CM significantly improved EAE, associated with the reduction in the extent of demyelination and inflammatory cell infiltration in the spinal cord. Treatment with SHED-CM reduced the expression levels of such pro-inflammatory cytokines as IL-2, IFN-γ and IL-17 in the spinal cord and splenic $CD4^+$ Th cells. [Conclusions] SHED-CM demonstrated immunomodulating and neuroprotective properties in EAE, suggesting that SHED-CM may be a promising therapeutic strategy for MS.

O-23-5

C-C chemokine receptor4 antagonist Compound 22 ameliorates experimental autoimmune encephalomyelitis

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Objective: C-C chemokines and chemokine receptors (CCRs) play important roles in the immune response. We previously reported the pathogenic role of CCR4 in experimental autoimmune encephalomyelitis (EAE) using the CCR4 knockout mouse (CCR4-KO) models. Recently, a novel small-molecule CCR4 antagonist, Compound 22 has been reported to inhibit CCR4. We examined whether CCR4 antagonism ameliorates EAE using Compound 22. Methods: Female C57BL/6 mice and CCR4-KO were sensitized with myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ to develop EAE. Compound 22 (10mg/kg) or dimethyl sulfoxide (DMSO) as control was injected intraperitoneally weekly, after sensitization or after disease onset. Recall response was evaluated by proliferative responses and cytokine productions. Results: Compound 22 significantly ameliorated the severity of EAE when treated before the neurological onset in wild type mice. Maximal scores in mice treated with Compound 22 and DMSO were 0.8 ± 1.1 and 2.6 ± 1.5, respectively (mean ± standard deviation; $P < 0.05$). Cumulative scores were 10.3 ± 10.6 and 23.0 ± 12.3, respectively ($P < 0.05$). In wild type mice treated after onset or in CCR4-KO, there were no significant differences in disease severity. Th1/Th17-related cytokine concentrations in culture supernatants were significantly reduced in Compound 22-treated mice ($P < 0.05$); IFN-γ (Compound 22 vs. DMSO; 183 ± 138 vs. 893 ± 490 pg/ml), IL-6 (44.9 ± 23.7 vs. 119 ± 30.6 pg/ml), and IL-17a (70.0 ± 33.7 vs. 177 ± 118 pg/ml). Conclusion: CCR4 antagonists might be potential therapeutic agents for multiple sclerosis.

O-24-1

パーキンソン病患者のリハビリテーション効果と前頭葉機能との関係

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【目的】パーキンソン病(PD)では，認知面で前頭葉機能の低下が報告されており，前頭葉機能障害と歩行障害との関係も示唆されている．今回我々は，歩行機能の低下したPD患者に対するリハビリテーション(リハ)効果を調べ，前頭葉機能との関係を検討した．【方法】 対象は歩行速度が50m/min以下のPD患者22例．認知面の評価として，入院時にMini-Mental State Examination(MMSE)，Wisconsin Card Sorting Testの達成カテゴリー数(WCST-CA)，Frontal Assessment Battery(FAB)を測定した．5週間の集中的な入院リハを行い，前後で，運動症状の指標として，50m歩行の歩行率，歩行速度，歩幅，Functional Independence Measure(FIM)，Unified Parkinson's Disease Rating Scale(UPDRS)パートII，パートIIIを，非運動症状の指標としてWCST-CA，Zung's Self Depression Scaleを測定した．リハ効果は歩行速度が20%以上改善した例を改善群，それ以外を非改善群とした．入院中の投薬内容は変更しなかった．【結果】歩行速度の改善群は14例，非改善群は8例で，改善群では歩行速度とともに，歩行率，歩幅，FIM，UPDRSも有意に改善したが，非改善群ではFIM，UPDRSは改善したが，歩行率，歩幅は改善しなかった．非運動症状は両群とも改善しなかった．改善群，非改善群いずれにおいてもMMSEは正常で，改善群27.2，非改善群27.3と有意差を認めなかった($p=0.931$)が，WCST-CAは，改善群で3.6，非改善群で1.9と改善群で有意に高く($p=0.047$)，FABも改善群で13.4，非改善群で10.6と改善群で高い傾向にあった($p=0.076$)．【考察】歩行機能が落ちていても前頭葉機能が保たれている症例では，短期集中的なリハによる歩行機能の改善が期待できる．

O-24-2

アデノシンA2A受容体拮抗薬がパーキンソン病の疲労感・うつに及ぼす影響

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【目的】アデノシンA_2A受容体拮抗薬がパーキンソン病の疲労感・うつに及ぼす影響を検討する．【方法】① 21歳以上 ② MMSE 24点以上 ③ 経口レボドパ製剤を投与中 ④ motor fluctuationを認める を満たす孤発性パーキンソン病患者を対象とした．文書による同意を得た後に，イストラデフィリン20mg朝食後を4週間投与し，その後，40mg朝食後を4週間投与した．投与前，20mg投与から4週間後，4mg投与から4週間後に，On時のUPDRS-part Ⅲ，Parkinson Fatigue Scale（PFS-16），Patient Health Questionnaire（PHQ-9）を評価するとともに，イストラデフィリンによる有害事象を評価した．本研究の実施は徳洲会グループ共同倫理委員会で承認された．【結果】2015年11月30日の時点で14例が登録された（男性9例，女性5例，72.1±5.7歳，罹病期間 93.8±61.5月）．イストラデフィリン20mgの投与によってOn時のUPDRS-part Ⅲが22.6±11.6点から11.1±7.2点に低下した．PFS-16の低下は3例で認められ，うち1例では日中の眠気が消失した．また，PHQ-9の低下も3例で認められ，日中の眠気が1例で消失，1例で軽減した．重篤な有害事象は認められなかった．【結論】イストラデフィリン20mgはパーキンソン病患者のOn時の運動機能を改善する．また，イストラデフィリンは，側坐核殻部のアデノシンA_{2A}受容体に対するアデノシンの作用を拮抗することによって覚醒系を維持する可能性が示されているが，今回の結果から，パーキンソン病における疲労感やうつの一部に日中の眠気が関係し，これらがイストラデフィリンによって改善する可能性が示唆された．

O-24-3

Effectivity of rotigotine patch on motor and cognitive dysfunctions in Parkinson's disease dementia

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Aim: Utility of dopamine agonists (DAs) for patients with Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) has not been elucidated because the previous RCTs of DAs have excluded demented patients. Daytime sleepiness occurs frequently and discourages use of DAs in PDD/DLB. This study aimed to demonstrate effectivity and safety of rotigotine transdermal patch (RTP) on motor and cognitive dysfunctions in these patients.**Methods:** An open-label study. The subjects were patients with PDD/DLB with Parkinsonism who needed improvement in motor dysfunctions. Primary outcomes, cognitive functions by MMSE, MoCA, and ADAS-cog, BPSD by NPI-Q, and daytime sleepiness by Epworth Sleepiness Scale (ESS), were examined before and after RTP treatment.**Results:** The subjects (n=6, age 79±5, H&Y 3.5±1.1; M±SD) were treated with RTP 9-13.5 mg/day for 60±42 days. Motor improvement occurred in 67% of the subjects. Total scores of MMSE (18.8±3.6 at baseline), MoCA (12.0±4.4), ADAS-cog (20.1±8.6), NPI-Q (severity 4.5 ± 4.7, caregiver distress 5.3 ± 6.6) and ESS (8.0 ± 2.5) did not change after RTP. Executive function by MoCA tended to improve after RTP (from 0.5±0.8 to 1.3±0.5, p = 0.06). Scores of the other 5 cognitive domains by MoCA did not change after RTP.**Conclusions:** A new non-ergot dopamine agonist, rotigotine patch, is effective in improving motor symptoms in patients with PDD/DLB without worsening dysfunctions in any cognitive domains, BPSD or daytime sleepiness. Rotigotine patch may improve executive function in PDD/DLB which is related to dopamine deficiency in the brain.

O-24-4

Safety and efficiency of anti-parkinson drugs for DLB/PDD patients

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[Objective] One of the characteristic features of DLB (Dementia with Lewy Body) is high sensitivity to medicine, including not only neuroleptic drugs but also anti-parkinson drugs. Once hallucinations or systematized delusions were induced, it is too difficult to control psychiatric disorders as well as parkinsonism. The aim of this study is to decide the best anti-parkinson drug (s) for the treatment of parkinsonism with DLB and PDD (Parkinson's disease with Dementia) patients. [Methods] 28 patients diagnosed with DLB and 20 diagnosed with PDD were examined. Their histories of prescription medication and those of side effects were obtained retrospectively from medical records. [Results] Among 48 patients, 9 cases were not prescribed any anti-parkison drugs at all. Another 21 cases had some side effects, such as temporary hallucinations, delusions or nausea. Anti-parkison medications causing frequent side effects included trihexyphenidyl (100%), amantazine (67%), istradefylline (63%), selegiline (50%) and dopamine agonists (33%). On the other hand, entacapone (10%), zonisamide (11%) and levodopa with carbidopa or benserazide (13%) seemed to be relatively safer for DLB/PDD patients. As to dopamine agonist, rotigotine (25%) showed lower rate of side effects than pramipexole (45%) and ropinirole (40%). [Conclusions] For the treatment of parkinsonism in cases of DLB/PDD, levodopa/carbidopa or benserazide is the first choice, however, if more anti-parkinson therapy is necessary, the second candidate is zonisamide and/or entacapone from the viewpoint of safety.

O-24-5

Triple Neurotransmitter Replacement Therapy can improve clinical symptoms in PSP patients

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Objective: Recent research has shown that the noradrenergic, dopaminergic, and cholinergic neural pathways are disabled in progressive supranuclear palsy (PSP) patients. Supplementation and restoration of the balance of these 3 pathways might be an effective treatment for patients with PSP. **Methods**:We administered replacement therapy for these 3 neurotransmitters to 9 patients with probable PSP who were newly diagnosed according to the standard criteria under the consent of the patients. All of the patients were within 2 years after the onset of the symptoms. Three patients received daily carbidopa/levodopa, droxidopa, and rivastigmine, and the other 6 galantamine instead of rivastigmine for 6 weeks. The study protocol was approved by the local ethics committees. We monitored clinical symptoms, subjective complaints, daily activities, and caregivers' observations. Patients were assessed with the timed up-and-go test (TUG), Frontal Assessment Battery (FAB), Mini-mental State Examination (MMSE), Hasegawa dementia rating scale-revised (HDS-R) and Functional Independence Measure (FIM). **Results**:Notable improvements in their clinical symptoms and performance were obtained. The mean TUG improved from 20.96sec at study entry to 17.39sec, mean FAB from 9.2 to 12.2, mean MMSE from 24.0 to 25.6, mean HDS-R from 21.7 to 24.1, and mean FIM 95.8 to 106.7 after the treatment without remarkable side-effects. **Conclusions**: Simultaneous supplementation of dopamine and noradrenaline together with acetylcholine is beneficial for the treatment of patients with PSP in early stages.

O-25-1

Early functional network alterations in asymptomatic elders at risk for Alzheimer's disease

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[Introduction] The detailed pathophysiological processes underlying the long-lasting preclinical period of Alzheimer's disease (AD) are not well understood. Therefore, establishment of "downstream" markers that can monitor pathophysiological changes during the preclinical period of AD is important, and our study aimed to explore these markers using magnetoencephalography (MEG). [Methods] Forty-five cognitively normal elderly subjects (mean, 75.2 ± 4.7 years; 20 males) were classified into Aβ-positive (CN+) and Aβ-negative (CN-) groups using Pittsburgh compound B PET. All subjects underwent fluorodeoxyglucose (FDG) PET, structural MRI, and 5 minutes of resting state MEG measurements. Phase-locking values were calculated to analyze functional connectivity (FC) in the default mode network. [Results] In CN+ individuals, local FC in the precuneus was significantly decreased. Conversely, inter-regional FC, including connections between the precuneus and the bilateral inferior parietal lobules, were significantly enhanced especially in the low frequency bands in CN+ individuals. These FC changes were significantly correlated with the cerebral Aβ deposition but not with FDG-PET or MRI volumetry data. Individual assessments demonstrated that most of CN+ individuals did not show any metabolic or anatomical changes. [Conclusion] These results suggest that FC alterations are associated with Aβ deposition and could be detectable using MEG before metabolic and anatomical changes are seen. Thus, MEG is suggested to be useful as one of the earliest downstream markers of AD.

O-25-2

Changes in brain alpha7 nicotinic receptors and amyloid deposition in Alzheimer's disease

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[Objective] To investigate the relation between α7 nicotinic acetylcholine receptor (nAChR) and β-amyloid protein (Aβ) deposition in the Alzheimer's disease (AD) brain by measuring the quantitative levels of α7 nAChR availability and Aβ accumulation in vivo.[Methods] 20 drug-naïve AD patients and 20 healthy elderly adults underwent a series of neuropsychological tests, positron emission tomography with α7 nAChR tracer [^{11}C]MeQAA and Aβ tracer [^{11}C]PIB. The levels of tracer binding ([^{11}C]MeQAA BP_{ND}, [^{11}C]PIB SUVR) were compared with clinical measures for various cognitive functions using regions of interest (ROIs) method and statistical parametric mapping (SPM) analysis.[Results] The SPM analysis showed a significant reduction in [^{11}C]MeQAA BP_{ND} in the cholinergic projection region in AD with a variety of [^{11}C]PIB accumulation. Spearman rank correlation analyses showed positive correlations of [^{11}C]MeQAA BP_{ND} values in the nucleus basalis magnocellularis (NBM) region with scores of frontal assessment battery in AD. There was a significant negative correlation between [^{11}C]PIB SUVR and [^{11}C]MeQAA BP_{ND} in the NBM. The further regression analyses showed that the NBM [^{11}C]PIB SUVR was negatively correlated with the [^{11}C]MeQAA BP_{ND} in the MPF and medial parietal regions, whereas the relation in the same region was small. The SPM finding was compatible with these ROI-based results. [Conclusions] The present negative association between Aβ burden and α7 nAChR availability in the cholinergic system provides in vivo evidence of the mechanism in Aβ-linked cognitive decline in AD.

O-25-3

Diagnostic value of DAT-VIEW and DATQUANT for discriminating DLB from AD

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【目的】DAT-SPECTの画像解析として，DAT view，DATQUANTの相関と診断能の差について検討した．また，DLBの症状とDAT集積低下パターンの関連について検討した．【方法】対象は，DAT-SPECTを施行した177例（コントロール：15例，AD：71例，DLB：91例）．DAT viewにおけるSBRと，DATQUANTにおけるそれぞれのVOI（striatum, caudate, putamen, anterior putamen, posterior putamen）都の相関を求めた．また，ADとDLBの鑑別において，DATQUANTのどの部位が最も診断に適しているかをROC解析にて検討した．DLBにおいて幻視の有無，RBDの有無，parkinsonismの有無でDAT集積低下パターンを検討した．【結果】DAT viewのSBRとDATQUANT各部位は全て有意な相関（p＜0.0001）を認めた（相関係数： striatum: 0.79, caudate: 0.76, putamen:0.79, anterior putamen: 0.80, posterior putamen: 0.74）．DATQUANT各VOIにおけるADとDLBの鑑別においては，striatumで最も鑑別率が高かった（AUC=0.927 p＜0.001，感度87%，特異度95%）．DLBにおいては，RBD，幻視の有無で集積低下パターンに有意差は認めなかった．Parkinsonismの有無に関わらず，ADと比較し，全ての部位で有意な集積低下を認めた．また，DLB-parkinsonism（+）群において，DLB-parkinsonism（-）群と比較し，caudate以外の全ての部位で有意なDAT集積低下を認めた．Parkinsonismと，各部位のDAT集積の相関においては，全ての部位で有意な相関を認めた．【結論】DAT viewにおけるSBRは，認知症診療においては，有用な指標であると考えられた．DLBの症状において，parkinsonismのみがDAT集積低下と有意な相関を認めた．

O-25-4

F-methyl-curcumin-1 (FMeC1) is a potential diagnostic and therapeutic agent for Alzheimer's disease

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Aim: Recent experiments have reported that curcumin can pass through the blood brain barrier and bind to amyloid plaques as well as display anti-oxidant and anti-amyloid properties. The aim of this study is to find curcumin derivatives that have diagnostic and therapeutic potential for Alzheimer's disease (AD).**Methods:** More than 30 of curcumin derivatives were screened by binding ability to senile plaques in human brain sections and in vitro analysis. We selected two candidates, f-methyl-curcumin1 (FMeC1) and FMeC2. For MRI, FMeC1 or FMeC2 (200 mg/kg) was injected into the tail vein of six Tg2576, three APP/PS1 and six control mice. Then, amyloid imaging was employed using a 7.0 T MR scanner. For therapeutic experiments, 36 model mice and 12 wild mice were divided into four groups; control diet, curcumin, FMeC1 or FMeC2 group. Mice were fed with a standard chow diet (AIN-93M) with or without curcumin, FMeC1, or FMeC2 (500 ppm) for 6 months from 9-month-old. Behavioral tests were conducted from 14.5 months of age, and mice were sacrificed at 15 months of age for pathological analyses. All procedures were approved by the Animal Care and Use Committee and Ethical Committee of Shiga University of Medical Science.**Results:** FMeC1 but not FMeC2 successfully detected amyloid plaques in living mice. In the Morris water maze test, only FMeC1 showed a significant improvement on cognitive function compared to control group ($p < 0.05$). In addition, FMeC1 reduced Aβ aggregation and glial cell activity ($p < 0.05$).**Conclusion:** FMeC1 is a potential diagnostic and therapeutic agent for AD.

O-25-5

Disease-Modifying Effect of Solanezumab in Extension Study in Japanese Alzheimer's Disease Patients

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Objective: Disease-modifying (DM) effect is thought to slow the progression of disease by modifying the underlying biological pathology in Alzheimer's disease (AD). Delayed-start analysis is considered to be used to provide evidence of DM effect and global Phase 3 solanezumab clinical trial data for mild AD patients imply the DM effect in the extension period. We applied delayed-start analysis design for Japanese patients. **Methods:** After completion of 2 identical global placebo-controlled randomized studies of 18 months (EXPEDITION 1/2), placebo (PLC) group started and solanezumab-treated (SOL) group continued solanezumab in the extension study (6 months). Delayed-start analysis was conducted using a single MMRM model based on all randomized Japanese mild AD sub-population. Cognitive function was assessed using the ADAS-Cog_{14}. We evaluated non-inferiority of the difference in efficacy at the end of extension period compared with that at the end of placebo-controlled phase. **Results:** Sixty-one Japanese patients with mild AD were randomized to PLC and 65 to SOL groups, and 52 PLC and 53 SOL patients completed 6 months of extension (delayed-start) phase. Significant less cognitive decline in SOL group at the end of placebo-controlled phase (LS mean differences: -2.89, p=0.045) was preserved until the end of 6 month-extension period (LS mean differences: -5.90, p=0.002) with meeting pre-defined non-inferiority criteria. **Conclusions:** The results show the consistency with global delayed-start data and suggest preserved efficacy of solanezumab in Japanese patients with mild AD.

O-26-1

Antibodies to paranodal and juxtaparanodal proteins in CIDP and MMN

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[Objective] IgG4 antibodies against such paranodal proteins as neurofascin-155 (NF-155) and contactin-1 have been reported to be present in sera from a subset of patients with CIDP. Such antibodies-positive-CIDP patients have common features. Here, we investigated the antibodies to several paranodal and juxtaparanodal proteins in CIDP and MMN. [Methods]Using ELISA, we examined IgG antibodies to paranodal and juxtaparanodal proteins (NF-155, contactin-1, contactin-2 and caspar-1) in 112 patients with CIDP, 58 with MMN and 30 normal subjects. Moreover we examined subclasses of the positive-IgG antibodies. [Results]Of the 112 patients with CIDP, ten had antibodies to NF155, two had antibodies to contactin-1, one had antibody to contactin-2 and no patients had antibodies to caspar-1. Patients with MMN and normal subjects did not have antibodies to any of the above antigens. Anti-NF155 antibodies in seven patients and anti-contactin-1 antibody in one patient were of IgG4 subclass, although the subclass of the antibody could not be determined in the remainders. Six of the seven with anti-NF-155 IgG4 antibody and a patient with anti-contactin-1 IgG4 antibody had ataxia. A patient with anti-contactin-1 IgG4 antibody had severe disability. Moreover, we could obtain the clinical information of two patients with anti-NF-155 IgG4 antibody, and they were refractory to IVIg. [Conclusions]Among the paranodal and juxtaparanodal proteins, NF-155 and contactin-1 are the target antigens in a subset of CIDP. By contrast, any of those antigens may not be targets for MMN.

O-26-2

Useful laboratory markers for predicting anti-NF155 antibody status among CIDP patients

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Objectives: To find significant laboratory markers for predicting anti-neurofascin (NF) 155 antibody status among patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).**Methods:** Fifty electrophysiologically definite CIDP patients diagnosed in our department and 6 anti-NF155 antibody-positive CIDP patients from other institutes were enrolled. Pathological findings of sural nerve specimens from three anti-NF155 antibody-positive CIDP patients were evaluated.**Results:** We identified a total of 15 anti-NF155 antibody-positive CIDP patients. The average CSF protein level was 356 mg/dl and all of them were above 100 mg/dl. When the cutoff value of CSF protein level was set at 200 mg/dl, sensitivity and specificity for predicting anti-NF155 antibody positivity were 88.9% and 87.2%, respectively. Nerve conduction studies revealed marked delay of distal latency in all anti-NF155 antibody-positive patients. All of seven cases examined by MRI neurography showed marked nerve root hypertrophy. All of three biopsied sural nerve specimens showed subperineurial edema and occasional presence of paranodal demyelination without vasculitis, infiltration of inflammatory cells, and onion bulb formation.**Conclusions:** Extremely high CSF protein levels (>200 mg/dl) and marked nerve hypertrophy on MRI neurography are positive predictor for anti-NF155 antibodies while less than 100 mg/dl CSF protein level, normal distal latency, and onion bulb formation and infiltration of inflammatory cells in the sural nerve are negative predictor for the antibodies.

O-26-3

Clinicopathological features and the efficacy of immunomodulating therapy in CIDP model mice

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[Objective] To clarify the property as a CIDP model, we observed natural history of CD86/B7-2 knockout non-obese diabetic (NOD) mice by clinicopathological and electrophysiological analysis followed by evaluation for responsiveness of immunomodulating therapeutics. [Methods] The subjects are 20 female CD86/B7-2 knockout NOD mice for natural courses and 23 ones for therapeutic efficacy. The evaluation scales are body weight, cage activities, foot-printing from 10 ages of weeks. The electrophysiological and pathological findings of sciatic nerves were also examined. For the intervention, each mouse (total 12 female CD86/B7-2 knockout NOD mice as an actual drug group) was administered by human immunoglobulin (weekly 2mg/g body weight, i.p.) from 10 ages of the weeks while placebo group (11 mice) was treated by intraperitoneal saline. Both groups were compared clinicopathological differences as above.[Results] CD86/B7-2 knockout NOD mice showed apparent worsening in cage activities and foot-printing around 15 to 20 ages of weeks. Nerve conduction studies suggested demyelination followed by axonal dysfunction. In pathological findings, inflammatory monocytes were remarkably infiltrated around demyelinating nerves. From the intervention analysis, a differences of body weight became significant between actual and placebo group (before administration; placebo 23.6 ± 1.9g vs. immunoglobulin 23.7 ± 1.4g, 5 weeks later; placebo 25.3 ± 1.8g vs. immunoglobulin 26.5 ± 0.8g).[Conclusions] Phenotypes as well as therapeutic efficacy of CD86/B7-2 knockout NOD mice were resembled to human CIDP.

O-26-4

Amyloid formation of C-terminal portion of transthyretin

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Background: C-terminal fragments of transthyretin (TTR) were reportedly found in tissue amyloid deposits in familial amyloid neuropathy (FAP) and senile systemic amyloidosis (SSA). However, pathological roles of the fragments of TTR in FAP and SSA remain to be elucidated.Methods: To examine amyloid formation mechanism of the full-length and fragments of TTR, recombinant full-length TTRs (wild-type and V30M) and TTR fragments (N-terminal and C-terminal portions) were employed in this study. Amyloid formation of those TTRs in test tube and in cell culture was analyzed by Thioflavin T assay and cell-based assay, respectively. In addition, effect of amyloid fibrils on apoptosis was investigated in cell culture.Results: The C-terminal fragment of TTR formed amyloid fibrils in PBS, but not the N-terminal and full-length TTRs. That fragment of TTR also formed amyloid deposits on cultured cells. Amyloid deposits derived from the C-terminal fragment of TTR induced apoptosis in cultured cells.Conclusion: The C-terminal portion of TTR may play an important role on amyloid formation in FAP and SSA.

O-26-5

Construction of a Niemann-Pick Disease Type C modeling system and drug screening using iPS cells

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Aims: Niemann-Pick disease type C (NPC) is a lysosomal storage disease characterized by abnormal accumulation of free cholesterol and glycolipids. We established induced pluripotent stem cell (iPSC) lines from NPC patients. Hepatocyte-like cells (HLCs) and neural progenitors derived from the iPSC lines accumulated cholesterol and displayed impaired autophagy and ATP production.Methods: We developed a new Sendai virus vector (TS12KOS), which has improved efficiency, does not integrate into the cellular DNA, and can be easily eliminated. We studied iPSC lines derived from three patients with Niemann-Pick disease type C.Results: Hepatocyte-like cells (HLCs) and neural progenitors derived from the iPSC lines accumulated cholesterol and displayed impaired autophagy and ATP production. A molecular signature related to lipid metabolism was also impaired in the NPC-iPSC-derived HLCs. We also newly found that 2-hydroxypropyl-γ-cyclodextrin (HPGCD) could reduce the cholesterol accumulation and restore the functional and molecular abnormalities in the NPC patient-derived cells, and do so more effectively than 2-hydroxypropyl-β-cyclodextrin (HPBCD) treatment. In addition, NPC model mice showed an improved liver status and prolonged survival with HPGCDs.Conclusion: These findings indicate that iPSC-derived cells can phenocopy human NPC. iPSC lines derived from patient cells are powerful tools to study cellular models of NPC, and HPGCD is a potential new drug candidate for future treatment of this disease.

口演

5月20日（金）

O-27-1
Withdrawn

O-27-2
MCI screening test is correlated with CSF Ab40/Ab42 and valuable for MCI clinical trial

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【目的】軽度認知障害（MCI）の臨床治験において，血清のMCIスクリーニング検査は効率的に候補者を選別できるかを評価をおこなう【背景】MCIは認知障害が軽度であり，画像変化も軽微であり，十分なバイオマーカーも存在しないために診断が難しい．抗アミロイド療法などにおけるMCIの臨床治験では，厳格な選択・除外基準であったり，症状がMCIであっても髄液所見やPETでアミロイドの蓄積を認めなかったりすることがあり，failure rateが高い．最近本邦で開発されたMCIスクリーニング検査が商業的に利用可能となった（MCBI inc）．このテストは血清のトランスサイレチン，アポリポプロテインA1，補体C3を測定し，MMSEの点数を加味した上で，MCIのリスクをA（低リスク）からD（高リスク）の四段階に分けている（http://mcbi.jp/news/info/2015/pdf/20150626_02.pdf）．現在までMCIスクリーニング検査が治験の患者の選別に有用であるかのデータはない．【方法】99m Tc-ECD SPECTで後方優位の脳血流低下を示し，MCIの治験参加希望があり，同意を得られた連続10名の患者で，MCIスクリーニング検査を施行した．9名から髄液を採取した．【結果】6名の患者がD判定，2名の患者がC判定であった．それら8名全ての患者が髄液でAβ40/Aβ42の上昇を認めた（平均15.6，カットオフ9）．1名の患者がB判定でAβ40/Aβ42の上昇は認めず（6.9），1名のA判定患者は心理テストの点数がよいため治験に参加できず，髄液は採取しなかった．【考察】MCIスクリーニング検査の点数は髄液のAβ40/Aβ42と相関するようであった．脳血流シンチ（SPECT）との組み合わせにより，治験において効率的にMCIの患者選別を行うことができると思われた．

O-27-3
Diagnostic Accuracy of 123I-MIBG Imaging in DLB After Three Years Follow-up: A Multicenter Study

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[目的]　全国多施設共同研究「Lewy小体型認知症(DLB)とAlzheimer病(AD)における心臓交感神経機能評価の診断的意義に関する研究」(DLB診断研究プロジェクト)における登録症例の3年後臨床診断を確認し，MIBG心筋シンチの診断精度を再検討する．[方法]　DLB診断研究プロジェクトにて登録した133例（probable DLB 61例，possible DLB 36例，probable Alzheimer AD 46例）を対象とした．AD dementiaの診断はNINCDS-ADRDA診断基準，DLBの診断はDLB国際ワークショップ診断基準改訂版を用いた．登録3年後に主治医より記載された臨床評価票に基づき，臨床評価委員会にて3年後臨床診断を確定した．登録3年後の臨床診断におけるprobable DLB群，probable AD群の鑑別について，登録時MIBG心筋シンチの初期像H/M比，後期像H/M比を用いてROC曲線を求め，AUC，感度・特異度を算出した．[結果]　死亡や転医により68例が脱落し，評価し得たのは65例（登録時診断：probable DLB 22例，possible DLB 10例，probable AD 33例）だった．3年後の臨床診断はprobable DLB 30例，possible DLB 3例，probable AD 31例，抑うつ1名だった．登録3年後の臨床診断におけるprobable DLB群とprobable AD群の鑑別において，MIBG心筋シンチ初期像H/M比の診断能はAUC 0.91 感度 0.80 特異度 0.94，後期像H/M比はAUC 0.92，感度0.87，特異度 0.87であり，登録時の臨床診断による解析と比較してより良い診断精度を示した．[結論]　早期のDLB診断におけるMIBGの有用性が示唆された．

O-27-4
PiB-PET study focusing on dementia with Lewy bodies and Parkinson's disease withdementia

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【背景】レビー小体病(LD)患者におけるアミロイド集積の有無と臨床・画像的な影響を検討した．【対象と方法】認知症を伴うパーキンソン病(PDD)及びレビー小体型認知症(DLB)患者を対象に，アミロイド集積(PIB-PET)，糖代謝(FDG-PET)，脳血流シンチを測定した．【結果】PDD症例は2例（78歳，83歳）で，認知症発症からPET撮像までの罹病期間は6.5± 0.50年，DLB症例は7例（75±3.46歳），罹病期間は3.72±4.29年であった．PIB陽性のPDD（1例）とPIB陽性のDLB（3例）を併せてPIB陽性LDとし，PIB陰性LD（PDD1例，DLB4例）と比較した．PIB陽性LDのMMSEは17.3±6.76点で，陰性LDの23±4.95点より低い傾向を示した(p=0.184)．認知症発症後の罹病期間は，PIB陽性LDで4.01±1.83年，陰性LDで5.3±4.85年(p=0.483)と，陽性LDでは罹病期間が短いのにMMSEが低値を示した．またPIB-PET陽性LDでは後頭葉の血流・代謝低下に加えて楔前部での低下を認めたが，帯状回後部の血流・代謝は保たれていた．【結論】PIB陽性LDでは，陰性LDよりも認知症状がより速く低下し，陰性LDの血流・代謝低下領域にアルツハイマー型の低下領域が加わることが示され，LDにおける認知機能低下にアミロイド病理が影響する可能性が示唆された．

O-27-5
Vitamin B 12 Supplment may have an effect on cognition: VITATOPs, a randomized controlled study

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ObjectiveEpidemiological studies suggest elevated homocysteine as a risk factor for dementia, however it is unclear whether reducing homocysteine levels with vitamin B and folate supplementation influence cognitive outcomes. We examined the effects B-vitamins on long-term cognitive outcomes in patients with recent cerebrovascular events.MethodsIn this extension of VITATOPS trial, 359 patients with recent stroke or transient ischemic attack and cognitive impairment no dementia (CIND) were randomly assigned to double-blind treatment of daily placebo or B-vitamins and followed up for 1 to 5 years. The primary outcome was cognitive changes measured by serial standardized neuropsychological scales and the data analysed using the generalized estimating equation (GEE) models.ResultsThere was no difference in neuropsychological scales and mental status serial neuropsychological scales and mental status between patients treatment and placebo group. In a sub-group of patients with recent lacunar stroke (n=230), B-vitamins therapy led to a transient improvement of cognitive function in attention (mean change 0.11 versus -0.06 for placebo, p=0.032) at second year of follow up. In hypertensive patients, B-vitamin therapy led to a improvement in attention which was stable (mean change 0.15 versus -0.1 for placebo, p=0.021) .ConclusionsDaily administration of B-vitamins did not modulate cognitive outcomes. However, it might have transient effect in CIND patients with recent lacunar stroke or hypertension, probably due to stabilization of cerebral small vessel disease.

O-27-6
Apomorphine improves memory function and insulin resistance in Alzheimer's disease

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【目的】我々は，パーキンソン病のドパミンアゴニストであるアポモルフィン(APO)がアルツハイマー病(AD)のモデルマウスの記憶障害を改善することを見出した．今回は，AD患者に対してAPO市販薬の注射薬を投与し，認知機能障害に対する有効性を検証する．また，ADマウス脳における作用機序を解析する．【方法】72～79歳の軽度～中等度ADでコリンエステラーゼ阻害薬内服中の患者（男3名／女2名）で，APO注射薬を週1回1 mgを皮下注射し，治療前，4週，12週後にMMSE，ADAS-Jcog，Neuropsychiatric Inventory（NPI）を実施した．また，ADモデルの3xTg-ADマウス12ヶ月齢に対してAPO注射薬5 mg/kgあるいは生食を週1回計5回皮下注射し（各群n=7），脳組織におけるインスリン分解酵素(IDE)およびセリンリン酸化型インスリン受容体基質1（pS-IRS1）の蛋白レベルをウェスタンブロットおよび免疫染色で解析した．【結果】認知機能検査の平均スコアは，治療前MMSE 19.2・ADAS-Jcog 18.2・NPI 8.6，4週後MMSE 17.8・ADAS-Jcog 15.8・NPI 5.8，12週後MMSE 19.75・ADAS-Jcog 14.25・NPI 4.75であり，ADAS-JcogおよびNPIで改善が見られた．特に，ADAS-Jcogで単語の再認（平均5.6→3→2.25），NPIで無為の改善が見られた．一方，APO治療3xTg-ADマウスにおいては，脳組織でIDEの増加，pS^{616}，$pS^{636+639}$ IRS1の低下が見られ，脳神経細胞のインスリン抵抗性の改善が示唆された．【結論】APOは，AD脳のインスリン抵抗性を改善して記憶機能を回復する治療薬となる可能性がある．

O-28-1

脳アミロイドアンギオパチー患者におけるPIB集積の検討

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【目的】脳アミロイドアンギオパチーは髄膜や脳内の血管壁にアミロイド化したタンパクの沈着を認める疾患である．以前より高齢者に反復して生じる脳葉型脳内出血の原因として知られ，臨床症状や脳MRI検査，病理学的検査などにより診断される．本疾患では大脳皮質での出血は後頭葉において高頻度にみられるが，その原因はまだ明らかではない．今回，我々はPIB-PETを用いて脳アミロイドアンギオパチー患者におけるアミロイド沈着の分布を評価した．【方法】脳出血またはクモ膜下出血を発症し，臨床的に脳アミロイドアンギオパチーと診断された患者5名を対象とした．患者の年齢は28歳～74歳で，男性3名，女性2名であった．全ての患者でPIB-PET検査を実施し，PIB集積の有無，集積部位の分布を評価した．PIB-PETスキャンには，250-350mBq（当院プロトコル）または400-500mBq（J-ADNIプロトコル）の[11C] PiBを注射後，60分または70分間の動的スキャンを実施し，PETカメラには島津社製Eminence Bを用いた．【結果】全ての症例においてPIB集積を認め，前頭葉，頭頂葉，外側側頭葉優位の集積を認めた．アルツハイマー型認知症患者に類似した集積分布を示し，後頭葉への高度の集積は認めなかった．【結論】脳アミロイドアンギオパチー患者において，PIB-PET検査はアミロイドを検出するが，PIB集積の分布は血管壁のアミロイド沈着を直接は反映せず，基礎にあるアルツハイマー型認知症を示唆する可能性がある．

O-28-2

取り下げ演題

O-28-3

PF1+2を用いたワルファリンやNOAC療法中の抗凝固作用の差異に関する検討

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【目的】プロトロンビンがトロンビンへ変換される時に産生される凝固系分子マーカーのプロトロンビンフラグメント1+2（PF1+2）は鋭敏な凝固系評価指標である．本研究の目的は抗凝固療法中のPF1+2の動態を各経口抗凝固薬毎に明らかにすることである．【方法】2012年8月から2015年11月までに非弁膜症性心房細動などに伴う脳梗塞の再発予防として外来で経口抗凝固療法中であった27例（男性17例，女性10例，77±6歳）を対象に血漿中のPF1+2を内服2-6時間後に測定し，正常範囲内（69-229 pmol/L）にあるか否かを検討した．外来通院中であった新規経口抗凝固薬（NOAC）の種類を変更した症例を含んでおり，延べ症例数および測定回数はそれぞれワルファリンが7例70回，ダビガトラン150mg BID（D150）が4例27回，110mg BID（D110）が6例41回，リバーロキサバン15mg QD（R15）が6例37回，10mg QD（R10）が6例29回，アピキサバン5mg BID（A5）が2例5回，2.5mg BID（A2.5）が2例13回であった．【結果】ワルファリン群のPT-INRは中央値1.96（IQR 1.83-2.13），PF1+2は中央値111（IQR 95-139）であり，上限以上の値はなかったが，5例13回（19%）でPT-INRに依存せず正常下限未満であり，8回はPT-INR 2.5未満で観察され，その1例で脳出血を発症した．D150，D110，R15，R10，A5，A2.5のPF1+2はそれぞれ中央値116（IQR 99-136），132（IQR 99-162），109（IQR 100-125），133（IQR 100-177），88（IQR 76-102），148（IQR 93-167）であり，正常下限未満の値はみられなかった．正常上限以上の値はD110で1例1回とR10で2例2回みられたが，脳虚血症状は随伴しなかった．【結論】PF1+2の正常下限未満の値はワルファリン療法中にのみ，かつPT-INRに依存せずに観察されたことから，NOACと比較してワルファリン療法中の頭蓋内出血発症率が高い原因の一つとして，ワルファリン療法による過度のトロンビン産生抑制が関与していることが示唆された．

O-28-4

心房細動を有する脳梗塞患者の虚血性脳卒中再発リスクスコア評価：SAMURAI-NVAF研究

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【目的】心房細動を有する患者における塞栓症発症のリスク評価として，様々なリスクスコアが報告されている．今回我々は非弁膜症性心房細動を有する脳梗塞患者の虚血性脳卒中再発のリスクについて報告のある6つのリスクスコアを用いて評価を行った．【方法】多施設共同SAMURAI-NVAF研究に登録された非弁膜症性心房細動を有する，発症7日以内の急性期脳梗塞患者1192例を対象とした．登録期間は2011年7月1日から2014年3月31日まで，追跡期間は中央値482日であった．塞栓症のリスクスコアとしてCHADS$_2$（低・中リスク 0-1，高リスク 2-6），CHA$_2$DS$_2$ -VASc（0-1，2-6），Framingham（0-15，16-31），NICE，ACC/AHA/ESC，Eighth ACCP（後者3つは項目の組み合わせでリスクレベルを評価）を用い，それぞれのリスクスコアにおいて高リスク群と低・中リスク群とに分類して，虚血性脳血管障害（脳梗塞，一過性脳虚血発作）の再発予測の有用性について検討した．【結果】経過中に脳梗塞が89例，一過性脳虚血発作が6例に生じた．各スコアの低・中リスク群に対する高リスク群の虚血性脳卒中発症率の粗ハザード比は，順に1.7（1.0～2.8），3.0（1.1～12），1.5（1.0～2.3），1.9（1.2～3.1），1.8（1.1～3.0），1.6（1.0～2.7）で，いずれも高リスク群で有意に発症率が高かった．【結論】CHADS$_2$，CHA$_2$DS$_2$-VASc，Framingham，NICE，ACC/AHA/ESC，Eighth ACCPいずれのリスクスコアも，非弁膜症性心房細動患者の虚血性脳卒中再発を予測するのに有用であった．

O-28-5

Efficacy and implications of isoform selective Histone deacetylase inhibitors for cerebral ischemia

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Background: Epigenetic mechanisms involving chromatin-modifying enzymes and remodeling factors are implicated in the neurological disorders. Histone acetylation is regulated by the opposing action of HATs and HDACs. HDACs are grouped into four classes, which are further classified into 18 isoforms. Available HDAC inhibitors (HDACi) are nive inhibit multiple HDACs, but different HDACs serve distinct functions. It remains to be clarified whether the isoform-selective HDACi is crucial for neuronal survival after stroke. **Methods:** Primary rat neuronal cultures and brain endothelial cells were examined. We have screed original HDACi library. To assess co-treatment effect of HDACi, oxygen-glucose deprivation have been performed. **We examined whether** K-560 could across the blood-brain-barrier (BBB) using LC/MS-MS. **In vivo,** middle cerebral arteries were occluded for 60 min with suture. **Results:** Ischemia induced dephosphorylation of class I and II-HDAC. Among original **library, we identified** HDAC1 and 2-specific inhibitor HDACi, **K-560.** Treatment with K560 attenuated neuronal death. K560-treated cells have activated survival signaling of mTOR-Akt at early phase after ischemia. The class II-selective inhibitor MC-1568 could not inhibit the cell death. K-560 could across BBB and showed the acetylation of the histone 3 in the brain. **Conclusion:** This showed that the neuroprotection of **K-560,** at least in part, was mediated by the induction of mTOR signaling after ischemia. Further studies are needed to elucidate functions of individual HDAC and their potential as therapeutic agents.

O-28-6

Gradual carotid stenosis in mice closely mimics hypoperfusive vascular dementia

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Objective: Existing rodent models of vascular cognitive impairment (VCI) show abrupt change in cerebral blood flow (CBF) and do not completely mirror clinical pathogenesis of VCI. Therefore, we tried to establish a mouse model of VCI where CBF gradually decreases with subsequent motor and cognitive impairment.Methods: Adult C57BL/6J male mice were subjected to gradual common carotid artery stenosis (GCAS) surgery (n= 12) using an ameroid constrictor (AC) vessel-constricting device with inner diameter of 0.75 mm or sham surgery (n = 10) .Results: The common carotid arteries narrowed gradually after gradual constriction of ACs over 28 days after GCAS, with subsequent 80% area stenosis due to smooth muscle cell proliferation and macrophage infiltration in the tunica intima. The 28-day survival rate was 100%. Arterial spin labeling demonstrated gradual and continuous reduction of cortical and subcortical CBF (ratio to the preoperative value) to 54.6% and 51.5%, respectively, over 28 days. However, magnetic resonance angiography showed increment of collateral flow signals in the leptomeningeal artery. Rarefaction and proliferation of astrocytes and microglia with loss of oligodendrocytes was found in the white matter at 32 days. The rotarod test showed motor impairment whereas the Y-maze test showed that working memory was impaired.Conclusions: The GCAS model successfully generated gradual and continuous CBF reduction over 28 days, with replication of key histological, radiological, and behavioral features associated with cerebral hypoperfusion leading to VCI.

O-29-1

CASE SERIES: EXPERIENCE IN THE MANAGEMENT OF AUTOIMMUNE ENCEPHALITIS IN PHILIPPINE GENERAL HOSPITAL

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Objective: The study will describe & discuss the proven cases of autoimmune encephalitis particularly its clinical presentation, neuro-diagnostic results (imaging, CSF analysis, electroencephalogram), tumor surveillance, treatment modalities, outcomes and gaps of management in the local setting.*Method:* Chart review of 6 cases admitted in a tertiary hospital that have confirmed antibodies in the cerebrospinal fluid was done. The CSF and serum samples were all tested and confirmed by the Neuroimmunology Laboratory (IDIBAPS) in Barcelona, Spain.*Results:* There were 6 cases of autoimmune encephalitis admitted in a government tertiary hospital. There were 4 cases of anti-NMDA receptor encephalitis, a case of anti-AMPA receptor encephalitis and a case of mixed autoimmune encephalitis (anti-NMDA & anti-AMPA receptor). Two cases of which had ovarian teratoma. Headache was the common prodromal symptom and psychiatric symptoms were prominent clinical features during the early course of the disease. Patients that had dysautonomia and decrease sensorium during the course of illness were associated with poor outcome. Methyprednisolone pulse therapy was the most used first line treatment and the time of onset to recognition and treatment was an average of 1 month.*Conclusion:* In conclusion, autoimmune encephalitis is an under-recognized disease and should always be considered among patients with encephalitis. The early recognition, aggressiveness and prompt treatment are the keys to better outcome for these patients.

O-29-2

Analysis of neurodegeneration with astrocytopathy in neuromyelitis optica and multiple sclerosis

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder of the CNS characterized by aquaporin-4 (AQP4) autoantibodies. Previously, we reported more severe visual impairment and worse prognosis in NMOSD patients, compared to multiple sclerosis (MS) patients. Objective: To characterize neurodegeneration and to elucidate neuro-glial interaction in the CNS of NMOSD and MS. Methods: Neuropathological assessments were qualitatively and quantitatively conducted in optic nerve tissues from 13 patients with NMOSD, 7 patients with MS, and 8 patients with other diseases as controls. Results: All patients with NMOSD had typical pathological findings including pattern-specific loss of AQP4 and glial fibrillary acidic protein immunereactivity and immunoglobulin deposits colocalizing with a product of complement activation in a vasculocentric pattern. Damaged axons including axonal swelling and spheroids were evident in plaques, periplaque white matter (PPWM) of NMOSD. Particularly, there were a number of amyloid precursor protein^{+} damaged axons in plaques and PPWM of NMOSD, compared to those in MS. The density of SMI-31^{+} axons was significantly decreased in plaques ($1336 \pm 1059/mm^3$) and PPWM ($3025 \pm 811/mm^3$) of NMOSD, and in plaques ($1658 \pm 1005/mm^3$) and PPWM ($3700 \pm 1982/mm^3$) of MS, compared to disease controls ($7259 \pm 1914/mm^3$) ($P<0.0001$). Conclusions: These data indicated that severe and widespread neuroaxonal damage beyond demyelination area may explain severe impairment and worse prognosis of NMOSD.

O-29-3

Pro-inflammatory cytokine elevation in the CSF of anti-MOG+ neuroinflammatory disorders

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[Objective] To evaluate cytokines level in the cerebrospinal fluid (CSF) collected in acute attack of patients with anti-myelin oligodendrocyte glycoprotein (MOG) +, anti-aquaporin4 (AQP4) +, multiple sclerosis (MS), and non-inflammatory controls. [Methods] We collected CSF samples of 10 MOG+, 10 AQP4+, 12 MS, 17 controls. In all patients with MOG+ or AQP4+, antibody status was confirmed both in serum and CSF using cell-based assays. All the samples were collected in the acute phase (<14 days from onset) before any treatment. 27 cytokines were measured by a commercially available multiplex bead assay. [Results] In interleukin (IL)-6 and IL-8, cytokine levels were elevated in MOG+, AQP4+, and MS compared to control, and AQP4+ group had higher levels compared to other groups (IL-6 : MOG+ 13.8 (2.3-16668.7) pg/ml, AQP4+ 348.2 (28.9-7845.8) pg/ml, MS 9.2 (4.5-44.8) pg/ml, IL-8 : MOG+ 105.2 (53.2-2715.5) pg/ml, AQP4+ 252.8 (60.3-783.8) pg/ml, MS 76.7 (66.8-224.1) pg/ml). On the other hand, IL-17 level was also elevated compared to controls, but MOG+ group had higher levels compared to other groups (MOG + 22.9 (5.5-139.4) pg/ml, AQP4+ 7.2 (4.9-58.0) pg/ml, MS 6.9 (4.9-44.5) pg/ml, control 4.9 (4.9-4.9)). Moreover, IL-9 and IL-12 levels were elevated in MOG+ group compared to other groups (IL-9 : (MOG+ 7.9 (3.4-15.1) pg/ml, AQP4+ 3.7 (1.7-10.0) pg/ml, MS 4.4 (0.7-8.3) pg/ml, control 2.1 (1.8-2.2)). [Conclusion] Pro-inflammatory cytokines are elevated in MOG+, AQP4+ and MS compared to control. There is an elevation of Th17 cytokine in both MOG+ and AQP4+ groups, but the detail cytokine kinetics is distinct.

O-29-4

Anti-myelin oligodendrocyte glycoprotein antibody among autoimmune encephalitis

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Objective: To clarify whether anti-myelin oligodendrocyte glycoprotein (MOG) antibody (ab) is associated with autoimmune encephalitis patients with clinical features.Background: MOG is a glycoprotein associated with the myelination of nerves in the central nervous system (CNS). Recently, anti-MOG ab had been detected in the serum of various CNS demyelinating diseases.Methods: We tested consecutive 24 serum samples of steroid responsive encephalitis patients. Anti-MOG ab was detected by a sensitive in-house cell-based assay. Clinical and radiological features of anti-MOG ab positive patients were investigated.Results: All 4 patients were positive for anti-MOG ab. All of them were negative for anti-AQP4, NMDAR, VGKC ab in serum and CSF. All of them were male. Median age of onset was 37 (range 23-39). All of them developed seizures. Urinary disturbance and optic neuritis was simultaneously observed in one patient. None of them developed myelitis. Although a clinical relapse was observed in one patient, all of them had good recovery by steroid treatment. Brain MRI showed cortical and sulcus lesions in all. Brain SPECT showed hyperperfusion at the region. CSF study showed moderate pleocytosis and mild elevation of the total protein level. Oligoclonal IgG bands were negative in all.Conclusion:We have detected anti-MOG ab in patients with steroid responsive autoimmune encephalitis with unique clinical features. Although it is unknown whether the anti-MOG ab is pathogenic, it may have the potential to be a specific marker for the autoimmune encephalitis with good prognosis.

O-29-5

Serology Tests in Autoimmune Encephalopathies- A Hospital Audit

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ObjectiveAutoimmune Encephalopathy (AE) is a potentially reversible acute encephalitis. Prompt recognition and treatment is aided by the identification of anti-NMDA receptor/VGKC/GAD antibodies, but their value on health outcomes is unknown.**Methods**In this retrospective audit (January 2010 to September 2012) 27 subjects at a UK district general hospital who were found to have a positive anti-NMDA receptor/VGKC/GAD antibody result, or had a diagnosis of "autoimmune encephalopathy" and had a request for these antibodies made were identified with a subgroup of 13 having definite AE (clinically and/or serologically).All were analysed for age, ethnic origin, sex, neurology diagnosis, antibody result, presenting history, examination, EEG, CSF and MRI findings, Neurologist involvement, treatments offered and outcome.**Results**The following are the salient points:1.The anti-VGKC antibody is tested less commonly for suspected AE than for other indications (e.g. neuromyotonia) and its specificity increases with titres. Anti-NMDA receptor antibodies are more specific in young than older adults.2. AE has a good outcome with early immunosuppressive treatment. 3.Typical history is very suggestive, but neurology examination, and CSF/EEG/MRI findings lack individual specificity while enabling (with specialist neurology input) a prompt diagnosis collectively. **Conclusions**In AE Early immunosuppressive treatment ensures good outcome irrespective of the serology, an observation even more relevant in low income settings.We suggest prospective studies on the role of serology testing in suspected AE.

O-29-6

The neuroradiological and immunological analysis of neuro-Behçet's disease

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[Objective] Neuro-Behçet's disease (NBD) is an inflammatory disorder, but the detail remains unknown. The objective of this study is to elucidate the characteristic features of NBD. [Methods] We investigated the clinical, immunological and radiological analysis of ten cases with NBD. [Results] The cases (male: female = 8: 2) showed acute course (3/10), chronic progressive course (1/10), and mixed course (6/10). The age of onset was median 42 years old (range, 21-55) and four cases had a positive HLA-B51 status. Patients with acute course were characterized by diplopia, trunk ataxia, and dysuria, whereas patients with chronic progressive course were characterized by cognitive and psychiatric impairment. The MRI findings showed lesions in medulla oblongata (2/10), pons (5/10), midbrain (3/10), thalamus (3/10), internal capsule (3/10), basal ganglia (2/10), corona radiata (6/10), and cerebral white matter (3/10). Interestingly, tumefactive ring enhancement on T1-weighted gadolinium contrast was seen in four cases and the three of them showed multiplicity. All patients with chronic progressive or mixed course showed atrophy in the brainstem and/or cerebrum. CSF analysis showed mild pleocytosis (6-58/mm^3), mononuclear predominance (9/9), and the elevation of IL-1β (1/9), IL-6 (6/9), IFN-γ (4/9), CCL2 (2/9), CXCL8 (6/9), CXCL9 (2/9), and CXCL10 (3/9). [Conclusion] These results indicated that NBD was characterized by acute and/or chronic autoinflammatory features including accumulation of neutrophils, macrophages and T_H1 lymphocytes in the brain with host predisposition, HLA-B51.

20日(金) 口演

O-30-1

Muscle MRI in riboflavin responsive lipid storage myopathy

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Objective: Riboflavin responsive lipid storage myopathy (RR-LSM) is the most common lipid storage disease characterized by chronic or fluctuate muscle weakness at adulthood. Clinically, this disease is usually difficulty to do differential diagnosis with inflammatory myopathy and muscular dystrophy. We summarize the characteristics of muscle MRI in RR-LSM.**Methods**: The 16 patients included 12 male and 4 female, the average age of onset was 33.3 years, and the average duration was 57 months. All patients showed fluctuate proximal weakness in limbs with elevated serum creatine kinase (normal to 3000U/L). Needle EMG showed myopathic or neurogenic changes. Muscle pathology showed a large number of lipid droplets in muscle fibers. Genetic tests present compound heterozygous mutations in ETFDH gene. Muscle MRI was performed in all patients with RR-LSM and 258 disease control patients (180 cases with inflammatory myopathy and 78 cases with limb-girdle muscular dystrophy) to observe edema and fatty infiltration in gluteus maximus and thigh muscles.**Results**: Thigh MRI revealed fatty infiltration in 13 patients and edema in 2 patients. The severity of fatty infiltraton varied minially in different muscles with the total fatty infiltration scores between 2 to 23. The gluteus maximus (23), the long head of biceps femoris (19) and semimembranosus (18) were most involved. All control patients showed no similar changes.**Conclusion**: RR-LSM usually showed mild fatty infiltration with regular distribution pattern. Posterior thigh muscles involved more apparent in some patients.

O-30-2

Clinical Research of Becker Muscular research using nationwide patient registry

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Objectives: Currently, it is difficult to obtain adequate numbers of patients to conduct a natural history study for rare diseases such as Becker muscular dystrophy (BMD). One potential way to address this issue is to use patient registry data. To conduct a phenotype analysis of BMD, we used data from Remudy, a national registry for neuromuscular diseases in Japan.Methods: We analyzed Remudy data from patients with dystrophinopathy. All patients who were either ambulant at age 13 or predicted to be ambulant by age 13 were included in the analysis, which examined data on ambulation, cardiopulmonary function, and genotyping. For clinical evaluation comparisons, patients administered steroids were excluded.Results: As of September 2015, 289 BMD patients (17.6% of entire dysferlinopathy) were registered in Remudy. Mean patient age was 27.6 ± 15.9 (range, 2-78) years, and 43% of patients were ambulant. Patients with cardiomyopathy and respiratory failure were 35% and 27%, respectively, and 20 patients required a ventilator. The most frequent genetic mutation was exon deletions (70%), followed by point mutations (20%) and duplications (10%). The most frequent mutation was ex45_ex47del (54 patients). There were a total of 81 combinations of exon deletions and duplications.Conclusions: Patient registries are useful tools for clinical research. Cooperation with other international registries such as TREAT-NMD may represent a possible strategy for detailed analysis of genotype-phenotype relationships in BMD.

O-30-3

Novel mutation of STIM1 causes dysregulation of Ca2+ homeostasis in tubular aggregate myopathy

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[Purpose] Tubular aggregate myopathy (TAM) is a disorder characterized by slowly progressive muscle weakness and the pathological feature is the appearance of tubular aggregates in skeletal muscle. Last year, in this meeting, we presented a TAM family with a novel cytoplasmic mutation in stromal interaction molecule 1 (STIM1), a Ca^{2+} sensor in sarcoplasmic reticulum. In the present study, we investigated the pathomechanism leading to TAM in this family. [Methods] We expressed the cytoplasmic mutant of STIM1, p.Ile484ArgfsX21, in cultured cells and analyzed their functional significance. We further measured the intracellular Ca^{2+} concentration using Fura-2. [Results] We transfected C2C12 myoblasts with STIM1 and demonstrated that the cytoplasmic mutant exhibited aggregation-like appearance and failed to form puncta upon depletion of Ca^{2+} by SERCA1 inhibitor tapsigargin, indicating disturbed STIM1 signaling. Further, we revealed decreased intracellular Ca^{2+} influx by the cytoplasmic mutant, which is in sharp contrast to the increased Ca^{2+} influx by the EF hand mutant. [Conclusion] Several mutations in STIM1 have been identified so far in TAM and all of them reside in the EF hand region. These mutants are thought to cause constitutive activation of the store operated Ca^{2+} channel. In contrast, the intracellular localization and the Ca^{2+} response of the cytoplasmic mutant are distinct from those of the EF hand mutant. Collectively, the novel STIM1 cytoplasmic mutation causes dysregulation of Ca^{2+} homeostasis via different mechanism from that proposed previously in TAM.

O-30-4

Follow up study of autoimmune necrotizing myopathy with anti-signal recognition particle antibodies

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Objective: Autoimmune necrotizing myopathy with anti-signal recognition particle (SRP) antibodies is a common type of autoimmune necrotizing myopathy. Previous report indicated that the disease is poor responsive to steroid therapy. Therefore, we do follow up study in 15 cases of autoimmune necrotizing myopathy with anti-SRP antibodies with immune therapy.**Methods**: 15 patients were all female, aged between 4-13 years old, the disease duration was 2 - 6 months. The serum anti-SRP antibody was positive. All patients showed muscle strength of 2-3 grades in proximal muscles and 4-5 grades in distal muscles in all limbs. Serum creatine kinase (CK) were 4660-7456IU/L (normal 18 - 173 IU/L). Electromyography showed myopathic changes. Muscle biopsy showed necrotic myopathy without inflammatory infiltrate. All the patients were treated with high dosage of prednisone, some patients combined with immunosuppressive therapy (tacrolimus or methotrexate), some patients with intravenous immunoglobulin. In the follow up study for 3-6 months we compared thigh MRI changes before and after treatment.**Results**: After treatment muscle strength of 4-5 grades in proximal muscles and normal in distal muscles in all limbs. Serum CK were normal-500 IU/L. Thigh MRI showed mean edema scores was 37.7, and mean fatty infiltration scores was 29 before treatment, 19.3 and 15.4 after treatment.**Conclusion:** Autoimmune necrotizing myopathy with anti-SRP antibodies is good responsive to treatment with corticosteroid, with or without immunosuppressive drugs and intravenous immunoglobulin.

O-30-5

Endoplasmic reticulum stress in murine model and patients with inclusion body myositis

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[Objective] Increasing evidences suggest that TDP-43 might be involved in the pathophysiological mechanisms of sporadic inclusion body myositis (sIBM). We have established skeletal muscle-specific wild-type TDP-43 transgenic mice as a murine model of sIBM. Although the murine model showed clinical and pathological phenotypes resembling sIBM, the precise mechanism by which overexpression of TDP-43 caused myodegeneration is still remained unclear. [Methods] We examined an immunohistochemical analysis of endoplasmic reticulum (ER) stress markers by using specimens of muscular tissues of the murine model and patients with sIBM. [Results] TDP-43 transgenic mice as well as patients with sIBM showed increased expression of ER-resident chaperones such as BiP, calnexin and GRP94. CCAAT/enhancer-binding protein homologous protein (CHOP) immunoreactivities were observed in the muscle fibers of TDP-43 transgenic mice and patients with sIBM. Interestingly, cytoplasmic 5'-nucleotidase 1a (NT5C1A), which is a target of autoantibody observed in the sera of patients with sIBM, aggregated and colocalized with TDP-43 in degenerative muscle fibers of TDP-43 transgenic mice and patients with sIBM. [Conclusions] ER stress pathways might be involved in the pathogenesis of TDP-43 transgenic mice and patients with sIBM. These findings suggest that NT5C1A associated with TDP-43 might play a pivotal role in the pathophysiological mechanisms of skeletal muscular degeneration in sIBM.

O-30-6

Oral administration of erythromycin decreases RNA toxicity in myotonic dystrophy

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Objective: Myotonic dystrophy type 1 (DM1) is caused by the expansion of a CTG repeat in the 3' untranslated region of DMPK. The transcripts containing an expanded CUG repeat (CUG^{exp}) result in a toxic gain-of-function by forming ribonuclear foci that sequester the alternative splicing factor MBNL1. Although several small molecules reportedly ameliorate RNA toxicity, none are ready for clinical use because of the lack of safety data. Here we undertook a drug-repositioning screen to identify a safe and effective small molecule for upcoming clinical trials of DM1.Methods: We examined the potency of small molecules in inhibiting the interaction between CUG^{exp} and MBNL1 by in vitro sequestration and fluorescent titration assays. We studied the effect of lead compounds in DM1 model cells by evaluating foci reduction and splicing rescue. We also tested their effects on missplicing and myotonia in DM1 model mice.Results: Of the 20 FDA-approved small molecules tested, erythromycin showed the highest affinity to CUG^{exp} and a capacity to inhibit its binding to MBNL1. Erythromycin decreased foci formation and rescued missplicing in DM1 cell models. Both systemic and oral administration of erythromycin in the DM1 model mice showed splicing reversal and improvement of myotonia with no toxicity. Long-term oral administration of erythromycin at the dose used in humans also improved the splicing abnormality in the DM1 model mice.Interpretation: Oral erythromycin treatment, which has been widely used in human with excellent tolerability, may be a promising therapy for DM1.

O-31-1

Serotonergic changes in putamen versus caudate of dopa-responsive dystonia and Parkinson's disease

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[Objective] AD dopa-responsive dystonia (DRD) is caused by mutations in the GCH1 gene, which encodes GTP cyclohydrolase I (GTPCH), the first enzyme in the biosynthesis of tetrahydrobiopterin (the cofactor for tyrosine and tryptophan hydroxylases [TPH]). As in Parkinson's disease (PD), an increased frequency of nonmotor symptoms has been recently reported in DRD. To evaluate possible serotonin deficiency and the intra-striatal pattern of serotonergic changes in GTPCH-deficient DRD vs PD, we measured brain levels of serotonin markers in these disorders. [Methods] Striatal tissue was obtained from 2 GTPCH-deficient DRD cases (Case 1: 68 years, Case 2: 19), 5 PD patients (66-81), and 10 elderly (58-80) and 5 young (24-48) controls. Serotonin transporter (SERT) and TPH protein levels were determined by Western blot. [Results] In both disorders, caudate was affected more than putamen by loss of SERT; Case 1 (122% [putamen] vs 63% [caudate] of elderly control means), PD (52% vs 35%), and Case 2 (82% vs 43% of young control means). Regarding TPH protein levels, the same intra-striatal pattern was observed in Case 2 (123% vs 62%). [Conclusion] The major finding of our study is that the intra-striatal pattern of changes of serotonin markers in GTPCH-deficient DRD was similar to that in PD; the pattern was substantially different from that of decreases of dopamine markers (putamen is affected more than caudate). Our data suggest that, as reported in PD, any functional impairment due to striatal serotonergic changes might primarily involve the caudate nucleus in GTPCH-deficient DRD.

O-31-2

Relation of acute levodopa challenge and striatal dopamine transporter density in Parkinson disease

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[Objective] Acute levodopa challenge is a widely used clinical technique. Relationship between the test and presynaptic dopaminergic neuronal function is critical to understand the test results. Here, we assessed correlation between levodopa responsiveness of major signs of idiopathic Parkinson disease (PD) and [^{123}I]FP-CIT SPECT uptake. [Methods] We recruited 24 patients with PD. Patients skipped all antiparkinsonian medications at least 12 hours and were challenged with a single dose of 250/50 levodopa/carbidopa. Major signs of PD were measured using three subscales extracted from the Unified Parkinson's disease rating scale (UPDRS): bradykinesia, rigidity and tremor subscales. By dividing the on score by the off score, improvement ratio was calculated. SPECT studies were evaluated with specific binding ratio (SBR). The data were analyzed using Pearson's correlation coefficient. [Results] During the off state, bradykinesia subscale had the highest correlation with SBR ($r = -0.582$, $p = 0.009$) compared with rigidity ($r = -0.406$, $p = 0.049$) and tremor ($r = -0.117$, $p = 0.586$). The improvement ratio of bradykinesia subscale had the highest positive correlation with SBR ($r = 0.542$, $p = 0.006$) compared with rigidity ($r = 0.458$, $p = 0.024$) and tremor ($r = -0.146$, $p = 0.497$). [Conclusion] The present findings indicate that presynaptic dopaminergic neuronal function reflects best in bradykinesia. In addition, our data suggest that patients with higher SBR had better improvement of bradykinesia in acute levodopa challenge.

O-31-3

Altered functional connectivity associated with striatal dopamine depletion in Parkinson's disease

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＜Introduction＞ Cortico-basal ganglia circuit model, or firing rate model, successfully link striatal dopamine depletion and bradykinesia in Parkinson disease (PD). However, the model provokes several conflicts with clinical observations. For example, the model is difficult to reconcile with the fact that lesions in the motor thalamus were found to relieves tremor and rigidity, rather than worsen bradykinesia in PD patients . **＜Methods＞** Seventeen PD patients and 16 healthy control subjects (HC) underwent [^{11}C]- CFT PET. Whole brain BOLD fMRI, T1 weighted image and field map data were also acquired with a 3T scanner. Analyses were performed using FMRIB Software Library (FSL) v5.0.8 tools. First, we set regions of interest (ROIs) on striatal area showing significant ^{11}C-CFT binding reduction in PD compared to HC. Then, we examined functional connectivity of the ROIs in PD and HC. **＜Results＞** The striatal ROIs demonstrated functional connectivity with cortical motor areas in HC but not in PD, suggesting a disruption of normal cortico-basal ganglia network in PD. In addition, functional connectivity strength of the ROIs within the striatal areas positively correlated with the severity of bradykinesia but not with the tremor in PD, implicating a relation between emergences of abnormal subcortical network and bradykinesia in PD. **＜Discussion＞** Based on the present findings, we propose that striatal dopamine depletion generate abnormal local striatal functional connectivity leading to bradykinesia in PD.

O-31-4

MIBG myocardial scintigraphy identifies premotor PD during a negative DAT scan period

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Objective We report four patients who, during a negative DAT scan period, were revealed to have positive MIBG test that suggests premotor PD.**Background** In Parkinson's disease (PD), there is no large report to compare sensitivity and specificity between dopamine transporter (DAT) scan and metaiodobenzylguanidine (MIBG) myocardial scintigraphy among these pre-motor PD cohorts.**Methods** The inclusion criteria were: at least one of known nonmotor features of PD (autonomic, REM sleep behavior disorder, cognitive, or psychiatric symptoms); those who underwent DAT scan and MIBG test. Among these, we excluded motor disorder indicating PD; apparent neurologic diseases other than PD; apparent cardiac, gastrointestinal or prostatic diseases; and drugs that might affect DAT scan or MIBG test.**Results** Among 1500 outpatients, four patients fulfilled the above criteria. Most of them were referred patients in order to explore neurologic etiologies of syncope, constipation, RBD, and memory disorder. They were uniformly elderly (mean 78 years), 3 male, one female. All patients could walk independently. Neurologic diagnosis of these patients were pure autonomic failure, one, constipation with RBD, one, RBD, one, mild cognitive impairment, one. In these patients, all had abnormal MIBG test but none had abnormal DAT scan.**Conclusions** Pathologically, it is shown that degeneration and Lewy neurites in the myenteric and cardiac plexus can appear earlier than in the brain. Considering the present study results, MIBG test is able to identify premotor PD during a negative DAT scan period.

O-31-5

Depletion of Nigrosome1 in parkinsonian brains as shown by loss of swallow tail sign on 3T MRI-SWI

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＜Objective＞ Macroscopic change of the parkinsonian brain is so subtle that conventional MRI is unable to differentiate Parkinson's disease (Pd) from normal subjects (NSs). Yoshikawa et al (2004) had shown microstructural change in parkinsonian substantia nigra (SN) by MRI, their procedures were too complicated to use in daily clinics. According to the recent reports, nigrosome1 (NS1) in SN is the most vulnerable part in parkinsonian brain, and its depletion leads to the loss of so-called "swallow tail sign"(STS) in SN on susceptibility weighted images (SWI). Our aim of the study is to see whether NS1 depletion is observed in various parkinsonian brains by SWI. ＜Methods＞ We prospectively recruited the patients with Pd and other parkinsonism (OP): PSP, MSA-P, CBS, drug-induced parkinsonism. Age-matched NSs were also examined. MRI was taken by GE Discovery MR750w 3.0T with 3D-SWI (TR59.3ms, TE1.8ms, Thickness2.0mm). Two observers independently diagnosed STS on both sides of SN, and categorized into present or unidentifiable by visual impression. Presence of STS was analyzed by Fisher's exact test, and P-value less than 0.05 was considered significant. ＜Results＞ We examined 15 parkinsonians (Pd 7, OP 8: mean age: 75.5) and ten NSs (mean age: 72.2). STS was unidentifiable in 11 out of 14 SNs in Pd, while STS was confirmed in all NSs. STS was significantly lost in Pd ($p<0.0001$: Sensitivity 78.6, Specificity 100%). However, patients with OP did not show significant loss ($p=0.176$). ＜Conclusion＞ Loss of STS on 3T MRI-SWI would be a plausible tool for the diagnosis of Pd.

O-31-6

Synaptic vesicle dynamics are regulated by Parkinson's disease-associated proteins Vps35 and LRRK2

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[Object] Dysfunction of dopaminergic neurons in the midbrain is a feature of Parkinson´s disease (PD). Recent studies by our group and others suggested that PD causative or risk genes play roles in the synapse vesicle (SV) dynamics. However, physiological roles of these proteins and their functional interaction are not well understood. This study examined functions of PD causative genes, Vps35 and LRRK2 in the SV dynamics and their functional interactions using *Drosophila*.[Methods] Neural activities were analyzed by using live imaging and electrophysiological technique in Vps35 and/or LRRK2 knock-out (KO) flies. Furthermore, ultrastructural SV morphological phenotypes were observed by using electron microscopy. Ectopic expressions of LRRK2, Vps35 and Rab small GTPase proteins were induced by the molecular genetical technique to examine their therapeutic potentials against the dysfunction of SV dynamics.[Results] Reduced expression of Vps35 caused the abnormal neural activity and ectopic expression of wild-type (WT) Vps35 rescued it whereas the expression of a pathogenic form of Vps35 failed. Ectopic expression of LRRK2 WT or specific Rab GTPases rescued the abnormal neural activity in Vps35 KO flies. Ultrastructural observation revealed morphological changes of SV in the Vps35 KO flies and these phenotypes were rescued by the expression of Vps35 WT but not a PD mutant.[Conclusion] SV dynamics are regulated by Vps35 in conjunction with LRRK2 and beneficial effects by manipulation of Rab GTPase activities are suggested in PD caused by *LRRK2* and *Vps35* mutations.

O-32-1

Progressive motor deficits in patients with lenticulostriate artery territory infarcts

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Purpose: We explored factors associated with progressive motor deficits (PMD) in lenticulostriate artery territory (LSA) infarcts patients. Methods: Acute 523 consecutive patients were studied. The PMD were categorized into 3 groups: no PMD, minor PMD and major PMD. Minor PMD was defined as worsening by 1 point in the NIHSS but recovered afterwards and major PMD was worsening by ＞1 points in the NIHSS and afterwards thoroughly progressed. DWI of LSA were divided into proximal type and distal type. The proximal type was divided into anterior type and posterior type. Systolic blood pressures on admission (SBP) were categorized into 5 groups: G1; ＜140mmHg, G2; 140-159, G3; 160-179; G4;180-200 and G5;＞200. Higher NIHSS was defined as ＞4. Atherosclerotic diseases of the middle cerebral artery were classified as normal, mild stenosis (＜50%) and severe stenosis (＞50%). A median value of modified Rankin scale 1 month after ictus were, no PMD (n=302): 1, minor PMD (n=112): 1 and major PMD (n=109): 4. Odds ratios (OR) of predictors for major PMD were calculated. Results: Female, anterior and posterior type, mild stenosis, higher NIHSS and G4 and G5 od SBP were significant by uni-variate analysis. Anterior type (OR: 10.2, p＜0.0001), posterior type (156.1, p＜0.0001), mild stenosis (3.0, p=0.014) and higher NIHSS (4.3, p=0.0002) were independently associated with major PMD. Conclusions: Posterior rather than anterior proximal type was far strongly associated with major PMD probably due to anatomical fact that corticospinal tracts posteriorly crossed the LSA territory.

O-32-2

The impact of worsening renal function in admitted patients with acute ischemic stroke

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Purpose: To determine the risk factors and impact of worsening renal function (WRF) during hospitalization in patients with acute ischemic stroke. **Methods:** We retrospectively analyzed 276 consecutive patients who were admitted to our hospital with acute ischemic stroke. Patients with minor stroke who did not have blood tests more than once or hemodialysis patients were excluded. WRF was defined as an increase in serum creatinine ≧0.3mg/dL from admission. We compared the cardiovascular risk factors, NIH stroke scale on admission, stroke subtypes, in-hospital mortality, and functional outcome at the time of discharge between patients with and without WRF. **Results:** In a total of 250 patients (mean age 74.1±11.8 years, 144 men and 106 women), 27 patients developed WRF. In-hospital mortality rates were 3/27 (11.1%) versus 6/223 (2.7%) in the patients with and without WRF, respectively. Age, sex, prestroke functional status, and stroke severity on admission were not significantly different between the two groups. The patients with WRF had higher rates of renal dysfunction on admission (P ＜0.001) and chronic heart failure (P ＜0.001). The patients with WRF tended to have a higher rate of cardioembolism and a lower rate of small-vessel occlusion compared with the patients without WRF. The rate of mRS ≧3 at the time of discharge was higher in the patients with WRF (P=0.03). **Conclusion:** WRF during hospitalization after acute ischemic stroke was associated with renal dysfunction on admission, chronic heart failure, and unfavorable outcome.

O-32-3

Primary disease and genetic polymorphism of Trousseau syndrome at Kure Medical Center

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【目的】Trousseau症候群(本症)は悪性腫瘍の遠隔効果により神経症状を生ずる傍腫瘍神経症候群の一つであり，悪性腫瘍に伴う血液凝固能亢進により脳梗塞を生じる病態である．腺癌が多く，予防にはヘパリン製剤が効果的とされているが，その約半数にはすでに遠隔転移を伴う進行癌があり，生命予後はきわめて不良とされる．本症への癌の遺伝子多型の影響については知見が集積されていないため，当院における本症について原疾患の種類や遺伝子多型について検討した．【方法】2014年1月より2015年10月までの期間に当院で診断した本症を集積し，それぞれの原疾患や生存期間，遺伝子多型について比較検討した．【結果】22ヶ月間に本症を12症例認め，4例が肺癌，3例が膵癌，2例が胃癌であった．他に食道癌・子宮体癌・悪性胸膜中皮腫・びまん性大細胞性型B細胞リンパ腫が各1例であった．うち1例は胃癌と肺癌を併発していた．病理学的には腺癌が7例を占め，2例が扁平上皮癌であった．Stageは1例がⅢa期で他はⅣ期と進行例が多かった．本症においてEGFR・ALK遺伝子変異は3例で検査され，EGFRのみ陽性例を1例認めた．HER2は1例で検査され陰性であった．同期間に当院にてEGFR遺伝子変異を検査された肺腺癌は44例であり，そのうち17例が陽性であった．肺腺癌による本症では，EGFR遺伝子変異は2例で検査しており，陽性は1例であった．【結論】当院の本症例では12例中7例が腺癌であり，既知の報告に合致したものであった．当院において本症を合併した肺腺癌症例のEGFR陽性率は1/2であった．肺腺癌全体ではEGFR遺伝子変異例で1/17例(5.88%)，変異のない例で1/27例(3.70%)が本症を発症していたが，有意差は得られなかった．肺癌におけるEGFR遺伝子変異陽性例では肺塞栓症が起きやすいとの報告もあり，今回の結果は母集団の数が少ないための可能性もあるため，今後のデータの集積を行っていく予定である．

O-32-4

Microglia-derived NO activates astroglial pentose-phosphate pathway through the Keap1/Nrf2 system

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Purpose: Reactive oxygen species (ROS), nitric oxide (NO), and inflammatory cytokines produced by toll-like receptor 4 (TLR4) activation play harmful roles in stroke. Although astroglia exhibit pro-inflammatory responses upon TLR4 stimulation by lipopolysaccharide (LPS), they may also play cytoprotective roles through the activation of the pentose-phosphate pathway (PPP). We explored the mechanisms by which astroglia reduce oxidative stress in concert with microglia. **Methods:** *In vitro* experiments were performed using cells prepared from Sprague-Dawley rats. Coexisting microglia in astroglial cultures were eliminated chemically using L-leucine methyl ester (LME). Cells were exposed to LPS (0.01 mg/mL) or hypoxia (1% O_2) for 12-15 hours. The PPP activity was measured using [^{14}C]glucose. ROS and NO production were measured using fluorescent indicators. The involvement of Nrf2 was evaluated using immunohistochemistry. **Results:** Chemical depletion of co-exiting microglia eliminated both increases in PPP and the nuclear translocation of Nrf2 observed in astroglia with microglia. LPS induced ROS and NO production in astroglial-microglial cultures, but not in microglia-depleted cultures. U0126, an upstream inhibitor of MAPK, eliminated LPS-induced NO production and PPP activation in astroglial-microglial cultures, indicating that microglia-derived NO mediated astroglial PPP activation. Hypoxia-induced astroglial PPP activation was independent of the microglia-NO pathway. **Conclusion:** Astroglia in concert with microglia may play a protective role against oxidative stress in stroke.

O-32-5

Selective inhibition of NR2B attenuates ischemic neuronal injury in neuronal culture and rats

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Introduction: The global NMDA receptor antagonists have been clinically failed to show efficacy, because NMDA receptor subunits have different effects. While NR2A is involved in cell survival, NR2B is shown to promote neuronal death. The present study is aimed to investigate whether the selective inhibition of NR2B is neuroprotective, using *in vitro* and *in vivo* model. **Methods**: Primary rat cortical neurons were exposed to lethal 210-minute OGD or 15-minute 100 μM glutamate, then NR2B antagonist Ro25-6981 (Ro), other NMDAR antagonists or vehicle was administered after injury. Neuronal death was quantified by LDH assay, and the expression of fodrin, CaMKIV and TRPC6 was evaluated by Western blot. MCA of Wistar rats was occluded permanently by filament, then Ro or vehicle was given intraperitoneally 3 hours after MCAO. Protein expression of cortex was evaluated 12 hours after MCAO, and TTC staining was performed 48 hours after MCAO to estimate infarction. **Results**: Ro was protective against OGD and glutamate toxicities compared with vehicle. Neurons treated with Ro were shown to attenuate the proteolytic level of fodrin and CaMKIV. Ro treatment resulted in a significant reduction of cerebral infarct volume of rats. The proteolysis of fodrin and CaMKIV in Ro group was significantly reduced compared with vehicle group in the penumbra area. The TRPC6 expression in Ro group was less increased in both *in vitro* and *in vivo*. **Conclusion**: Inhibition of NR2B attenuates neuronal injury of OGD and glutamate stress, and reduces infarct size via inhibition of fodrin and CaMKIV proteolysis.

O-32-6

Accumulation of adiponectin in the rat brain under chronic cerebral hypoperfusion

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Purpose: Cerebrovascular white matter lesions are believed to be responsible for cognitive impairment and are caused by chronic cerebral hypoperfusion. Adiponectin, an adipocyte derived plasma protein, increased in the lesions after acute cerebral ischemia, and have a protective effect against ischemic neuronal injury. However, the role of adiponectin under chronic cerebral hypoperfusion remains unclear. To elucidate the role of adiponectin under chronic cerebral hypoprfusion, we investigated the expression of adiponectin and its receptor after the permanent occlusion of both common carotid arteries in rats. **Methods:** Male Wistar rats were anesthetized, and then both common carotid arteries were ligated with silk sutures. At 1, 3, 7, 14 and 30 days after the ligation of the common carotid arteries, the animals were deeply anesthetized and perfused. Four animals were examined for each post-ischemic period. As controls, four animals were subjected the same surgical procedures without the carotid ligation. Serial sections were immunostained with anti-adiponectin or anti-Adiponectin Receptor 2 (ADR2) antibody. **Results:** The number of adiponectin-immunoreactive vessels increased in corpus callosum, caudoputamen, internal capsule, optic tract and cerebral cortex in ischemic groups. ADR2 were expressed on the cerebral vessels in the corresponding regions. **Conclusion:** Since both adiponectin and ADR2 were expressed on the vessels in the brain, the receptor-mediated mechanisms of tissue protection by accumulation of adiponectin may be induced under chronic cerebral hypoperfusion.

O-33-1

本邦初のSCA10の一家系における表現型の比較検討

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【目的】SCA10（spinocerebellar ataxia type 10）はataxin10遺伝子のイントロンに存在するATTCTの繰返し配列の異常伸長が原因とされるトリプレットリピート病の一つで，小脳失調の他，てんかん発作が臨床的な特徴である．メキシコならびに南米からのSCA10家系の報告があるものの本邦からの報告はこれまでにない．今回遺伝子解析にてSCA10と診断し得た親子例の表現型の異同について報告する．【症例】発端者（40才台女性）；34歳頃から歩行が困難となった．その後構音障害が出現し，体幹失調とともに緩徐に進行しているが現在も就労している．頭部MRIにて小脳の萎縮を認めた．38才時複雑部分発作初回発作有り．カルバマゼピンの内服にて再発はみられていない．母（60才台）；35歳頃歩行障害で発症し，その後構音障害出現．55歳頃痙攣発作出現し抗てんかん薬内服開始となった．その後4，5年経過した頃から発作が頻回となり，嚥下障害，認知機能障害も出現した．現在は座位保持も不可能で簡単な問いかけに答えるのみであるが，錐体路徴候，パーキンソニズムを認めていない．頭部CTでは小脳，前頭葉の萎縮を認めた．【結果】サザンブロッティングおよびRepeat Primed PCRにより異常伸長アレルのリピート数を推定したところ，発端者のATTCT配列の繰り返し回数は13/1500，母のそれは18/1500であった．家系内に他に小脳失調，てんかん発作を呈するものはなく，両者においてATTCTの繰返し配列の異常伸長がみられたことからSCA10と診断した．これまで本邦ではSCA10の報告はなく，本邦初の家系と考えられた．【結論】サザンブロッティングで推定されるリピート数は母子の間で差がなく，小脳失調の発症年齢もほぼ同じであり，母性伝達の場合いわゆるanticipationが認められないとする報告と一致した．一方でてんかん発作の初発年齢は20年近く離れており，リピート数と初発年齢の関係は症状毎に異なるものと考えられた．

O-33-2

Atrophy of cerebellum and corpus callosum in different subtypes of spinocerebellar degeneration

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[Objective]To explore a sensitive biomarker for predicting disease progression in patients with neurodegenerative cerebellar ataxia, we correlated the International Cerebellar Ataxia Rating Scale（ICARS）score with MRI-based cerebellar volume and corpus callosum area among different clinical subtypes of spinocerebellar degeneration（SCD）and multiple system atrophy（MSA）. [Methods]We studied 15 CCD, 26 SCA（SCA1: 3, SCA2: 3, SCA3: 5, SCA6: 9, SCA31: 2, SCA unknown type:4）, 24 MSA patients（MSA-C: 21, MSA-P: 3）and 30 normal controls. Patients were followed up to six times for 91 months. Cerebellar volumes and corpus callosum area were measured using TRI/3DVOL software（RATOC System Engineering, Co）. Cerebellar volume was normalized by anteroposterior diameter of cranium（Volume index, Vdx）. [Results] Cross sectional studies in SCD and MSA demonstrated that Vdx were significantly correlated with total score（Ro=.404）, domain I（Ro=.598）and domain II（Ro=.310）of ICARS. No significant correlation was observed in CCA. Mean callosal area in CCA, SCA and MSA were 591.3 ± 131.5, 600.2 ± 102.1, and 675.2 ± 126.6, respectively and significantly different（p = .034, Kruskal-Wallis test）. In longitudinal follow-up study demonstrated that initial atrophy volume in Vdx during 12-24 months significantly correlated with subsequent annual atrophy of cerebellum（r=0.618, p=.000）.[Conclusion]Corpus callosum area is different among CCA,SCA and MSA. Vdx may be a sensitive biomarker for predicting disease progression.

O-33-3

多系統萎縮症における栄養状態とBody mass indexの検討

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【目的】多系統萎縮症（MSA）の病期の進行に伴う栄養状態の変化については，ほとんど検討されていない．本研究では，適切な栄養管理を行うために，各病期の栄養状態とbody mass index（BMI）を検討した．【対象・方法】2001年から2014年までに当科に入院したprobable MSAの135例（男性65例，女性70例）を対象とした．評価項目はADLによる病期（自立/車いす/寝たきり），嚥下障害の有無，摂取カロリー，BMI，血清アルブミン値・総コレステロール値，リンパ球数とした．【結果】自立群/車いす群/寝たきり群はそれぞれ53名，53名，29名であった．嚥下障害の頻度は，病期の進行に伴い増加した（9.4/39.6/79.3%）（p＜0.05）．摂取カロリーも病期の進行に伴い低下し（中央値1800/1600/1500 kcal）（p＜0.05），自立群と車いす群・寝たきり群の間で有意差を認めた．血清アルブミン値は病期の進行に伴い低下し（中央値4.20/3.90/3.45 g/dl）（p＜0.05），自立群と寝たきり群，車いす群と寝たきり群の間で有意差を認めた，総コレステロール値，リンパ球数，BMIに有意差はなかった．【考察・結論】病期の進行に伴う血清アルブミン値の低下は，嚥下障害の出現と摂取カロリーの低下が原因と考えられた．一方，総コレステロール値やリンパ球数は，単独では栄養状態を鋭敏に反映する指標とはならない可能性がある．さらにBMIに変化を認めない点は，摂取カロリーと消費カロリーの減少の程度が同等である可能性が考えられた．以上より，MSAではBMIが保たれていても，嚥下障害に伴う摂取カロリーの減少により低栄養状態を呈しうること，その指標として血清アルブミン値が有効である可能性が示唆された．

O-33-4

痙性対麻痺に対するITB療法の治療効果臨床評価尺度の作成に向けて

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【目的】痙性対麻痺における髄腔内バクロフェン（ITB：intrathecal baclofen）療法導入例は今後も増えていくと考えられる．ITB療法の治療評価に関する報告は過去にも成されているが，標準的に利用されている評価尺度は存在しない．今回，ITB療法の臨床評価尺度の作成へ向け，痙性対麻痺患者におけるITB療法の症状改善効果について検討した．【方法】ITB療法導入後の純粋型痙性対麻痺5例において，両側の股関節，膝関節，足関節，計6カ所の平均Ashworth scale，10メートル歩行における歩様・歩数・歩行時間，自動運動による下肢関節（股関節，膝関節，足関節）可動域の3項目に関する，ITB療法導入前後の2点間比較を行なった．日常生活における自覚的な改善点や，当科で独自に作成したITB両方導入前後の症状自己評価スケールを参考評価項目とした．【結果】痙縮は全例で改善を認め，下肢平均Ashworth scaleは0.68 ± 0.39ポイント低下した．下肢関節可動域は，平均で股関節18 ± 12°，膝関節23.4 ± 23.4°，足関節40.2 ± 34.2°の可動域改善を得た．1例を除き，10メートル歩行の歩数が減り，歩行時間が短縮した．歩数の改善は平均2.1 ± 2.9歩，歩行時間の改善は平均3.4 ± 3.4秒であった．また，痙縮の改善に伴う筋痛や筋痙攣頻度の軽減や，睡眠の質の改善を得た症例もあり，これらの点は症状自己評価スケールに反映されていた．【結論】総じて，全例ともITB療法の有効性が確認され，いずれの評価項目も患者の臨床症状の変化を反映していた．臨床評価尺度の作成にあたっては，痙縮と下肢の可動域，歩様を中心とした客観的な評価項目の他に，患者による自己評価も有用な評価項目となり得ると考えられた．今後，具体的な臨床評価尺度作成に向け，評価の継続，妥当性の検討を行なう．

O-33-5

QAI1, a polyglutamine protein oligomerization inhibitor, exerts disease-modifying therapeutic effect

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[Objective] To identify therapeutic molecules for polyglutamine（polyQ）diseases, which inhibit the misfolding and oligomer/aggregation formation of polyQ proteins. [Methods] Various small chemical compounds known to affect protein folding were screened for their ability to inhibit polyQ aggregation *in vitro* using a turbidimetric aggregation assay. Conformational change of the polyQ protein was assessed by native polyacrylamide gel electrophoresis. *In vivo* effect of the identified compound was analysed in *Drosophila, C. elegans* and two mouse models of polyQ diseases. [Results] We identified PolyQ Aggregation Inhibitor 1（QAI1）as an aggregation inhibitor of polyQ protein. QAI1 is known to cross the blood-brain barrier and has been safely used for the treatment of other human diseases. QAI1 inhibited the toxic β-sheet conformational transition and oligomer formation of the polyQ protein, which are the upstream processes of protein aggregation. *In vivo* effect of QAI1 was confirmed in two invertebrate polyQ models. In addition, oral administration of QAI1 ameliorated the motor impairment and suppressed the neuronal inclusion body formation in spinocerebellar ataxia type 1 knock-in（SCA1-KI）mice as well as spinobulbar muscular atrophy transgenic mice. Furthermore, administration of QAI1 to SCA1-KI mice after their symptom onset ameliorated the motor impairment. [Conclusion] QAI1 is a disease-modifying therapeutic candidate for multiple polyQ diseases. We are currently planning a clinical trial to investigate the efficacy of QAI1 in polyQ disease patients.

O-33-6

Screening for polyglutamine aggregation inhibitors that suppress neurodegeneration in fly models

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[Objective] The polyglutamine（polyQ）diseases, including Huntington's disease and spinocerebellar ataxias, are caused by an expanded polyQ protein, which is prone to form aggregates and eventually accumulate as inclusion bodies in affected neurons. Since its aggregation process is considered to be toxic to the neuronal cells, inhibition of polyQ aggregation would be a promising therapeutic strategy. In this study, we aimed to identify the chemical compounds suppressing the polyQ protein toxicity by inhibiting polyQ aggregation both *in vitro* and *in vivo*. [Methods & Results] First, a high-throughput screening using the turbidimetric assay was performed to search for the chemical compounds inhibiting the polyQ aggregation *in vitro*, and we identified 15 chemical compounds as strong polyQ aggregation inhibitor. Next, to investigate the therapeutic efficacy of these chemical compounds *in vivo*, we administered these chemical compounds orally to the transgenic polyQ disease model flies expressing the truncated form of the mutant MJD protein with an expanded Q78 repeat（MJDtr-Q78 flies）. We found that 8 chemical compounds successfully rescued the compound eye degeneration in the MJDtr-Q78 flies. [Conclusions] Our study demonstrated that polyQ aggregation inhibitors rescue polyQ-induced neurodegeneration, indicating the suppression of polyQ aggregation could be an effective therapeutic strategy for the polyQ diseases. In addition, we emphasize that our screening approach is highly effective for identifying therapeutic candidates from the large chemical compound library.

O-34-1

Effect of repetitive transcranial magnetic stimulation on stroke patients with severe palsy

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【目的】脳卒中の維持期リハビリテーションにおいて，上肢運動機能改善を目的とした反復経頭蓋磁気刺激（rTMS）とリハビリテーションの併用治療が注目されている．本治療は軽度麻痺者が対象となることが多いが，重度麻痺者においても治療効果がみられたとの報告がある．今回，我々は本治療を行った脳卒中患者の中で治療前の随意運動が不能な例における治療効果を後方視的に調査した．【方法】対象は慢性期脳卒中患者40例で，rTMSは非損傷側の一次運動野の手領域に刺激強度は安静時運動閾値90%，刺激頻度1Hz，刺激回数880回，1日2セット，12日間で施行した．リハビリテーションはrTMS後に90分間行った．評価はfugl Meyer Assessment上肢項目（FMA上肢）を使用し，肩関節，手関節，手指それぞれについて治療前後で比較した．手関節と手指は随意運動不能例（FMA0点）と随意運動可能例に分類し，再解析を行った．【結果】全体FMA上肢点数は26.1±16.8点から31.0±17.5点と有意な改善がみられた．各関節については肩関節は17.2±8.1点から20.4±8.2点，手関節が2.2±3.0点から2.6±3.4点と改善がみられたが，手指は5.0±4.9点から5.4±5.1点と有意な改善はみられなかった．手関節と手指での随意運動不能例は手関節において40例中23例，手指は12例であった．これらの随意運動不能例のFMA上肢点数は手関節で0.3±0.9（23例中4例改善，p=0.13）に改善し，手指では0.9±0.9点と有意な改善がみられた（12例中7例改善，p<0.05）【結論】脳卒中慢性期の上肢運動麻痺に対して，低頻度反復経頭蓋磁気刺激とリハビリテーションの併用治療は重度麻痺においても有効な可能性が示唆された．

O-34-2

Effects of rTMS on upper limb hemiparesis and cortical activation changes in post-stroke patients

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【目的】慢性期脳卒中後上肢麻痺患者に対する低頻度rTMS＋集中的作業療法の改善効果と脳機能画像（fMRI）の変化について検討した．【方法】対象は発症から1年以上経過した慢性期脳卒中片麻痺患者30例．方法は非病変側大脳半球運動野の手領域に1Hzの低頻度rTMSを20分間行い，続いて集中的作業療法を1時間行った．これを1セッションの訓練として行い，2週間の入院期間中に合計18セッション施行した．入院時と退院時に上肢機能検査と脳機能画像検査（fMRI）を行った．上肢機能検査は，Fugl-Meyer Assessment（FMA），Wolf Motor Function Test（WMFT），Action Research Arm Test（ARAT），Modified Ashworth Scale（MAS），Motor Activity Log（MAL）を行った．fMRIは，運動課題として麻痺側手指の開閉運動を行った．画像解析にはSPM8を用いた．関心領域を両側のBroadmann 4野・6野に設定し，脳活動の偏り（左右差）の指標であるLaterality Index（LI）を算出した．【結果】上肢機能検査では，FMA，WMFT，ARAT，MAS，MALにおいて治療後に有意な成績の改善が認められた（P<0.05）．fMRIでは，多くの症例において治療前には麻痺手運動時に両側運動野の広範な活動が認められたが，治療後には活動が病変側に収束し，健常者の活動パターンに近づく傾向が認められた．これに合致して，Laterality Index（LI）は治療後に有意な増加が認められた（P<0.05）．LIは，WMFT成績と有意な相関が認められた（r=－0.421，P<0.05）．【結論】低頻度rTMSと集中的作業療法の併用治療は慢性期脳卒中患者の上肢麻痺改善に有効であること，この改善には脳の活動性の変化が関与していることが示唆された．

O-34-3

fNIRS-mediated Neurofeedback combined with mental practice enhances gait recovery after stroke

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Objective:We are conducting a randomized clinical trial to investigate whether functional near infrared spectroscopy mediated neurofeedback system（fNIRS-NFB）targeting the SMA activity combined with mental practice would augment the post-stroke balance recovery.Methods:Subacute stroke patients with subcortical lesions（N = 31, 23 males, Age : 60.1 ± 11.6, 117.0 ± 20.7 days from onset）with written informed consent have participated. In addition to the usual inpatient rehabilitation up to 180min/day, they participated 6 sessions of mental practice with motor imagery of gait and postural related task concurrent with neurofeedback of the SMA activation. Clinical measures including Berg Balance Scale（BBS）, Gait speed, and 3m-Timed Up-and-go test（TUG）are assessed. Subjects are randomly assigned to 2 groups（REAL and SHAM）. Neither patients nor physicians did not recognize which group they were assigned（double-blinded）.Results:Baseline clinical characteristics were comparable between two groups. There was significant interaction between gait and balance measures including BBS and TUG with significant improvement in the REAL group（$F_{2,29}$=7.26, p<0.005 and $F_{2,29}$=3.39, p<0.05, respectively）. Comparing the before and after fNIRS-NFB, only REAL group showed significant increase of gait task related cortical activation in the SMA. There was no side-effects associated with fNIRS-NFB in both groups.Conclusion: This interim analysis comfirmed the feasibility and safety of fNIRS-NFB for the post-stroke patients and suggested augmenting effect on gait and balance recovery.

O-34-4

NIRS-mediated neurofeedback for cerebellar ataxia: potential for augmenting rehabilitative outcome

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Purpose: Degenerative cerebellar ataxia is the progressive and intractable disorder involving the cerebellum and its related brain network. Previous studies showed that supplementary motor area（SMA）may compensate balance impairment caused by impaired cerebellar related functional network. To investigate if SMA facilitation ameliorates balance disorder with degenerative ataxia in a cause-and-effect manner, we used a NIRS-mediated neurofeedback（NF）to modulate neural activity voluntarily with real-time feedback.Methods: We recruited 20 patients with degenerative ataxia（11 men, age 58.7 ± 11.8, disease duration 7.5 ± 4.9 years）. All patients underwent 4 week intensive rehabilitation. In the first 2 weeks, they participated in 6 sessions of NIRS-NF targeting SMA activity combined with motor imagination of gait and postural-related task. Clinical measures including Scale for the assessment and rating for ataxia（SARA）, gait speed, and Timed-up & go test（TUG）were assessed before, immediately after, and 2 weeks after feedback. Patients were randomly assigned to Real-FB（feedback of their own brain activity）or Sham-FB（feedback of other subjects' data）in a double-blind manner.Results: After 4 weeks of intensive rehabilitation, both groups improved their clinical status significantly. Repeated measures ANOVA revealed significant interaction between group × time in TUG（repeated-measures ANOVA, $F_{2,36}$ = 3.4, p < 0.05）.Conclusions: NIRS-NF combined with rehabilitation might improve of balance disorder with degenerative ataxia.

O-34-5

Effect of electrical stimulation of the suprahyoid muscles by pushing a bar-type electrode device

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[Objective] The purpose of this study was to investigate movement of the hyoid bone during electrical stimulation of the suprahyoid muscles by pushing an electrode to muscles using a bar-type device and comparing the movements while swallowing liquids.[Methods] Six volunteers without dysphagia participated. To reduce skin electrical impedance, the electrode was pushed to the muscles using a bar-type electrode device. Volunteers received surface electrical stimulation at midpoints between the chin and the hyoid by pushing the electrode device, which was recorded videofluoroscopically. The volunteers swallowed 10 ml of diluted barium liquid, and movements were recorded again. Displacements of the hyoid were calculated. Movements caused by surface stimulation were compared to movements while swallowing liquids. [Results] Elevation and anterior excursion of the hyoid by electrical stimulation were 65% and 85% of those of the excursion while swallowing liquids, respectively. Elevation of the hyoid was significantly less than the elevation that occurred while swallowing liquids（p < 0.05）, whereas anterior excursion of the hyoid was similar to the excursion that occurred while swallowing liquids. [Conclusions] This study suggests that surface electrical stimulation of suprahyoid muscles by pushing an electrode using a bar-type device causes elevation and anterior excursion of the hyoid bone, as is observed during normal physiologic swallowing. To determine the effect of electrical stimulation using a bar-type electrode device in dysphagia patients, further studies are required.

O-35-1

レスパイト入院に関する神経難病患者へのアンケート調査

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【目的】全国の神経難病患者からレスパイト入院に関するアンケート調査を行い，レスパイト入院の問題点を抽出した．【対象と方法】レスパイト入院実態調査に協力の得られた病院や訪問看護事業所で担当している在宅難病療養者に調査の紹介と調査票の配布から222例の回答を得た．調査票は疾患名，気管切開や人工呼吸器の有無，利用しているサービス，レスパイト入院の有無，回数，日数，レスパイト中のリハビリやコミュニケーション等を問い，自由記載も求めた．【結果】222例中113例がALSで，呼吸器装着120例，気管切開101例，TLSが36例．60-70代の患者が3分の2を占めた．レスパイト入院は76%が経験し，14日以内がほとんどを占めた．入院中のリハビリは75%が受けており，コミュニケーションは，文字盤を利用している患者の多くは文字盤を利用するが，意思伝達装置は47例中13例が使用していなかった．入院前にコミュニケーション能力の調査があると答えたのは39例のみで，入院中のコミュニケーション支援人材の利用は10例にとどまっていた．レスパイト経験のある患者169人中167人がレスパイト入院は役に立つ，あるいはどちらかというと役に立つと回答した．レスパイトが困難な理由として，「受け入れ先がない」が一番に挙げられた．一方経験のない患者がレスパイト困難と考える理由は「患者の拒否」であった．【考察】レスパイト入院への患者側の要望は高いことが判明したが，自由記載では介護者の苦悩，入院中の身体介護とコミュニケーション不足の指摘も多かった．神経難病の特殊な状況を理解し対応できる病院が各地域とも限られており，今後どのような施設にレスパイト入院を求めていくのかは課題であると考えられた．また，レスパイト中のヘルパーやコミュニケーション支援人材の利用は少なく，これらのマニュアル化なども必要と考えられた．

O-35-2
神経難病患者レスパイト入院に関する全国調査（二次調査報告）

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目的：重症神経難病患者・介護者にとってレスパイト入院は有用である．2014年一次調査として，全国の日本神経学会　教育施設・准教育施設・教育関連施設（以下医療機関）および全国訪問看護事業団，難病看護学会関係施設の総計5082施設に神経難病患者のレスパイト入院に関する全国アンケート調査を施行した．それぞれ57.3%，27.6%，35.8%の施設でレスパイト入院を施行との結果を受け，二次調査を実施した結果を解析．方法：一次調査で協力同意を得た医療機関および訪問看護ステーションからの二次調査票回答を集計．結果：医療機関：送付 341件，回答178件，訪問看護：送付574件，回答307件．医療機関：レスパイト入院受け入れ可能：118件（66%）．対象患者はALSが225件と最も多く，レスパイト入院受け入れ期間は，8－14日（132件）で，受け入れ病床は一般病床が最も多かった．ALSのTV（285件）やNIPPV（75件）の受け入れも合計360件ほど見られた．また，80%程度の施設でレスパイト入院中のリハビリテーションが施行されていた．レスパイト入院受け入れが困難な理由としては，看護体制の問題が大きかった．訪問看護：レスパイト入院を依頼している　206/301件　依頼件数　5名以下が175件と最多，疾患はALSが最多（135件），ALSの呼吸器装着78件であった．レスパイト先は，病院以外にも確保している施設は多かった．レスパイトケアの依頼が困難な理由としては，本人の理解が得られない場合が多かった．結論：レスパイト入院は都市部を中心に全国的に普及しており，利点・問題点は共通するものがある．医療機関と訪問看護では利点・問題点の違いも浮き彫りにされた．

O-35-3
神経疾患患者のPEGで生ずる倫理的側面の課題と対応ー造設後のQOL及び尊厳の検討

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【目的】神経疾患により嚥下障害を認め，物が飲み込めなくなった時，栄養補給の選択肢として胃瘻PEGがあげられる．その運用とICの進め方についてはマニュアル化され，多くの神経内科医が実施している．しかし，PEGを受けた患者のQOLと尊厳についてはリハビリテーションや介護の現場で深刻化の傾向にある．Murphy(2000)や Bernat(2001)では，PEGは宗教や心理的要因も関わる事実が指摘され，本報告の医療専門職養成校の実習後レポートでも「倫理的配慮が必要と思われる事」の最上位にPEGを認める．よって本発表では，これら実習後レポートを分析すると同時に，PEG後の患者の抱える課題について生命倫理の視点から分析及び検証を試み，今後の対応策を考察する．**【方法】**①実習後レポートは，3か月間実習の約一か月後（2014年12月）に医療倫理学講義の課題として80分の授業時間内に作成された．A4版一枚表に課題を記し裏面に名前を記した．分析時は表面のみコピーしプライバシーに配慮した．分析は基本的にKJ法に従い，記載された内容を類別し集計した．②PEGと記したレポートの内容を分析し，患者の病状・ADL，医療従事者や主治医と当該患者の関係，倫理的配慮が必要と感じる理由などを抽出し，Beauchamp & Childress（1989）に基づき倫理的分析を行い倫理的課題の明確化を試みた**【結果】**①実習後レポートで倫理的配慮が必要と感じた事象は11個認められ，42名中6名がPEGをあげ最上位であった．②PEGをあげる理由として「食の楽しみの喪失」「残存機能を活かす機会の減少」「自己決定に基づくか否か不透明」「通常の食べ方から遠のくことで生ずる自己喪失感」などがあげられた．これらに対し倫理的分析を行った結果，普遍的倫理のひとつ「無害性の視点」から求められる対応，即ち「患者らにPEGによって生ずる不都合や不利益を予測し，出来るだけ回避する対応」の必要性が示唆された．

O-35-4
長期TPPV管理下の神経筋難病患者における特注スピーキングカニューレの検討

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【目的】神経筋患者は呼吸筋麻痺により気管切開を伴う人工呼吸管理（TPPV）に至ることがあり，本邦ではTPPV導入率が増加傾向にあるが，TPPVに移行すると患者は自身の声を利用したコミュニケーションを行うことができなくなる．今回，当院に長期療養中の患者において，特注スピーキングカニューレを用いて言語コミュニケーションを試みた神経筋疾患3名について報告する．【方法】本研究は当院倫理委員会にて承認を得て行った．症例1：Duchenne型進行性筋ジストロフィー（DMD） 22歳男性．症例2: 筋萎縮性側索硬化症 68歳男性．症例3: DMD 28歳男性．いずれの症例も巨舌ないし舌萎縮が軽度の症例であり，既にTPPVを導入されていた．カニューレに2箇所の小孔を開孔した特注カニューレを用いて，TPPVにおける発声を促した．会話の状況や合併症の有無について観察した．【結果】人工呼吸器ついては，平均換気量保持（AVAPS）機能とリーク補正機能を有する機種を使用した症例2および症例3で発声可能となり，会話可能となった．特注スピーキングカニューレは4週間連続使用可能であり，呼吸器の設定の変更も必要としなかった．発声の機序としては，吸気の声帯へのリークによるものと考えられた．最長10ヶ月を経過したが，使用中の呼吸苦の訴えや呼吸器関連肺炎などの合併症はなかった．AVAPS機能を持たない呼吸器を使用した症例1では発声は可能であったが，換気量を維持することが困難であったため使用を中止した．【結論】一部の長期TPPV管理下の神経筋難病患者において，開孔した特注スピーキングカニューレを使用することで特別の管理を必要としなくとも発声・会話が可能となり，言語コミュニケーションに関するQOLの向上が期待できる．

O-35-5
在宅人工呼吸器の遠隔監視，アラーム通報の試み

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【目的】人工呼吸器を装着した神経難病患者の在宅療養は，患者・家族が不安を抱えながらの生活である．これは，人工呼吸器が生命維持に関わる機器であり，機器の異常やアラーム発生時に迅速な対応が求められることにある．ICTを利用して機器の遠隔監視やアラーム通報が可能となれば対応が的確かつ迅速になり，安全と安心を得られることから，在宅用人工呼吸器の遠隔監視について試みた．【方法】在宅に設置した人工呼吸器チェスト社VIVO50を用い，USB端子から出力したデータをデバイスサーバとVPNネットワークを介して病院内に設置したPCとリモートデスクトップを用いたタブレット端末上に表示させた．また，監視用モニターを用いて状態観察を同時に行った．さらに，機種に寄らないシステムの開発を目的として，オリジン医科工業社製の人工呼吸器Puppy-XのRS232Cポートから専用ルータを介して専用のクラウドサーバへの伝送の構築と閲覧・通報ソフトの開発を行った．【結果】VIVO50のUSBポートから出力したデータをデバイスサーバ，VPNネットワーク，Vivo専用閲覧ソフトを用いて遠隔に設置した電子端末でリアルタイム閲覧が可能であった．また，人工呼吸器Puppy-Xに専用ルータを付加し，専用クラウドサーバへのデータの伝送，機器稼働状況のリアルタイム表示，アラーム通報も可能にした．【結論】在宅用人工呼吸器のリアルタイムの遠隔監視，アラーム通報は可能であり，実現すれば在宅療養患者，介護者，支援者に安全と安心を与えることのできるシステムと考えられる．今後は安全性試験，実証実験に加え，運用ガイドラインの策定が必要である．

O-35-6
進行期の神経難病患者の身体合併症入院とその原因

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【目的】　当院神経難病センターは，神経難病を初診から看取りまで，在宅療養＋定期的レスパイト入院を中心に，地域で一貫したチーム医療を提供している．進行期の神経難病は，原疾患の進行に加え，身体合併症の併発により，ADLレベルが低下し，予後に影響することもよく経験される．今回，在宅の神経難病患者の身体合併症入院の実態をまとめた．【方法】2010-2014年の5年間に，筋萎縮性側索硬化症（ALS），多系統萎縮症（MSA），パーキンソン病（PD）関連疾患の患者の，原疾患の診断，治療，レスパイト入院以外の，身体合併症の入院とその原因をまとめた．【結果】ALSは，全体で85-107回（14-21人）/年の入院があり，合併症入院は計18回（ALS入院の4.2%），年齢69±10歳で，内訳は肺炎67%，その他33%（5疾患）であった．同時期のALSの死亡は，呼吸不全12例，肺炎2例，その他1例．MSAは，全体で82-125回（20-24人）/年の入院があり，合併症入院は56回（MSA入院の10.3%），年齢64±9歳で，肺炎55%，尿路感染症20%，胃腸炎9%，その他16%（8疾患）であった．死亡は，肺炎4例，その他2例．PDは，全体で75-127回（28-37人）/年の入院があり，合併症入院は126回（PD入院の24.5%），年齢79±9歳で，肺炎49%，尿路感染症10%，脳卒中7%，心不全5%，骨折4%，その他25%（意識障害，イレウス，熱中症，てんかん，など23疾患）で，ほぼ全例がYahr 3-5度であった．死亡は，肺炎5例，心不全2例，その他4例．他科入院は，骨折等で整形外科4例（PD），悪性腫瘍で外科2例（ALS, PD）があった．【結論】ALSの身体合併症入院は肺炎が主で比較的少なく，死亡原因は現疾患による呼吸不全が大半を占めた．MSAの合併症入院は多く，肺炎（死亡原因として最多）と尿路感染症が主であった．PDは，高齢であり，合併症入院はさらに多く，肺炎（死亡原因として最多）と尿路感染症が多かったが，その他にも多岐に渡る合併症が見られるので注意が必要である．

O-36-1
リアルタイム脳機能モニタリングを目指してー新たな脳波ヘッドセットの開発

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【目的】非痙攣性てんかん重積状態（NCSE）は，非常に高頻度で，多少とも治療可能であるにもかかわらず（当科連続入院例の5.1%），早期診断の困難性により多くの例は見逃されている．われわれは，脳神経救急・集中治療の質の向上を目指して，意識レベル障害，意識変容，心肺蘇生，発作性神経症候等の治療中にも測定可能な脳波評価システムを開発中であるが，本報告では新たな脳波ヘッドセット開発の進捗状況について報告する．【方法】さまざまな処置を行う際にその妨げとならずかつ有効な脳波を測定するために，次の4課題をクリアするべく研究開発を行った．1）毛髪上から装着できて一定時間使用可能な非侵襲的な新しい電極の開発，2）モンタージュ省略，3）ブルートゥース導入によるワイアレスな装置，4）一定時間記録できる内部メモリ．【結果】電極開発は，従前より用いられていた皿電極用のジェルの素材を大幅に変更し，さまざまな候補素材から電気抵抗が少なく導電性に優れ，かつ一定時間継続使用できる素材を確定した．皿電極の形状も大幅に変更し，独自形状の電極を開発した．ファントムによる計測でも，臨床上，問題無いことを確認した．モンタージュ省略により脳波計測システムのヘッドセットは小型となったが，これにブルートゥースによるワイアレス化と内部メモリ，バッテリーを組込んだ新しいヘッドセットを開発・設計，試作した．【結論】完成したヘッドセットは従前の医療現場における医療機器の規制の範疇で動作することを確認し，実用化に向けた段階に至っている．本報告では，この新しい脳波計測システムの現状と今後の課題を呈示する．

O-36-2

MRI陰性てんかんの診断におけるMRI postprocessingの有用性の検証

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【目的】部分てんかんの診断・治療において，焦点部位と病理学的背景の同定は非常に重要であるが，MRIで病変が見えない「MRI陰性てんかん」ではしばしば困難である．この問題を克服するため，近年MRI postprocessingによる微細な構造異常の検出法が開発されている．本研究では代表的な2つの手法を併用し，その臨床的有用性を検証した．【方法】MRI陰性部分てんかん患者の連続例20名（15～44歳）を対象とした．3テスラ3D-T1強調画像を用いて後方視的に以下の解析を行った．解析1：画像解析ソフトfreesurferを用いて皮質厚と灰白質・白質コントラスト（灰白質・白質境界に隣接する灰白質と白質の信号比）を算出し，健常対象群30名と統計学的に比較した．解析2：灰白質・白質境界に近い信号値の脳領域を強調するjunction image（Huppertz 2005）を作成して健常対照群と比較し，局所的異常が同定されれば，その情報をもとに，改めてT1強調画像を詳細に視察した．解析1は限局性皮質形成異常（FCD），解析2はFCD及び異所性灰白質に対して鋭敏な手法である．【結果】20名中3名で以下の構造異常が同定された．症例1では解析1において，左前頭葉の一部で灰白質・白質コントラストが有意に低下しており，FCDが示唆された．同部位は発作症状，脳波所見から推定された焦点部位と良く合致した．症例2では解析2において，皮質下白質の帯状の異常が判明し，T1強調画像の再検討により，軽度の皮質下帯状異所性灰白質と考えられた．症例3では同様に解析2によって左側頭葉の皮質下白質に微細な構造物が同定され，同部位は脳磁図で推定された焦点部位と良く合致した．症例2，3の構造異常はいずれも当初の読影では指摘されていなかった．【結論】MRI postprocessingはMRI陰性てんかんの診断・治療方針決定において，付加的価値があると考えられた．また，今回用いた2つの手法は互いに相補的であることが示唆された．

O-36-3

てんかん発作で救急外来を受診した成人患者における予後決定因子の検討

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【目的】てんかんの発作で救急外来を受診した患者における，入院期間の延長，退院時予後の増悪にかかわる因子を検討した．【方法】てんかんの発作で救急外来を受診した210例（男116例，女94例．年齢47～102歳，平均74±11歳）を検討．入院期間が14日以上，退院時のm-Rankin scaleが1以上増悪する因子として，年齢，性別，重積の有無，来院時の血液ガスpH，施設入所の有無，入院時の合併症の有無を多変量解析で検討した．【結果】てんかんのタイプは，部分てんかん（全般化含む）195例，全般てんかん8例，不明7例であった．入院時の合併症は39例に認められ，内訳は脳梗塞12例，脳出血7例，肺炎7例，脳炎3例などであった．入院期間が14日以上となる因子は，年齢（オッズ比 1.06，95％CI 1.002～1.136，p=0.04）施設入所（オッズ比 5.36, 95％CI 1.13～2.68, p=0.03），合併症の有無（オッズ比 245.1，95％CI 1.67～4.38，p＜0.0001）であった．退院時のm-Rankin scaleが1以上悪化した因子は，合併症の有無（オッズ比 15.10，95％CI 1.71～3.16，p=0.0002）であった．入院時の血液ガスpHと重積の有無は入院期間や予後に影響を与えなかった．【結論】てんかん発作で救急外来を受診した患者は，入院時の合併症の有無が予後を決定することが示唆された．

O-36-4

自己免疫機序が関与するてんかん症候群の診断アルゴリズム構築の試み

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【目的】自己免疫機序の関与するてんかん症候群の存在が示唆されているが，その診断において特異的な検査は確立していない．今回我々はToledanoら(2014)の治療プロトコルを参考に感度と特異度を考慮した診断アルゴリズムを作成し，それを用いて分類することで診断に寄与できるかを検討した．【方法】2012年1月以降にてんかん発作あるいはその疑いで当院神経内科を受診し，関連する診療情報の組み合わせから(治療抵抗性，脳MRI異常所見，髄液異常所見，FDG-PETでの代謝亢進部位の存在など)自己免疫機序の関与を疑った111例について検討した．そのうち，自己免疫以外に明確な原因が存在せず，また抗VGKC複合体抗体，抗GAD抗体，抗NMDA受容体抗体のいずれかを測定した70例について，アルゴリズムに従い後方視的に分類した．アルゴリズムでは，難治性でかつ急性あるいは亜急性の経過か，そうでなくても特定の臨床像を満たす群で臨床検査を追加検討し，それ以外はF群とした．それらを満たした群のうち，抗神経抗体陽性例をA群とした．抗体陰性例では，髄液異常所見，脳MRI異常所見，FDG-PETでの代謝亢進部位の有無を検討し，3項目とも満たす群をB群，2項目のものをC群，1項目のみをD群，いずれも満たさないものをE群とした．【結果】70例のうち女性は35例(50％)，発症年齢の中央値は54歳(範囲は9-74歳)であった．抗体陽性例は15例(21％)で，A群は11例(16％)であった．その他B群が2例(3％)，C群7例(10％)，D群10例(14％)，E群8例(11％)であった．A群とB-E群(計27例)を比較すると，A群のうち2項目以上を満たすものは7例(64％)で，B,C群の9例(B-E群の33％)より多い傾向があり，2項目以上満たすとより診断に近づくと思われた．【結論】広い臨床的疑い例から上記アルゴリズムが診断の助けになる可能性が示唆された．経過分析，今後症例の蓄積と前方視的な検討を重ね，臨床的に有用な診断アルゴリズムの構築が期待される．

O-36-5

良性成人型家族性ミオクローヌスてんかんにおけるてんかん性放電の睡眠による変容

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【目的】てんかんでは睡眠時にてんかん性放電が増加することが多いが，良性成人型家族性ミオクローヌスてんかん(BAFME)における睡眠の皮質興奮性に与える影響を明らかにする．【対象・方法】①BAFME12名31件の脳波記録を解析対象とし，睡眠時・覚醒時のてんかん性放電の態様を比較した．睡眠もしくは覚醒脳波が記録全体の10％以下(6記録)，てんかん性放電が5回以下(18記録)，アーチファクトが多い(1記録)を除外し，最終的に5名(女性5名，平均年齢：49.6±20.3歳)の6脳波記録を解析した．②睡眠時無呼吸合併のためポリソムノグラフィーを行ったBAFME 1名(59歳女性)における脳波記録も解析した．【結 果】①脳波は覚醒(66.6％)と軽睡眠(第1，2期: 33.4％)に分類され，記録時間当たりのてんかん性放電は覚醒時(1.3±1.2回/分)が軽睡眠時(0.02±0.04回/分)に比べ頻度が高かった(P＜0.05)．②覚醒時に比べて，軽睡眠・徐波睡眠・REM睡眠時いずれでも記録時間当たりのてんかん性放電は減少していた．この傾向は睡眠時無呼吸の治療導入前後でも変わらなかった．【結論】検索できたBAFMEではてんかん性放電は睡眠時に減少した．Unverricht-Lundborg病でも類似の傾向を認めることがあり，皮質興奮性に関して両者が類似した病態を有する可能性を示唆した．

O-36-6

長時間ビデオ脳波モニターにおける抗てんかん薬の漸減・中止状況と発作出現時期の検討

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【目的】長時間ビデオ脳波モニタリングはてんかん発作型の診断やてんかん手術の術前検査などに利用される重要な検査である．数日間のモニタリング期間中に発作間欠期の脳波異常，発作症候および発作時脳波異常を捕捉するために，通常は抗てんかん薬を減量もしくは中止するが，発作頻度が多い場合や重積を生じる可能性がある場合は漸減し，発作が稀であると予想される場合は最初から中止する．今回，当院でモニタリングを行い，てんかん発作が捕捉された患者を対象に，抗てんかん薬の漸減・中止状況と発作の出現時期について検証した．【方法】2012年1月から2015年1月までに当院で長時間ビデオ脳波モニタリングを施行し，少なくとも1回は発作を認めた48名(32.1±11.7歳，男性23名，女性25名)を対象とした．検査前の抗てんかん薬の内服状況，検査時の薬の減量・中止状況を初回の発作が捕捉された日まで後ろ向きに検証した．【結果】検査前の平均投薬数は2.6±0.9剤，発作頻度の内訳は，複数回/週11名，複数回/月20名，複数回/年13名，1回/複数年4名であった．初回の発作が捕捉されるまでに要した日数は2.2±1.2日（1～7日）であり，複数回/週群は他群と比べ短かった．初日から薬を全て中止した症例は16/48（33％）であり，最終的に薬を全て中止した症例は34/48（71％）であった．初日に薬を全て中止した群と一部中止群で比較し，初回発作がみられた日における全発作数(N=16 vs 32, p=0.69)ならびに二次性全般化発作数(N=16 vs 32, p=0.99)に有意差はみられなかった．一方で，最終的に薬を全て中止した群は一部中止群と比較し，有意に二次性全般化発作数が多かった（N=34 vs 14, p=0.05）．【結論】検査前の発作頻度を参考に薬の漸減あるいは中止を行うことにより，平均して2.2日で初回の発作が出現した．薬を全て中止した群は一部中止群と比較して二次性全般化発作数が多く，安全性に特に留意する必要があることが示唆された．

O-37-1

Significance of Development and Reversion of Collaterals in outcome after Intravenous Thrombolysis

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【背景と目的】急性期脳梗塞に対する再開通療法において，側副血行路はPenumbra及びClotへ作用し，側副血行路発達と血栓溶解療法後の予後良好は関連する．我々は急性期脳梗塞において側副血行路が動的に変化することに着目して血栓溶解療法後の短期予後と長期予後に与える影響について検討した．**【対象と方法】**2007年から2012年までに2施設を受診した脳梗塞患者のうち，MRIにて中大脳動脈閉塞と診断，経静脈的血栓溶解療法を施行し治療後MRIを撮影した症例を対象とし，臨床情報，画像情報を収集した．MRIで評価可能な側副血行路サインであるMRAにおけるPCA laterality sign(PCAL)とFLAIR画像でのHyperintense vesselsを組み合わせ，側副血行路の動的な変化(Collateral Development and Collateral Reversion)と血栓溶解療法後の短期予後，長期予後の関連を後向きに解析した．**【結果】**48症例が選択基準に合致した．Collateral Developmentは短期予後良好と有意に関連していた(15/22 vs. 9/26, *P = 0.042*)．他因子で調整した多変量解析ではCollateral Developmentは短期予後良好の独立した予測因子であった（OR, 4.82; 95％ CI, 1.34 -19.98; *P = .015*）．Collateral Reversionは血管再開通と有意に関連し，多変量解析ではCollateral Reversionは長期予後良好を予測する独立した因子であった（OR, 5.07; 95％ CI, 1.38 -22.09; *P = .013*）．Collateral Reversionを有する症例では皮質領域の脳梗塞が有意に縮小していた(*P = 0.021*)．**【結語】**急性期脳梗塞において側副血行路は動的に変化し，治療反応性，予後に影響を与えると考えられた．側副血行の動的変化を促進させることは脳梗塞の新たな治療になりうると考える．

O-37-2

Analysis of recurrent stroke volume between warfarin and NOAC for post stroke prevention

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【目的】脳梗塞二次予防で新規抗凝固薬NOAC抗凝固薬を投与している84例について後ろ向きに使用状況および脳梗塞イベント再発を調査した．【方法】対象は2011年10月から4年間に当科で急性期脳梗塞治療を受け二次予防にNOACを導入された84例（平均年齢：80±9歳）．ワーファリンあるいはNOAC服用中の脳梗塞再発を比較した．再発症例においてワーファリンとNOACで病巣体積に差があるか計測ソフトMRIcronを用いて比較した．【結果】初発脳梗塞後にワーファリンを開始されたが，NOACに変更されたのは27例であった．27例のうち7例（25%）は脳梗塞を再発後にNOACに変更となった．NOACで二次予防開始になったのは57例でそのうち10例（17%）が再発し，3名が増量，7名が他のNOACへ変更された．ワーファリンで再発時のPT-INRは平均1.50で，ワーファリン治療域を下回っていた．ワーファリンとNOACで再発率に有意差はなかった．NOAC投与中に脳出血をきたした症例，および脳梗塞再発でtPA投与に至った症例は3剤ともなかった．再発17例において再発脳卒中体積はワーファリン群（7例）で27.4cm^3，NOAC群（10例）で3.3cm^{3}と有意にNOAC再発時の梗塞巣の体積は少なかった（p<0.01）．【結論】二次予防の抗凝固療法において脳卒中が再発した場合，ワーファリンに比較してNOACの病巣体積は少なくてすむ可能性がある．

O-37-3

Hematoma volumes and severity of spontaneous intracerebral hemorrhage in the patients with NOACs

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【目的】非ビタミンK阻害経口抗凝固薬（NOACs）の頭蓋内出血発症率は，ワルファリンより低いことがランダム化比較試験で示されている．NOACs療法中とワルファリン療法中の脳出血における，発症時の重症度や血腫量や臨床経過を比較検討した．【方法】2011年1月から2015年10月までに当院脳血管センターに急性脳出血で入院し頭部CTを撮像された連続372症例中，発症24時間以内に搬送され，ワルファリンまたはNOACsを内服中に発症した43症例（平均年齢72.5±11.9歳，男性74.0%）を対象とした．血腫量は5mm厚スライスで撮影したCTでABC/2法を用いて計測した．また，入院後血腫量の1.4倍以上の増大，外科的治療施行，もしくは死亡を経過不良群と定義した．【結果】対象43症例の内訳はワルファリン内服例が37例，NOAC6例（リバーロキサバン5例とアピキサバン1例）であった．来院時のNIHSSはワルファリン群（12，IQR: 5-22）がNOACs群（7，IQR: 1-12）より重症度が高い傾向であった（p=0.09）．入院時血腫量は，ワルファリン内服群（24.1ml，IQR: 7.4-72.4）がNOACs群（3.0ml，IQR:0.7-11.0）より有意に大きかった（p=0.01）．ワルファリン群では29例（78.4%）で第Ⅸ因子複合体による是正処置を行った．経過不良群はワルファリン群とNOACs群で有意な差異はなかった（62.2% vs. 33.3%，p=0.19）．【結論】NOACs療法中の脳出血は，ワルファリン療法中と比較して，発症時の重症度が低い傾向にあり，血腫量が小さい．両群間の経過不良に差異がなかったのはワルファリン群の急性是正処置の関与が示唆される．

O-37-4

Rehabilitation after Stroke from Post-Acute to Longterm: A Population-based Study in Taiwan

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Purpose: To examine the potential dose-dependent effects of rehabilitation services on reducing morbidity and mortality after stroke in a population sampling data.***Methods:*** By a retrospective cohort study from claims data of Taiwan's National Health Insurance program, acute stroke hospitalized with ICD-9-CM codes 430 to 437 between 2004 and 2005 were extracted and followed-up until death or end of 2007. Main outcome events (OEs): vascular readmissions/all-cause mortality (VE), all-cause readmissions/mortality (OE1), and all-cause mortality (OE2).***Results:*** 4,594 first-ever acute stroke patients survived initial hospitalization with mean age 66.7 years and 56.7% male were observed for 32.2 months. Rehabilitation utilization was 46% in total from 20% for TIA to 59% for ICH patients. VE, OE1, and OE2 were identified in 36.4%, 79.6% and 17.7% of patients, respectively. High-dose rehabilitation was associated with reduction in VE (HR 0.68, 0.58-0.79), OE1 (HR 0.79, 0.71-0.88), and OE2 (HR 0.56, 0.44-0.71). Low-dose rehabilitation was associated with lower risk of VE (HR 0.77, 0.68-0.87) and OE1 (HR 0.77, 0.71-0.84), but not OE2 (HR 0.91, 0.77-1.07). VE, OE1 and OE2 were reduced in the inpatient plus outpatient group and the outpatient group, but not the inpatient group. The benefits seemed applicable to age groups, sex, severities and comorbidities, but not hemorrhagic stroke.***Conclusion:*** This study suggested a dose-dependent effect of rehabilitation on reducing subsequent risks of vascular events, all-cause readmissions/ mortality, and mortality after stroke.

O-37-5

Effects of yokukansan on NO, OH- metabolism during cerebral ischemia and reperfusion in mice

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Objective: It is suggested that herbal medicine yokukansan (TJ-54) may affect serotonergic and glutamatergic neuron. The purpose of this study is to investigate the effect of TJ-54 on the nitric oxide production and hydroxyl radical metabolism during cerebral ischemia and reperfusion in mice. **Methods:** C57BL/6 [n=13] were used. TJ-54 300 mg/kg/day was given in 5 mice for ten days, and eight mice were used as control. Both NO and hydroxyl radical metabolism were continuously monitored by *in vivo* microdialysis. Microdialysis probes were inserted into the bilateral striatum. The *in vivo* salicylate trapping method was applied for monitoring hydroxyl radical formation via 2,3-DHBA, and 2,5-DHBA. Forebrain cerebral ischemia was produced by occlusion of both common carotid arteries for 10 minutes. Levels of NO metabolites, nitrite (NO_2^-) and nitrate (NO_3^-), in the dialysate were determined using the Griess reaction. **Results:** 1) Blood pressure; There were no significant differences between the groups. 2) NO_2^-; TJ-54 group (52.2 ± 13.5) showed significantly lower than that of the control group (94.6 ± 21.7) 30 minutes after reperfusion ($p<0.05$). 3) NO_3^-; There were no significant differences between the groups. 4) 2,3-DHBA; There were no significant differences between the groups. 5) 2,5-DHBA; TJ-54 group (18.1 ± 8.53) showed significantly lower than that of the control group (23.0 ± 9.47) during ischemia. ($p<0.05$). **Conclusion:** These *in vivo* data suggest that TJ-54 effect on hydroxyl radical metabolites in mice, and may have neuroprotective effect against cerebral ischemic injury.

O-37-6

A novel partial agonist-like RANKL peptide inhibiting TLR-induced inflammation in ischemic brain

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[Objective] RANKL/its receptor (RANK) signal was reported as an inhibitor for inflammatory cytokines from activated microglia/macrophages in ischemic brain, whereas augmentation of RANKL/RANK signal also accelerate osteoclast differentiation. To overcome the problem, we designed the RANKL-based peptides which suppressed TLR2 and 4-mediated cytokines without activating osteoclast differentiation.[Methods] Several candidate peptides were designed as; MHP1 and 13 including part of β D, DE loop, β E, and part of EF loop; MHP3 and 4 including CD loop, DE loop, and β D. The effectiveness was examined in MG6 cells (microglia), RAW 246.7 cells (macrophage), primary neuron-glia mixed culture, and tMCAO model in mice.[Results] Treatment of MHP1 was effective in inhibition of LPS-induced microglia activation and MHP13 was less effective. MHP3 and MHP4 did not show any effects. The co-treatment of MHP1 also attenuated the LPS-induced cell death and cytokine secretion in primary neuron-glia mixed culture cells. The inhibitory effects of MHP1 was dependent on RANK which was confirmed by knockdown experiment. In mice stroke model, administered MHP1 (i.c.v.) reduced infarct volume with reduced activation of microglia and macrophages. Importantly, MHP1 did not stimulate the osteoclastic differentiation but inhibit RANKL-induced osteoclastic differentiation.[Conclusions] MHP1, a partial agonistic peptide of RANKL, lacked the action of osteoclast differentiation, but attenuated the TLR2/4-induced cytokine via RANK which might be a promising tool for ischemic brain.

O-38-1

The SMN gene copy number states in Japanese ALS patients

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[Objective] SMN protein has important roles in the pathogenesis of motor neuron disease. The decrease of the amount of SMN proteins causes spinal muscular atrophy (SMA). The amount is regulated by the two homologous genes; SMN1 and SMN2, and mainly expressed by SMN1. A small amount of SMN protein is expressed by SMN2. Deletion of SMN1 causes SMA, and the SMN2 copy number states (CNS) modulates the phenotype. The association between the SMN CNS and amyotrophic lateral sclerosis (ALS) has been investigated. Lee showed the association of SMN2 deletion among ALS in Korea (Lee. et al. Yonsei Med J. 2012). But the effects vary among different countries (Wang. et al. J Neurol Sci. 2014). Indeed, there are the ethnic differences of SMN CNS in normal population. The investigation in different countries is important to confirm the association between SMN CNS and ALS. Here we investigated the SMN CNS in control and sporadic ALS patients in Japan. [Methods] We used TaqMan droplet digital PCR (ddPCR) method using QX200 (Bio-Rad) to determine SMN1 and SMN2 CNS in 447 Japanese ALS patients and 299 controls from JaCALS samples, which is the ALS gene bank in Japan. Primer and TaqMan probe sequence were referred as the previous report (Zhong. et al. Lab Chip. 2011). [Results] The deletion of SMN2 genes increases the risk of developing ALS significantly (Odds ratio 1.43, 95% CI 1.06-1.93, p=0.02). [Conclusion] The deletion of SMN2 gene affects the risk of developing ALS in Japan, like Korea. The result indicates there might be similar genetic risk between SMN2 CNS and ALS in Asia.

O-38-2

Neuronal toxicity of TDP-43 is associated with the dysfunction of ribosomal proteins in axons

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[Objective] Mislocalization and deposition of an RNA-binding protein TDP-43 is a hallmark in neurons of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We hypothesized that the failure of axonal mRNA transport by TDP-43 is linked to the pathogenesis of ALS/FTLD, and identified mRNA of ribosomal proteins as targets of the transport by TDP-43. To know the association between the function of ribosomal proteins and neurodegeneration in ALS/FTLD, we aimed to analyze the expression and protective role of ribosomal proteins in relation to neuronal toxicity of TDP-43 *in vitro* and *in vivo*. [Methods] The effects of overexpression of ribosomal proteins were assessed in cortical neurons where TDP-43 expression was inhibited by shRNA, and in compound eyes of *Drosophila* overexpressing wild-type TDP-43. The mRNA levels of ribosomal proteins were measured in the white matter of frontal motor area of sporadic ALS patients (n=7). [Results] Disrupted axonal extension in TDP-43-down-regulated cortical neurons was mitigated by overexpression of ribosomal proteins. Degeneration of the compound eyes in TDP-43 transgenic flies was also suppressed by overexpression of the proteins. The mRNA of ribosomal proteins had a trend to decrease in the lesion of ALS patients. [Conclusions] The dysfunction of axonal mRNA transport of ribosomal proteins by TDP-43 can disrupt axonal architecture to cause neurodegeneration, which might be the pathogenic mechanism in ALS/FTLD. Enhancement of target mRNA transport in axons can be a prospective treatment strategy for ALS/FTLD.

O-38-3

Mislocated FUS is sufficient condition to lead ALS-phenotype in a dominant gain-of-function manner

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[Objective] Mutations in RNA-binding proteins, such as FUS and TDP-43, can cause neurodegeneration in amyotrophic lateral sclerosis (ALS). A major question is whether RNA-binding proteins-mediated neuronal loss is caused by toxic gain of function of cytoplasmic aggregates or by a loss of function in the nucleus. [Methods] To finish the above issue, we generated a transgenic (tg) mouse expressing the deletion of the nuclear localization signal in FUS (ΔNLS-FUS), which is related to familiar ALS, to analyze in vivo phenotype. Further, we crossed this ΔNLS-FUS tg mouse with the wild-type human TDP-43 tg mouse to evaluate conjoint phenotypic effect. [Results] ΔNLS-FUS tg mouse develops a progressive motor deficit and neuronal loss in the motor cortex, recapitulating the ALS-phenotype. ΔNLS-FUS strictly locate in the cytoplasm and form ubiquitin/p62-positive aggregates. Surprisingly, endogenous mouse FUS does not change in expression level, nuclear localization, and splicing activity, indicating a gain of function of mislocated FUS is sufficient condition in FUS proteinopathy. Double tg mouse (ΔNLS-FUS and TDP tg mouse) exacerbates pathological and behavioral phenotype, suggesting that both RNA binding proteins interact in a common pathological cascade. RNA-sequence analysis revealed transcriptome alterations including in genes that regulate dynein associated molecules and a regulator of endoplasmic reticulum stress. [Conclusions] Mislocation of FUS is sufficient condition for FUS proteinopathy. TDP-43 and FUS interact in a conjoint pathological cascade.

O-38-4

Deciphering the expression and function of C9ORF72 using mouse model

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[Objective] Recently, expansion of a noncoding hexanucleotide repeat in C9ORF72 was identified as a common cause of both amyotrophic lateral sclerosis (ALS) and frototemporal dementia (FTD). The normal physiological function of C9ORF72 and its expression pattern in the developing and adult nervous system have not been explored. We produced mice harboring a LacZ reporter gene targeted to the mouse ortholog of C9ORF72 and used them to study the gene's expression pattern and loss of C9ORF72 phenotype. [Methods] Using 7-9-week-old heterozygous mice, we studied the expression pattern of 3110040O21Rik using X-galactosidase staining. We also performed co-immunostaining with antibodies to beta-galactosidase (beta-gal) and antibodies that labeled relevant classes of neuronal and non-neuronal CNS cell type. We observed the survival and thoroughly analyzed the motor neuron system in these animals. [Results] In the brain, we found X-gal activity in the hippocampus, dentate gyrus, striatum, thalamus, brainstem nucleus, cerebellum and throughout the cortex. In the spinal cord, X-gal activity was distributed throughout the gray matter, with the highest levels being observed in the ventral horn (Suzuki N et al. Nat Neurosci 2013). We found premature death in heterozygous and homozygous C9ORF72 ortholog mutant mice. We also observed the motor neuron degeneration in those mutant.[Conclusions] The C9ORF72 ortholog was most highly transcribed in the neuronal populations that are sensitive to degeneration in ALS and frontotemporal dementia. C9ORF72 is important for the survival in the adults.

O-38-5

Investigation of TFG pathology in HMSN-P

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[Background] Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) is an autosomal-dominant neurodegenerative disorder caused by mutations in the TRK-fused gene (TFG). Neuropathological study in an autopsied case with HMSN-P demonstrated intracellular inclusion bodies immunoreactive for TFG, TDP-43, OPTN and ubiquitin. TFG has a biological role in protein sorting and trafficking at the endoplasmic reticulum-Golgi pathway. [Objective] To investigate whether TFG pathology share the same pathogenic pathway in amyotrophic lateral sclerosis (ALS). [Methods] Stable cell lines expressing human mutant TFG (P285L) were established to investigate an alteration of intracellular localization in the ALS-associated proteins. Transgenic mice (Tg) were generated that overexpress human mutant or wild type TFG, which were subject to behavioral analysis, pathological investigation by immunohistochemical staining, etc. [Results] In the cultured cells overexpressing human mutant TFG, TDP-43 positive cytoplasmic inclusions and translocation of TDP-43 and FUS from nuclear to cytoplasm were observed. In the Tg with human mutant TFG, weight reduction over 12 months and locomotor activity depression were detected. Sciatic nerve biopsy demonstrated loss of myelinated fiber and appearance of myelin ovoid and axonal dystrophy. [Conclusion] Mutant TFG shows the altered localization of the ALS-associated proteins, including TDP-43. Tg expressing mutant human TFG protein revealed degeneration of lower motor neurons. There is a pathologic overlap between HMSN-P and ALS.

O-38-6

Gene expression analysis in spinal cord of SOD1(G93A) mice after bone marrow transplantation therapy

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[objectives] Bone marrow transplantation (BMT) has been reported as an effective therapy for SOD1 (G93A) transgenic mice (SOD1-tg). In previous study, we determined numerous bone marrow cells migrating into the spinal cords, which was strongly associated with the therapeutic effects of SOD1-tg mice after BMT. The aim of this study is to address molecular mechanism by elucidating gene expression profiling in the spinal cords of SOD1-tg after BMT.[methods] (1) mRNA microarray analysis were performed in spinal cords isolated from SOD1-tg at 16-18 weeks old after BMT from wild type mice (WT) or SOD1-tg at 8 weeks old, which results were compared between two groups to evaluate gene expression profiling. (2) BMT were performed from GFP transgenic mice (GFP-tg) to SOD1-tg to be analyzed the origin of gene expression. To elucidate the gene expression in bone marrow cells migrating to the spinal cord, GFP positive cells were collected from spinal cords in SOD1-tg after BMT from GFP-tg. The gene expression were analyzed by quantitative PCR in GFP positive cells.[results] (1) The gene expression related with apoptosis, cytokines, inflammation, chemokines and CD markers generally decreased in BMT from WT to SOD1-tg group. (2) Several kinds of chemokines and their receptors were upregulated in GFP positive cells.[conclusion] Several kinds of chemokines and their receptors were considered to be related with migration of bone marrow cells under BMT therapy. It might be new strategy for treatment of motor neuron disease by modifying the expression of chemokines and their receptors.

O-39-1

Nationwide hospital-based survey of idiopathic normal pressure hydrocephalus (iNPH) in Japan

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[Background and Objective] We conducted a nationwide epidemiological survey on idiopathic normal pressure hydrocephalus (iNPH) and compiled a descriptive report on its clinical background.[Methods] In the first survey, the numbers of cases that met the diagnostic criteria of iNPH and patients who underwent shunt operation in 2012 were inquired. The second survey was performed concerning details of their clinical background.[Results] The estimated number of cases was 12,900, and patients who underwent shunt operation was 6700. The crude prevalence was estimated to be 10.2/100,000 persons. The age of onset was in the middle 70s. Significantly higher frequency of gait impairment in males and cognitive decline in females were observed as initial symptoms ($p<0.05$). The diagnosis of iNPH was definite iNPH in 52.4% patients. Gait impairment was observed most frequently in patients with definite iNPH (77.7%), and urinary incontinence was observed most in those with possible iNPH (33.8%). Hypertension was the most frequent comorbidity (40.0%), followed by diabetes (14.8%) and Alzheimer's disease (14.8%). Hypertension was observed more frequently in males, but diabetes was observed more frequently in females ($p<0.05$). LP shunt was the first choice (55.1%) of treatment of iNPH, followed by VP shunt (43.2%). [Conclusion] We carried out the world's first nationwide epidemiologic survey of iNPH, and clarified clinical characteristics according to gender and diagnostic level. A comprehensive therapeutic strategy based on the results of this study will be beneficial for patients with iNPH.

O-39-2

Tau imaging in patients with ALS/PDC in the Kii Peninsula

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[Objective] To elucidate the distribution of tau pathology in patients with amyotrophici lateral sclerosis/parkinsonism dementia complex in the Kii Penisula (Kii ALS/PDC) by tau imaging using [^{11}C]PBB3 as a ligand. [Methods] A 71 year-old man with progressive dementia and parkinsonism for 18 years (Pt1), a 81 year-old man with progressive dementia for 16 years (Pt2), and a 68 year-old man with progressive parkinsonism and upper motor neuron signs for 8 years (Pt3) participated in this study. Twenty one healthy volunteers (13 men and 8 women, 67 ± 6 years old) served as normal controls (NC). Dynamic PET scans were performed following [^{11}C]PBB3 injection, and an injection of [^{11}C]PiB, an amyloid imaging ligand, on the same day in each subject. Parametric PET images were generated by calculation of target-to-cerebellar cortex standardized uptake value ratios (SUVR). Two-sample t-test was performed on [^{11}C]PBB3 SUVR images between each patient and NCs using SPM5. Statistical threshold was set to P<0.001 (uncorrected). [^{11}C]PiB accumulation was assessed by visual inspection of SUVR images.[Results] All subjects except Pt2 were negative for PiB (amyloid). SPM analysis showed high PBB3 (tau) accumulation in fronto-temporal lobes, putamen, globus pallidus, subthalamic nucleus in Pt1. There was high PBB3 accumulation in fronto-temporo-parietal lobes in Pt2. There was high PBB3 accumulation in fronto-parital lobes, especially in the white matter, brainstem in Pt3. [Conclusion] [^{11}C]PBB3 PET detects the distinct distribution of tau pathology in each clinical phenotype of Kii ALS/PDC.

O-39-3

Modifiable risk factors for Alzheimer's disease: systematic review and meta-analysis

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Objective: Our present systematic review and meta-analysis was to roundly evaluate the association between Alzheimer's disease (AD) and its modifiable risk factors.Methods: We systematically searched PubMed and the Cochrane Database of Systematic Reviews from inception to July 2014, and the references of retrieved relevant articles. We included prospective cohort studies and retrospective case-control studies.Results:16906 articles were identified of which 323 with 93 factors met the inclusion criteria for meta-analysis. We found grade I evidence for 4 medical exposures (oestrogen, statin, antihypertensive medications and non-steroidal antiinflammatory drugs therapy) as well as 4 dietary exposures (folate, vitamin E/C and coffee) as protective factors for AD. We found grade I evidence showing that one biochemical exposure (hyperhomocysteine) and psychological condition (depression) significantly increase AD risk. We also found grade I evidence indicative of complex roles of pre-existing disease (frailty, carotid atherosclerosis, hypertension, low diastolic BP, T_2DM increasing risk whereas history of arthritis, heart disease, metabolic syndrome and cancer decreasing risk) and lifestyle (low education, high BMI in mid-life and low BMI increasing the risk whereas cognitive activity, current smoking, light-to-moderate drinking, stress, high BMI in late-life decreasing the risk) in influencing AD risk.Conclusions: Effective interventions in diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle may decrease new incidence of AD.

O-39-4

Microbleeds in clinical subtypes of AD on CSF and Neuroimaging markers

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[Objective] We aim to elucidate frequency or distribution of microbleeds (MB) in typical AD and AD patients that present with atypical clinical presentations.[Methods] We examined amnestic dominantly deficit early onset Alzheimer's disease (EOAD) (N=20), late onset Alzheimer's disease (LOAD) (N=20), and two atypical variants of l-AD (language dominantly deficit AD) (N=16) and v-AD (visuospatial dominantly deficit AD) (N=8) on CSF biomarkers ($A\beta_{1\text{-}42}$ and ptau-181) and Neuroimaging markers (^{11}C PiB-PET, ^{18}F FDG-PET, ^{99m}Tc ECD-SPECT). Among four types of AD, we analyzed the number and localization of MB, the localization and extent of PiB, CBF (cerebral blood flow) and glucose metabolism.[Results] Frequency of MB was observed most frequently in l-AD (63.5%), while less number of MB in v-AD (12.5%) compared with other subtypes of EOAD (35.0%) and LOAD (35.0%). Distributions of MB in l-AD were frequently observed in left frontal and temporal lobes compared with those in right side (p<0.01, respectively). l-AD showed CBF decrease significantly in left frontal, temporal and parietal lobes compared with those in right side (p<0.001, respectively). v-AD showed decrease of CBF in bilateral occipital and parietal lobes.[Conclusions] MB are thought to be related to speech dysfunctions in v-AD, also may be involved CBF decrease in left temporo-parietal and frontal lobes, which might be partly due to cerebral $A\beta$ angiopathy. The number of MB was observed little in v-AD, which might occur different pathogenic mechanisms from l-AD.

O-39-5

Long-chain omega-3 polyunsaturated fatty acids, Cerebral small-vessel disease, and Incident dementia

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[Objective] *Long-chain* omega-3 polyunsaturated fatty acids (PUFAs) have been identified as a potential protective factor for cognitive impairment. However, few prospective studies have explored the impact of PUFAs on dementia while taking account of cerebral small-vessel disease (SVD) and brain atrophy. [Methods] Within a cohort of patients with vascular risk factors and free of dementia, circulating levels of omega-3 (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) and omega-6 (dihomo-γ-linolenic acid [DGLA], arachidonic acid [AA]) PUFAs were measured at baseline. Brain MRI was used to determine SVD (lacunas, white matter hyperintensities and microbleeds) and medial-temporal lobe atrophy. Logistic regression analyses were used to estimate the cross-sectional association between PUFAs and MRI-findings. Cox proportional hazards analyses were performed to estimate the longitudinal association between PUFAs and dementia, adjusting for age, sex, APOE ε 4, educational level, vascular risk factors, and MRI-findings. [Results] In the 613 subjects (67.3 ± 8.4 years), multivariable analyses showed that any PUFAs was not significantly associated with each of SVD. During the mean 7.5-year follow-up, 48 subjects were diagnosed with dementia (Alzheimer's disease:24; vascular dementia:18). In multivariable Cox models, the relative risk of dementia was 0.42 (0.17-0.96, p = 0.040) in the highest versus lowest tertile of DHA. However, no associations were observed for EPA, EPA/AA ratio, or omega-6 PUFAs. [Conclusions] DHA may be associated with lower risk of dementia independently.

O-39-6

Withdrawn

O-40-1

Withdrawn

O-40-2

Validation of a Screening Questionnaire for X-linked Dystonia Parkinsonism (XDP)

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Objectives To develop and validate a simple, easy to use, community based, screening questionnaire for the diagnosis of X-linked dystonia parkinsonism (XDP), a movement disorder afflicting mostly men with roots from the Philippine island of Panay.**Methods** Community health workers administered an 11-item yes/no questionnaire, in the native Panay island language on 54 genetically confirmed XDP patients and 54 healthy controls all from the island of Panay. The questionnaire was made up of elements from existing questionnaires on Parkinson's disease and dystonia, and known clinical features of XDP. The subjects were partitioned into training and test data sets. To select which items were predictive of XDP the Clinical Utility Index (CUI) of each item was determined. Afterwards, multivariable binary logistic regression was done to build a predictive model that was subsequently run on the test data set.**Results** Four items on 'sustained twisting', 'jaw opening and closing', 'slowness in movement' and 'shuffling steps' were found to be the most predictive of XDP. All had at least a 'good' CUI. The questions demonstrated 100% sensitivity and 100% specificity (95% CI: 65.6-100%) in identifying XDP suspects when applied to the test data set for XDP.**Conclusion** The resulting 4-item questionnaire was found to be predictive of XDP. The screening instrument can be used to screen for XDP in a large-scale population based prevalence study.

O-40-3

An exploration of the origin of granulovacuolar degeneration bodies and rimmed vacuoles

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[Background] Inclusion-body myositis (IBM) and Alzheimer's disease (AD) are biochemically characterized by the presence of aggregated amyloid beta protein and tau protein. In addition, vacuolar change such as rimmed vacuoles (RV) and granulovacuolar degeneration bodies (GVD) are pathological features for IBM and AD, respectively. Previously, we demonstrated that RV and GVD share common molecules and these results led us to speculate that both of RV and GVD originate from the structures which are common to muscle cells and neuronal cells, namely, neuromuscular junction (NMJ) and postsynaptic spine. In this study, we explore the presence of the components of NMJ and/or postsynaptic spine in RV and GVD, respectively.[Methods] Subjects included seven cases of sporadic IBM (s-IBM) and two AD cases. We compared immunoreactivity and staining patterns for antibodies which are mainly present in NMJ, postsynapse and lipid raft.[Results] In all cases of s-IBM, RVs were immunopositive for dishevelled3 (Dvl3), PtdIns[4,5]P2 and prion protein and β-catenin. While p21-activated kinase1 (PAK1) and ADP-ribosylation factor 6 (Arf6) were not detected in RVs in all cases of s-IBM. In GVD bodies, Dvl3, PtdIns[4,5]P2, phospho-b-catenin and rapsyn were immunopositive.[Conclusions] The present study proves that GVD bodies are derived from postsynaptic components and RVs from NMJ, thus an origin of them has similar structures and function.

O-40-4 **海外最優秀候補演題**

Blood amino acids and acylcarnitines spectrums in Chinese patients with mitochondrial disease

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Objective To report the characteristics of blood amino acids and acylcarnitines spectrums of patients with mitochondrial disease. **Methods** Fifty patients with mitochondrial disease, twenty patients with multiple acyl-CoA dehydrogenase deficiency (MADD) and twenty-two cases of healthy adult controls underwent analysis of amino acid and acylcarnitines by tandem mass spectrometry. Non-parametric analyses were used to compare the level of amino acids and acylcarnitines between each of mitochondrial disease, MADD and healthy control groups and one another among three groups. **Results** The median level of glutamate and ornithine in patients with mitochondrial disease was 89.80 μmol/L and 27.70 μmol/L, respectively, lower than 113.46 μmol/L (P=0.002) and 33.52 μmol/L (P=0.010) in MADD, respectively, 107.33 μmol/L (P＜0.001) and 34.08 μmol/L (P＜0.001) in healthy control, respectively. The median level of alanine/glutamate ratio was 2.72 in mitochondrial disease, which was higher than 1.86 in MADD (P＜0.001) and 1.55 in healthy control (P＜0.001). The median level of C5OH was 0.33 μmol/L in mitochondrial disease, higher than 0.19 μmol/L (P=0.011) in MADD and 0.20 μmol/L in healthy control (P＜0.001). The diagnostic sensitivity and specificity of alanine/glutamate ratio＞2.17 for mitochondrial disease was 76.00% and 85.71%, respectively. Conclusions mitochondrial disease have a specific pattern of blood amino acids and acylcarnitines spectrums. Blood amino acids and acylcarnitines spectrums may serve as a potential biomarker for mitochondrial disease.

O-40-5

Clinical characteristics and brain MRI features of nineteen patients with Kearns Sayre syndrome

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Objective To summarize the clinical characteristics and brain MRI features of patients diagnosed of Kearns Sayre syndrome (KSS). **Methods** 11 males and 8 females were involved. The mean age at diagnosis was 16.6 ± 6.1 years (8-31 years), while the mean age at presentation was 9.6 ± 4.3 years (2-16 years). At diagnosis, all patients had developed ptosis, external ophthalmoplegia and pigmentary retinopathy. 12 patients (63.16%) showed different degrees of heart block, 4 of whom developed from bundle branch block to atrioventricular block in 3 months to 6 years while 3 received permanent pacemaker implantations. 10 patients (52.63%) showed cerebellar ataxia and 4 underwent lumber puncture with increased CSF protein levels above 100mg/dL. Muscle biopsy was performed in 15 patients consistent with a mitochondrial myopathy. 12 patients underwent muscle tissue genetic testing for an mtDNA deletion consistent with KSS. Analyze the brain MRI results of 15 patient, and carry out follow-up in 12 patients. **Results** All 15 patients who took brain MRI showed abnormal signals in the brain, of which the percentage of high signals on T2WI detected in subcortical white matter, basal ganglia, thalamus, brain stem and cerebellum was 80.0%, 73.3%, 53.3%, 66.7% and 26.7%. Of the 12 follow-up patients, 7 were stable, 3 needed to walk with assistance because of ataxia, 2 were confined to bed because of heart failure. **Conclusion** The progressing rate of heart block varies in different KSS patients. Brain MRI showed multiple lesions in white matter, basal ganglia, thalamus, brain stem and cerebellum.

O-40-6 **海外最優秀候補演題**

Clinical features of MELAS: an analysis of 190 cases

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Objective To summarize the clinical features of Chinese patients with mitochondrial encephalomyopathy, lactate acidosis, stroke-like episodes(MELAS). **Methods** A total of 190 MELAS patients who presented to Peking University First Hospital between 1997 and 2015 were studied. The clinical features, including predisposing factors of stroke-like episodes, the onset symptoms and frequencies of various manifestations were analyzed and reported. **Results** In our cohort, the male-to-female ratio was 1.44:1. The median age of onset was 14 years (from 7 months to 45 years). The median onset age of the first stroke-like episode was 16 years (from 1 to 53 years). Fatigue and upper respiratory tract infection were the most common predisposing factors of stroke-like episodes(37.88% and 34.85%, respectively). Stroke-like episodes appeared in 70.53% patients as an onset symptom and developed in all patients with disease progression. The relatively commom neurological manifestations included seizure (89.42%), mental retardation or dementia (82.87%), headache (74.30%), hemianopia or cortical blindness (67.72%), exercise intolerance (50.87%). The common manifestations of extra-nervous systems included hirsutism (67.57%), vomiting (65.58%), fever (62.07%). **Conclusion** The majority of the patients in this study had the disease onset during childhood. There were more male MELAS patients than females. Most common clinical manifestations were seizure, mental retardation or dementia, headache, cortical blindness, hirsutism, vomiting and fever in this patient cohort.

口演

5月21日（土）

O-41-1

Long-term follow-up study of basilar artery diameter in patients with cardiobascular risk factors

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【目的】脳底動脈径の大きさは心血管イベント発症と関連することが横断研究で報告されている．今回，動脈硬化危険因子を有する症例の脳底動脈径の長期経過と心血管イベントの関連について検討した．【方法】50歳以上の動脈硬化危険因子を有する当院外来通院症例のうち，2001年以降，頭部MRI検査を7年半以上の間隔で再検した症例を対象とし，後方循環の形態により同側の後大脳動脈（P1）と後交通動脈（Pcom）の血管径を初回MRAで比較し，adult type（両側ともP1≧Pcom）/ fetal type（両側ともP1＜Pcom）/ othersに群別した．初回，再検時MRI T2強調画像の橋中部レベルでの脳底動脈（BA）短径をそれぞれ測定し，その経時的変化を⊿BAとした．初回BA径および⊿BAについて，動脈硬化危険因子，血液データ，頚動脈IMTなどとの関連性や心血管イベント発症の予測因子となるかを検討した．【結果】対象163例（平均年齢64歳，男性96例，平均観察期間 112ヶ月），adult type/ fetal type/ othersが各々120/10/33例．初回時のBA径平均はadult type/ fetal type/ othersでそれぞれ2.9/2.0/2.1 mmであった．⊿BAはadult type/ othersで平均0.41/ 0.37 mmの拡大を認めたが，fetal typeではほとんど変化を認めなかった．また，fetal typeを除いた153例の検討で，初回時のBA径の大きさがその後の心血管イベント発症と有意な関連があった．⊿BAは，動脈硬化危険因子と有意な相関はみられず，⊿BAの中央値で2群に分けた検討で，2群間に心血管イベント発症率に差はなかった．【結論】BA径およびその経時的変化には後方循環の形態が関連していた．BA径が大きいことは心血管イベントと有意な関連がみられたが，経時的な径変化は心血管イベントと関連がみられなかった．BA径の経年変化の意義について，文献的考察も加えて報告する．

O-41-2

Association of genetic polymorphisms SOD and GPx genes with cerebrovascular stroke

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Background:ROS is produced in very low amount in normal body physiology which is managed by endogenous antioxidant system that include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and antioxidant vitamins (E and C). Increased production of ROS occurs due to defects in the enzymes (SOD or GPx) involved in its utilization. The aim of this study is to demonstrate the association of SOD and GPx polymorphism in the development of cerebrovascular stroke, classified as small artery disease (SAD) and large artery disease (LAD)-stroke.**Methods:** Genotyping of SOD1 (rs1041740), SOD2 (rs4880), GPx1 (rs1050450) were performed by LightCyclerreal-time PCR using LightSNiP reagents while genotyping of GPx4 (rs713041) were done by PCR-RFLP. All biochemical parameter were measured in serum/plasma in automated clinical chemistry analyzer. **Results**: CC+CT/TT genotype of SOD2 compared with CC genotype significantly increased the risk of CVS, and SAD-stroke with AOR=1.57 (95%CI=1.10-2.24) and 1.64 (95%CI=1.17-2.41), respectively. Similarly, GPx4 (rs713041) demonstrated the significant association with stroke while GPx1 (rs1050450) showed no association at all. Among the different biochemical parameters, lipid and lipoprotein, glucose, HbA1C, Hcy were found significantly different with these SNPs between control and stroke cases. Conclusion: Our study demonstrates the significant association of SOD and GPx genetic polymorphism with cerebrovascular stroke and clearly states that genetic component of stroke is polygenic.

O-41-3
Withdrawn

O-41-4

Transbrachial Balloon Guide Use for Acute Recanalization Therapy

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【背景】脳虚血急性期の血管内再灌流治療において，手技中に血栓のmigrationを起こさないことは重要であり，Balloon guide catheter（BGC）の使用はその一助となる．BGCはその大径ゆえ通常は大腿動脈アプローチが選択されるが，シースレスに上腕動脈からでも挿入可能であり，大腿動脈からのアプローチが困難な場合にもBGCが使用可能である．【目的】BGCを上腕動脈から挿入して緊急再灌流療法を行うことの有用性と問題点を検討する．【対象・方法】対象は2014年1月から2015年10月までに当施設で，脳前方循環急性期虚血と診断され，BGCが上腕動脈から挿入され緊急再灌流療法が試みられた患者．患者背景，手技時間，再開通，遠位塞栓の有無，穿刺部・周術期合併症について後方視的に調査した．【結果】対象患者は17例．13例で右上腕動脈から目的の総頸・内頸動脈にBGCを留置できた．うち頸部ICA閉塞が5例，頭蓋内ICA閉塞が4例，M1閉塞4例．右頸動脈病変8例，左頸動脈病変5例．手技時間（穿刺-再開通）中央値は78分（IQR: 65-115），穿刺からBGCのBalloon拡張までの中央値は21分（IQR: 12-25）であった．術中に血栓がOptimo内腔に嵌頓し，その回収に難渋した症例があった．再開通はTICI 0が2例，TICI Ⅱaが1例，それ以外の患者ではTICI Ⅱb以上の再開通が得られた．術中の遠位塞栓が1例に生じたが，穿刺部およびその他周術期合併症は生じなかった．【結論】17例中13例で，BGCを上腕動脈から目標血管に誘導し，近位血流遮断下で緊急再灌流治療を行うことができた．BGCの誘導に時間を要した症例もあったが手技の習熟によって改善可能と思われた．BGCをシースレスに挿入しているため，BGC内に大量血栓が嵌頓したと考えられた際の対応が問題として残った．

O-41-5

Factors related to vessel injury complication after stroke thrombectomy using stent retriever

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【はじめに】Stent retriever（SR）使用例において，くも膜下出血（SAH）や再開通直後の血栓形成/再閉塞を経験した．いずれもSRの侵襲による血管傷害性合併症と考えられたため，関連する因子について検討した．【方法】SRを使用開始した2013年11月～2015年10月に血管内治療を施行した急性期脳梗塞連続80例のうち，中大脳動脈（MCA）をSRが通過した塞栓性閉塞例を対象とした．内頸動脈C2（中間カテーテル使用時は同カテーテル先端）～SR到達部までの分岐/屈曲部のなす角度を最終血管造影正面像（非再開通例では術中のカテーテル走行）から計測し，その総和を求めた．SRのMCA通過回数，角度の総和，および通過回数と角度の総和の積（angle-pass index：API）と血管傷害性合併症の関連を後方視的に検討した．【結果】30例（女性11例，年齢76.6±7.7歳，NIHSS中央値17，rt-PA静注療法施行率53.3%）を対象とした．TICI 2b/3再開通率は80%，病前自立25例における3カ月後（または退院時）mRS≦2到達率は48%で，血管傷害性合併症は8例（26.7%：SAH6例，再閉塞/血栓形成3例）に生じた．合併症群は非合併症群に比しMCA通過回数（中央値2回 vs 1回，p=0.097）が多い傾向にあり，角度の総和（中央値228度 vs 157度，p=0.035），API（中央値529 vs 259.5，p=0.005）は有意に高値であった．多変量解析ではAPIのみが血管傷害性合併症と有意に関連した（OR/100増加 2.57，95%CI 1.09-6.02，p=0.03）．ROC解析にてAPIが血管傷害性合併症を予測するカットオフ値は348（感度87.5%，特異度86.4%）であり，血管傷害性合併症におけるAPI＞348の調整ORは26.91（95%CI 1.56-462.82，p=0.023）であった．【結論】SR通過血管の分岐角度の総和と通過回数の積であるAPIにより，SRによる血管傷害性合併症が予測できた．

O-42-1

原発性進行性発語失行（ppAOS）の症候と経過

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【目的】Gorno-Tempiniら（2011）が提起した原発性進行性失語（PPA）の3つの臨床類型のうち，非流暢/失文法型（nfvPPA）は，発語失行（AOS: apraxia of speech）のみの群と，失語症状を合併する群（失文法型）に分離すべきとの見解がある．前者はppAOSと称され，病理学的にもFTLD-tauである可能性が高いと報告されている．そこで，本研究ではppAOSの診断として何が有用か検討することを目的とした．【方法】対象はnfvPPAの診断基準を満たし，かつ，A．進行性前部弁蓋部症候群，B．失語症を呈する群は除外した．従って，対象は進行性純粋AOSのみを認めた患者15名（男11，女4，平均年齢75.4歳：63～92歳）である．方法は，①各種高次脳機能評価，②MRI/MRA，③RI（脳血流SPECT，可能であれば^{123}Iイオフルパン SPECT）を施行し，経過を検討した．【結果】ppAOSとして，3つの臨床類型が推測された．1）2例は発症5～7年後もAOSのみで，^{123}Iイオフルパン SPECTは正常であった．2）1例は発症1年以内に体幹や四肢失調を認めた．3）10例のうち，2例は数年後にパーキンソニズムを呈し，CBSと診断された．8例はパーキンソニズムは呈さなかったが，発症2～5年以内に中心回症状（拙劣症and/or二点識別覚障害）を呈し，^{123}Iイオフルパン SPECTを施行しえた5例では，いずれも一側の基底核で低下を認め，CBSが疑われた．4）その他の2例は，発症2年以内に失語症状を呈し，失文法型に移行した．【結論】1．ppAOSの診断は発症から2年以降でAOSのみであることを条件にすると均一な症候群を得られる可能性がある．2．二点識別覚and/or拙劣症の合併，^{123}Iイオフルパン SPECTが診断の補助になる可能性が示唆される．

O-42-2

アルツハイマー型認知症患者の独居にかかわる要因の検討

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【目的】初診時アルツハイマー型認知症（AD）において，独居にかかわる要因を検討する．【方法】2010年1月1日～2015年9月30日に物忘れ外来を初診し，頭部MRIもしくはCT及び^{123}I-IMP SPECTを施行，NIA-AA診断基準でprobable AD dementiaと診断，家族・自己評価とも生活健忘チェックリスト（EMC）を施行した症例のうち，過去明らかな脳血管障害の既往や，頭部画像上皮質にかかる脳血管病変の存在する例を除外した73例で，年齢，罹病期間等の臨床的特徴，認知機能評価にMMSE，HDS-R，認知症の行動・心理症状（BPSD）評価のthe Neuropsychiatric Inventory（NPI），本人及び介護者評価の生活健忘チェックリスト（EMC），重症度評価のFunctional Assessment Staging（FAST）等で臨床症状を評価した．介護者の条件は，週3回以上本人と連絡をとり，状態の把握が可能な者とした．【結果】AD 73例中男性は22例．平均年齢79.0±6.1歳，平均罹病期間2.6±2.1年，MMSE 20.3±4.3点，NPI総得点 11.3±15.6点であった．独居群は18例（24.7%）で，同居群55例と比較し，17例が女性（p=0.0036）であった他は，年齢，罹病期間，認知機能に有意差はなかった．NPI脱抑制，異常行動ややる気スコアの得点は低く，EMCが介護者評価よりも自己評価が低く認知症の自覚がある症例は少なかったが，有意差はなかった．多変量解析では，性別，認知症の自覚があること，NPI項目では脱抑制，異常行動が独居と関連した．【結論】初診時，独居のAD患者は24.7%でほぼ女性であり，平均寿命や家事を行えるかなどの社会的要因が関与していると思われた．都市部である程度独居が可能かどうかには，認知機能よりも脱抑制，異常行動，アパシーなどのBPSDの関与や認知症の自覚の有無が大きいと考えられた．

O-42-3

新規に開発した多職種連携ITツールによる認知症高齢者の包括的医療・介護の実際と効果

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【目的】我が国の公的経済負担軽減の切り札として在宅医療・介護を支える地域包括ケアの確立が重要課題となっているが，認知症高齢者の適切なマネージメントなくしてその実現は困難である．種々の身体疾患やBPSDを併せ持つ認知症患者を在宅で支えるには，専門医・かかりつけ医や多職種の連携が必要であり，我々はそのための情報連携ツールを開発し実証を重ねてきた．今回異なる背景を有した認知症患者にこのツールを適用しその効果を評価することを目的とした．【方法】対象は4例の在宅認知症高齢者．アルツハイマー型認知症(AD)3例，レビー小体型認知症(DLB)1例．うち3例は独居(要介護1～3)で1例は家族同居(要支援2)．患者ごとに異なる在宅支援のための多職種チームに対して我々が開発した多職種連携ITツールを適用しその効果を評価した．AD2例については神経内科専門医とかかりつけ医が連携，残り2例については神経内科専門医が主治医として参加した．要介護以上の3名はいずれもBPSDが目立ち在宅処遇困難例であったが，多職種連携で在宅医療・介護をどこまで支えられるかを評価した．要支援のAD1例は早期未治療例であり，家族も連携に加わることで薬剤のスムーズな導入へむけての効果を評価した．【結果】徘徊や妄想を示す2例のAD患者は経過中骨折や頻回の転倒等の事象を来したが，今回の支援により各13ヶ月，及び10ヶ月の在宅が可能であった．また1例のDLB症例についても在宅継続中である．さらに13ヶ月の在宅症例において介護負担費用の軽減効果を検討したところ，施設入所に対して介護保険の9割給付額を約40万円軽減できることが明らかになった．AD早期未治療例については早期からITツールを介した連携を組むことで，円滑かつ確実な薬物導入と介護サービス導入が可能であった．【結論】我々の開発した医療・介護のための多織種連携ITツールは，認知症高齢者の在宅を支え介護負担費用の削減を図る上で有用と考える．

O-42-4

認知症を持つ要介護認定者におけるBPSDの有症率と介護負担，要介護度との関係

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【背景】認知症における行動心理症状（BPSD）は介護負担を増大させ，在宅生活を阻害する要因になっている．地域におけるBPSDの有症率調査では，疾患が限定されていたり，認知症と覚知された時点での調査であったり，MMSEなどの全般性認知機能検査によりカットオフが設けられていて，初期のDLBやFTLDが含まれていない可能性があるなど課題がある．【目的】認知症を持つ要介護認定者におけるBPSDの有症率調査を行った．次にBPSDと介護サービスや介護負担との関係性を評価した．【方法】まずY市の介護保険認定者12,677名から認知症自立度II以上で在宅療養中の利用者2,706名を抽出した．調査研究に同意したケアマネジャー（CM，160名）の担当する対象者5名を乱数表で無作為抽出し，CMより手渡しで配布した（全800名）．調査項目：対象者の性別，年齢，要介護度，介護者の年齢，性別，サービス利用頻度（通所・宿泊・訪問），入所希望の有無，ZBI8，NPI-Qおよび認知の変動であった．調査は任意で無記名郵送にて回収した．本研究は所属機関で倫理申請し承認された．【結果】236名から回収し（回収率30%），在宅療養中である利用者の介護者225名から有効回答を得た．BPSDは対象者の95%に認められた．有症率60%以上の症状は興奮，鬱，無為，睡眠障害，認知の変動であった．多幸（54.4%）や脱抑制（43.5%）も既報告より多く認められた．ZBI8とNPI-Q（重症度・負担度）には有意な相関が見られた（spearman ρ=0.57,0.65, p＜0.01）．要介護度はNPI-Qや介護負担度と有意な相関はなかった．【結論】BPSDはほぼ必発であり，BPSDにおける各症状の有症率は既報告よりも総じて高かった．以上より介護者から定期的にBPSDの程度について聴取し，適切な診断，本人の状況に応じた治療，ケアにつなげていくことが重要と考えられた．今後は独居および要介護認定未申請者を含めた地域における全数調査，前向き調査を行う必要がある．

O-42-5

脳血管障害患者の認知機能障害に対するリハビリテーションの有効性及び病型との関連

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【目的】前回，脳血管障害患者のリハビリテーションが認知機能改善に有効であることを報告した．今回，MMSE項目別障害頻度，NINDS-AIREN診断基準病型別改善度について検討した．【対象】回復期リハビリテーション病棟に入院された脳血管障害患者で，認知機能低下を認めた27例．男性17例，女性10例．年齢56歳～88歳，脳梗塞20例，脳出血7例．【方法】リハビリ開始時および終了時に，MMSE（Mini-Mental State Examination），HDS-R（長谷川式簡易知能評価スケール），FIM（Functional Independence Measure）を行った．【結果】1）MMSE項目別の障害を認めた例数は，全27例中①見当識 22例，②即時想起 0例，③注意・計算 23例，④遅延再生 22例，⑤物品呼称 6例，⑥文章反復 11例，⑦ 3段階命令 11例，⑧読字 4例，⑨書字 16例，⑩図形構成 16例であった．2）リハビリ開始時と終了時の認知機能検査では，①MMSEは開始時19.3±5.9点，終了時22.4±5.5点で有意(p=0.0040)な改善を認めた．②HDS-Rは開始時18.6±6.7点，終了時21.7±6.2点で有意(p=0.0026)な改善を認めた．③FIM認知項目でも開始時23.3±7.2点，終了時25.5±5.3点で，有意(p=0.0174)な改善を認めた．3）リハビリ開始時と終了時のMMSEによる認知機能検査では，27例中，改善18例，悪化8例，不変1例で，NINDS-AIREN病型別では，A）皮質性(6例)改善4例，悪化2例，B）戦略的単一部位(9例)改善5例，悪化4例，C）小血管病変性(5例)改善4例，悪化1例，D）脳出血性(7例)改善5例，悪化1例，不変1例．【結語】1）MMSEの項目別障害頻度では，注意・計算，見当識，遅延再生で障害頻度が高く，即時想起は保たれていた．2）リハビリ開始時と終了時の認知機能検査では，MMSE，HDS-R，FIM認知項目とも，有意な改善が認められた．3）タイプ別改善度では，脳出血性，小血管病変性で改善割合が高く，戦略的部位病変性では改善割合が低い傾向がみられた．

O-43-1

最大筋収縮時脳磁気刺激による運動・認知機能の変化に関する検討

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【目的】最大筋収縮時脳磁気刺激(TMS with MVC)が運動及び認知機能に与える影響について検討を行う．【方法】対象は正常成人8名(男性2名，女性7名，平均年齢: 31.6 ± 14.8才)．被験者を椅子に座らせ，右手親指と人差し指でボタン状ひずみゲージを最大筋力で摘ませ，左運動野に対し活動時閾値の110%の刺激強度で単発経頭蓋磁気刺激を加えた．これを10秒間に1回の間隔で4回繰り返して1クールとし，10分ごとに5クール繰り返した．刺激前後において被験者にWAIS-Rの数字の順唱と逆唱，符号検査を行わせた．磁気刺激中の右手指筋の運動誘発電位とつまみ筋力も記録した．対象として実刺激と同じ時間経過で偽刺激を行い，上記の結果と比較した．【結果】偽刺激に対して実刺激では，刺激前と比較して刺激後に数字の逆唱の点数が有意に増加し(p<0.05)，つまみ筋力が増強する傾向がみられた．他の検査では偽刺激と実刺激の間に有意差はなかった．【結論】今回の研究により，TMS with MVCは筋力と言語性記憶能力を向上させる可能性が示唆されたが，詳細については今後の更なる検討が必要と思われる．

O-43-2

初発小脳血管障害による小脳性認知・情動症候群のリハビリテーション転帰への影響

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【目的】小脳の認知・情動機能への関与が知られているが小脳損傷後のリハビリテーション(リハ)への影響は明らかでない．我々は血管障害による小脳性認知・情動症候群(Cerebellar cognitive affective syndrome：CCAS)の亜急性期以降の臨床的特徴およびリハ転帰について検討した．【方法】2012年8月から2015年7月までに当院回復期リハ病棟へ入院した脳血管障害連続1478例のうち，精神疾患既往，テント上病変併発例を除外した初発小脳血管障害患者44名(出血24/梗塞20，女性20，65±15歳)．入院期間中の情動障害(脱抑制や不適切な言動，情動平坦化や発動性低下)の有無によりCCAS群17名と非CCAS群27名に分け，臨床的特徴，病巣の分布，転帰について後方視検討した．【結果】両群で病名，性別，年齢，病前modified Rankin Scale(mRS)，入院時発症後日数に有意差なく，Mini Mental State Examination(22.7±6.7 vs 28.2±2.9, p＜0.005)，および能力障害指標であるFunctional Independence Measure(FIM)の運動・認知項目はCCAS群で有意に低かった(p＜0.001)．病変側や深部小脳核損傷や虚血血管領域に関連はなく，急性期脳室穿破や小脳虫部損傷例がCCAS群で有意に多かった(p＜0.05)．同等の在院期間中(平均88±49日)に，CCAS群で診療上の危険行為(11 vs 4名，p=0.001)が有意に多かった．CCASの回復期リハ入院期間中の不変や悪化は1/4にとどまり，FIMは運動・認知ともに非CCAS群と同等の利得だった．一方，CCAS群では自立歩行および介助歩行の累積達成率が低く(p＜0.005)，退院時mRS(2.8±1.3 vs 1.5±1.1, p＜0.005)および在宅復帰率(76.5% vs 96.3%，p＜0.05)も有意に低かった．【結論】初発小脳血管障害患者の約3割にCCASを認め，脳室穿破や小脳虫部損傷との関連が示唆された．CCASは回復期リハ期間後の運動機能予後や在宅復帰に影響を及ぼした．

O-43-3

急性期内包梗塞患者に対する反復経頭蓋磁気刺激の効果

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【目的】反復経頭蓋磁気刺激（rTMS）はリハビリテーションの分野で臨床応用が進んでいるが，急性期の脳卒中に対する効果は明らかではない．急性期脳梗塞患者に対するrTMSの安全性と有効性を確認する．【方法】発症から1週間以内の急性期内包後脚梗塞患者で上肢Brunnstrom stage III以下の患者を対象とし，患側上肢運動野興奮刺激（iTBS），健側上肢運動野抑制刺激（低頻度刺激），患側上肢運動野sham刺激（sham iTBS）の3群に割り付け，通常リハビリテーションの前に2週間（5日間×2）刺激した．その後2週ごとに8週間にわたり上肢機能や脳血流，運動誘発筋電位などを評価し，比較検討した．【結果】8週間後の評価では，sham刺激群と比較して患側興奮刺激群，健側抑制刺激群いずれもFugl-Meyer assessmentやStroke Impairment Assessment Set，Functional Independence Measure，Modified Ashworth Scale，握力などの評価項目の改善率が高い傾向を認めた．【結論】rTMSを脳梗塞急性期に使用することは，脳梗塞の回復に有効である可能性がある．

O-43-4

障害者総合医療療育施設における成人患者の摂食嚥下機能評価

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【目的】当院利用患者は幼児期から摂食嚥下機能評価・指導（ST）を受け，経口摂取をしている障害者患者が多い．そのような障害者患者と，成人になってからの障害者・神経難病患者を診ている成人病棟には，未だ嚥下サポートチームは完成しておらず，担当医がST指示を出して機能評価・指導をし，栄養科で食事指導をしている．摂食嚥下について当院利用患者の特徴を明らかにする．【方法】2007～2014年度に成人病棟からST指示が出された患者の臨床記録を後方視的に検討した．【結果】脳性麻痺，先天奇形，脳症・脳血管障害後遺症などの小児期からの障害者患者は31例，成人発症患者7例（脳血管障害2例，脊髄小脳変性症4例，神経ベーチェット1例）であった．ST施行時の平均年齢は38.3歳．独歩は2例，座位保持不能は21例で，知的障害がなかったのは1例と，知的・運動障害が高度な症例が多かった．ST指示は，経管栄養から経口摂取に戻したい家族の希望5例，病歴聴取で肺炎・嚥下障害悪化があったためが19例（50%），施設利用時の評価14例（36.8%）であった．STにより，経管栄養から経口摂取に1例は戻り，経管栄養に変更・継続は7例（18.4%）で，食べやすい食形態への変更は24例（63.2%）で，この中に施設利用時の評価例が9例含まれていた．経口摂取を控えることが勧められた2例の神経変性疾患患者は経口摂取継続への希望が強く，姿勢・食形態を含めた検討と指導のもと経口摂取を継続している．食形態変更が不要であった6例は障害者患者で平均年齢26歳と若い傾向があった．【考察・結論】本人・家族からのST評価希望は少なく，病歴からの肺炎罹患・嚥下障害悪化の聞き取りや施設利用時の評価が主であった．しかし，ST結果での食形態変更が多く，いかに評価を開始するかが今後の検討課題と判明した．STに姿勢評価や食事指導を加えることで，経口摂取を長く続けられる可能性がある．

O-43-5

当院におけるカニューレ留置症例に対する嚥下リハビリテーションの検討

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【目的】回復期病院において気管切開を有する症例は少なくなく，リハビリテーションを進めていく上で気管切開患者のカニューレ管理に関する治療指針は重要である．カニューレ留置症例の臨床的特徴，経過，転帰についてまとめ検討を行う．【方法】2012年9月～2015年10月までに入院時にカニューレを留置していた症例は28名であった．この28名の原因疾患，カニューレ抜去までの期間，FIM利得，入退院時のBMI，食形態，嚥下内視鏡・嚥下造影の結果，転帰先について後方視的に調査した．【結果】退院時，カニューレを抜去していた症例（抜去群）は18名，留置していた症例（留置群）は10名であった．抜去群は入院時と退院時のFIM利得の平均値は27.7であったが，留置群は1.2であった．退院時の食事は抜去群では18名中17名が3食経口摂取に至ったにもかかわらず，留置群は10名中1名しか3食経口摂取が可能にはならなかった．転帰先が自宅であった症例は抜去群では18名中12名であったが留置群では10名中3名であった．【結論】カニューレは嚥下，ADLに影響をきたす重要な因子である．適切に気管カニューレを抜去し嚥下リハビリテーションをすすめていけば経口摂取につながると考えた．

O-44-1

Orthostatic cerebral anemia-POTS,NMS,Migraine studied by head up tilt test

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[目的]起立時症状で2000年からヘッドアップチルト（HUT）試験を行った1202名（複数回検査者は初回のみ登録）で，体位性頻脈症候群（POTS），神経調節性失神（NMS），片頭痛（Migraine:M）と確定診断に至った症例での起立前後の平均血圧（aBP）・脈拍（HR）・前額部脳血液量の変化から心脳血管系自律神経機能障害の特徴を検討した．[対象]POTSが62名（25±12歳），NMSが44名（48±26歳），Mが149名（33±16歳），対照が105名（47±12歳）である．[方法]HUTは，チルト角60度，15分間起立を原則とし行い，aBP・HR変化は，肘窩で通常血圧計を用い1分毎，右第Ⅲ指でFinapresを用い1拍毎に測定し，前額部脳血液量変化は，近赤外線分光法によりΔヘモグロビン（Hb）変化量（酸素化:ΔoxyHb，脱酸素化:ΔdeoxyHb，その総和:ΔtotalHb）を測定し求めた．統計上の血圧は肘窩のもの，NMSの失神時の値は失神出現で直ちにtilt終了のため参考値である．[結果]　ΔBPではNMS失神前（以後NMS）=-10mmHgで対照=4mmHgに比し有意な（以後省略）低下を，ΔHRではPOTS=35bpm＞NMS=19bpmの順で対照=5bpmに比し上昇を示した．ΔoxyHbではNMS=-0.039＜M=-.025＜POTS=-0.022の順に対照=0に比し低下を，ΔdeoxyHbでは，NMS=0.029＞POTS=0.022＞M=0.019の順に対照=0.009に比し上昇を，ΔtotalHbではNMS=-0.010＜M=-0.006で対照=0.010に比し低下を示した．[考察]起立ストレスで，ΔoxyHbは血液酸素量変化を示し，その低下は動脈の収縮を反映し局所的ではあるが脳貧血を意味する．よってNMS＞M＞POTSの順で脳貧血が強いことが示唆される．　ΔtotalHbは容量血管（静脈系）の代償機構を示し，負値が大きくなる程，障害が大きい．よってNMS＞Mの順で代償機構の破綻が示唆された．ΔHRからはPOTS＞NIRSの順で心交感系機能亢進，ΔaBPからはNMSで血管交感系機能低下が示唆された．【結語】主にMが脳，POTSが心臓，NMSが心臓，脳と体血管の障害を示すが，脳循環障害の類縁性から"起立性脳貧血（を示す）疾患群であると考えられた．

O-44-2

Enhancement of coupling between slow waves and high gamma activities during slow wave sleep in human

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[Objective]Interaction between different frequency bands ("Cross Frequency Coupling (CFC)") is thought to be important for information processing in human brain, e.g. perception, visual, memory consolidation. Though slow oscillations (0.5-3.5Hz) during slow wave sleep (SWS) is known to couple with faster oscillations such as gamma (30-120Hz), dynamic change of CFC in different sleep stages has yet to be elucidated. The purpose of this study is to clarify the temporal dynamics of CFC in the human brain of different sleep stages. [Methods]Three medically intractable epilepsy patients with invasive recording for epilepsy surgery participated (IRB No.79). Electrocorticogram (ECoG) was recorded during a whole night with scalp EEG, EOG and EMG of the chin. Instantaneous amplitude of 2-300 Hz frequency band and phase of 0.02-20 Hz frequency band on ECoG were calculated in each sleep stage separately. After removing artifacts and spikes, correlation coefficients between the amplitude and the phase were calculated in each electrode. [Results]Among the whole electrodes investigated (209) across the patients, significant couplings between phase of delta (0.5-2Hz) and amplitude of high gamma (50-150 Hz) were observed in the following descending order: SWS (89), light sleep (37), waking (12), and REM sleep (10). High gamma tended to couple with the positive half wave of the delta activity ("UP state") [Conclusions]Coupling between high gamma and delta was enhanced at the "UP state" as sleep deepened, thus slow waves are not only sign of resting brain, but could modulate neuronal firing.

O-44-3

Withdrawn

O-44-4

Ultrasonographic evaluation of upper extremities in polio survivors (1)

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【目的】ポリオ患者罹患者(ポリオ)における臨床所見と神経筋超音波所見の特徴を明らかにする．ポリオにおける臨床所見と超音波所見の相関を検討する．【方法】対象はポリオ患者24名（M:F=11:13，平均60.3歳）と 年齢・体重調整した健常成人25名（M:F=121:133，平均58.9歳）について前向きに検討した．超音波検査装置はToshiba製Aplio XG, 15-18MHz周波数帯高周波リニアプローブを用いた．評価項目として両側頸部神経根（C5-C8），正中・尺骨神経の手首，前腕，肘，上腕の4点それぞれの断面積（CSA）と上腕二頭筋厚を計測した．臨床所見として両上肢（三角筋，上腕二頭筋，上腕三頭筋，手関節屈曲/背屈，手指屈曲/背屈）のManual muscle strength test（MMT）と肢ごとの合計値（MMT sum），重症度として**National Rehabilitation Hospital classification（NRH class）**分類を記録し統計学的に解析を行ったした．【結果】C5（p＜0.01），C7および（p＜0.05）C5-C8合計 CSA値（Root Sum）（p＜0.05）には健常成人群に比べてポリオ群では有意な低下を認めた．一方，正中神経手首部CSA（p＜0.01）はポリオ群で有意な増大を認めた（p＜0.05）．他部位のCSA，上腕二頭筋厚に明らかな有意差を認めなかった．臨床所見との検討ではMMT sumとRoot sumの間に有意な正の相関（r=0.407, p=0.001）を，Root SumとNRH classとの間に有意な負の相関（r=-0.409, p＜0.01 ）を認めた．【結論】神経筋超音波検査はポリオ罹患者の末梢神経・筋の評価に有用であった．また，筋力や重症度とも有意な相関を示した．ポリオ罹患者の正中神経手首部のCSA増大は日常生活での過伸展や使用過多による影響が考えられる．

O-44-5

Fasciculation potential in amyotrophic lateral sclerosis using high density-surface electromyography

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[Objective] To evaluate the fasciculation potentials (FPs) delivered from the patients with amyotrophic lateral sclerosis (ALS) using high density-surface electromyography (HD-sEMG).[Background] Detection of FPs is an important clue to the diagnosis of ALS, however, the number of muscle surveyed by invasive needle electrode is limited. Clinical utilization of HD-sEMG may be useful for recording FPs non-invasively, but it has not been verified whether FPs can be distinguished from motor unit potentials (MUPs).[Methods]19 ALS patients were participated. HD-sEMG electrode (12 Ag/AgCl coated 1-mm round plate electrodes arranged in a 3 x 4 rectangular matrix with a 5-mm interelectrode distance, original product) was placed on the belly of the intrinsic hand muscles. The signals were recorded monopolarly with reference electrode on the styloid process of the ulna. Three identical motor unit potentials were captured during minimally weak voluntary contraction. FPs were also recorded in a completely relaxed state. The waveforms and the spatiotemporal characteristics were compared between FPs and MUPs on offline analysis.[Results]FPs were detected in 19/57 muscles. 94% of FPs could be distinguished from MUPs with waveform comparison in monopolarly and bipolarly by visual inspection. 6% of FPs were identical with MUPs firing in minimally weak voluntary contraction.[Conclusions] FPs in ALS could been identified by using a HD-sEMG noninvasively. Whether some FPs, same as the MUP, were contraction fasciculation potentials or fasciculation potentials of the proximal origin, is unknown.

O-45-1

Turnover movements using a wearable accelerometer in patients with different types of motor deficits

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[Objective] We aimed to correlate between disease specific clinimetric scores and overnight monitoring data of turnover movements in patients with motor deficits caused by different diseases. [Methods] Overnight monitoring of turnover movements was performed in 93 patients consisting of Parkinson's disease (PD) (n=36, 74.5 ± 8.0 yr, UPDRS 48.2 ± 18.1), stroke with hemiparesis (n=18, 67.4 ± 15.6 yr, NIHSS 2.61 ± 1.46), Spinocerebellar degeneration (SCD) (n=16, 63.9 ± 11.2 yr), paraplegia (n=9, 55.3 ± 14.2 yr) and volunteers without motor deficits (n=14, 62.9 ± 17.8 yr). The number of overnight turnover movements (OTM) was correlated with clinimetric scores at day time.[Results] The mean number of OTM were 4.9 ± 4.3 times in PD patients, 7.4 ± 5.2 times in patients with hemiplegia, 9.3 ± 6.7 times in SCD patients, 7.2 ± 5.4 times in patients with paraplegia, and 18.6 ± ± 11.4 times in volunteers. Numbers of OTM in patients with motor deficits were smaller than that in volunteers.In PD patients, numbers of OTM were not correlated with Yahr staging (r=-0.304, p=0.068) nor UPDRS (r=-0.101, p=0.602). In SCD patients, SARA (r=-0.613, p=0.015) was significantly correlation with the numbers of OTM. In patients with hemiplegia, NIHSS (r=-0.328, p=0.171) was not correlated with the numbers of OTM. [Conclusions] In contrast to the other neurologic diseases, the numbers of OTM were not correlated with disease specific clinimetric scores in PD. To estimate the problems of turnover movements in bed, objective overnight monitoring using a wearable motion recorder may be especially useful in PD patients.

O-45-2

Anhedonia and its correlation with clinical aspects in Parkinson's Disease

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Background: Anhedonia is one of the non-motor symptoms observed in the Parkinson's disease (PD). However, there is no clear relationship between anhedonia and its correlation with other symptoms of PD.Objectives: The aim of this study is to evaluate the characteristics of anhedonia and its correlation with clinical aspects of PD in a relatively large cohort.Methods: We enrolled 318 patients with PD and 62 control subjects for this study. Patients and subjects were tested using the Snaith-Hamilton Pleasure Scale Japanese version and the Beck Depression Inventory 2nd edition for the assessment of anhedonia and depression. We also investigated the correlation among clinical aspects of PD, anhedonia, and depression in patients with PD.Results: The Snaith-Hamilton Pleasure Scale Japanese version and the Beck Depression Inventory 2nd edition scores were significantly higher in patients with PD than in control subjects (p=0.03 and p=0.0006, respectively). All PD patients with anhedonia had a significantly higher score on the unified Parkinson's disease rating scale (UPDRS) parts I and II compared to PD patients without anhedonia. Additionally, all PD patients with depression scored significantly higher on UPDRS part I -IV than PD patients without depression. The patients with anhedonia and without depression had mild motor severity and their treatment was relatively low dosage.Conclusions: These results suggest that anhedonia and depression are slightly linked, but not the same. PD patients with only anhedonia may be closely linked apathy found in untreated early stages of PD.

O-45-3

Difference of REM sleep behavior disorder between the onset of before and after Parkinson's disease

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Objective: RBD is important on not only preclinical symptoms of PD but also aggravating symptoms of PD. However, it is unknown whether the onset of RBD affect clinical characteristics of PD. A cross section study comparing clinical characteristics of PD between PD patients occurring before and after the onset of PD was conducted.**Methods:** Interviews regarding RBD symptoms were conducted and polysomnography was performed on 136 patients with PD. Patients were divided into group with RBD and without RBD. Moreover, group with RBD were categorized as group with RBD before onset of PD (RBD→PD) and that after onset of PD (PD→RBD). Two subgroups were compared on clinical characteristics of PD.**Results:** Forty seven PD patients with RBD had more severe parkinsonian symptoms, autonomic dysfunctions, and cognitive impairments than 89 PD patients without RBD. Moreover, thirty eight PD patients with RBD preceding PD (PD→RBD) had more patients with cognitive impairment than 9 PD patients with RBD that proceeding PD (RBD→PD). **Conclusion:** The occurrence of RBD after the onset of PD might be important for aggravating factors of cognitive function.

O-45-4

家族性進行性核上性麻痺の遺伝子解析に基づいた孤発性進行性核上性麻痺の遺伝子解析

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〔**背景，臨床像と目的**〕遺伝性進行性核上性麻痺(PSP)の報告はまれである．最近，常染色体優性遺伝性PSP家系を経験し，そのうち1例の剖検を施行した．発端者は現在64歳男性．43歳頃より記銘力障害，52歳頃より動作緩慢や易転倒性が出現し，53歳時に当科初診．認知機能障害(MMSE 12/30)，垂直性核上性眼球運動障害，頸部に強い筋強剛，姿勢反射異常，両側把握反射，吸引反射が認められた．母と兄に類症を認め，兄は発端者と同様の臨床経過と神経徴候を認め，64歳で死亡し剖検が施行された．母は80歳頃より姿勢反射異常で発症しており，認知機能障害の程度は子等のそれより軽度であった．いずれも臨床的にPSPと診断された．神経病理学的には海馬，淡蒼球，視床下核，黒質を中心に神経変性を認め，同部に神経原線維性変化が顕著であったが老人斑は認められず，3+4リピートタウオパチーの所見であった．本疾患の病態解明を目指し神経病理学的解析と遺伝子解析を行った結果を踏まえ，孤発性PSPを対象に遺伝子解析を行った．〔**結果および考察**〕過去に遺伝性PSPの原因遺伝子として報告されている*MAPT, DCTN1, TARDPB, C9ORF72*遺伝子を含む50遺伝子を候補遺伝子として解析したが，それらの遺伝子には原因となる変異を認めなかった．さらに，連鎖解析およびエクソーム解析を行ったところ，神経系に発現する遺伝子の1つに発症者特異的に新規missense変異が存在することを見出した．この遺伝子について，孤発性PSP 42例を対象に解析したところ，5症例において家系例とは異なる4種類の新規missense変異が認められた．これらの遺伝子変化は健常者データベースに記載が無いか，0.5%以下の極めて稀な変化である．新たに見出したこの候補遺伝子は中枢神経に特異的に発現するタンパクを翻訳する．現在，このタンパクの抗体を使用して神経免疫学的検討を進めている．

O-45-5

進行性核上性麻痺の自然史と経腸栄養による治療介入についての検討

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【目的】進行性核上性麻痺（PSP）では，嚥下障害はしばしばみられる症候であり，経腸栄養による治療介入が有効である．PSPの自然史と経腸栄養による長期効果について検討する．【方法】対象は当科にて診療を行い，死亡まで経過を確認できたPSP 21例（男性11例，女性10例）であり，臨床亜型はRichardson症候群（RS）18例（deficit PSP 3例，probable PSP 12例，possible PSP 3例），PSP-parkinsonism（PSP-P）3例（deficit PSP 1例を含む））であった．発症年齢，医療機関受診までの期間，車椅子生活までの期間，経腸栄養の介入，全経過について後ろ向きに検討した．【結果】RSとPSP-Pにおける各群間での比較では，発症年齢，医療機関受診までの期間，車椅子生活までの期間，全経過は，それぞれ71.4±7.0歳vs73.0±3.5歳，0.8±1.1年vs1.7±2.1年，3.9±2.2年vs6.3±5.5年，7.3±3.3年vs8.7±4.6年であった．経腸栄養による治療介入を行なわれたのは，RSにて7例（38.9%），発症後5.4±2.5年で開始となっていた．PSP-Pでは経腸栄養を行われた症例は，0例（0%）であった．RSのうち経腸栄養の有無における各群間での比較では，車椅子生活までの期間，全経過は，それぞれ4.1±3.0年vs3.7±1.6年，9.2±4.9年vs6.0±1.7年であった．【結論】RSと比較してPSP-Pでは，発症年齢が高く，医療機関受診までの期間，車椅子生活までの期間，全経過のいずれもが長かった．RSのなかで経腸栄養による治療介入を行った群では，治療介入しなかった群と比べ車椅子生活までの期間，全経過は延長し，積極的な栄養管理が有用であると考えられた．

O-46-1

Chronic hypoxia facilitates Alzheimer's disease through demethylation of gammasecretase

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ObjectiveEnvironmental factors and epigenetic mechanisms are believed to contribute to Alzheimer's disease (AD). We previously documented that prenatal hypoxia aggravated the cognitive impairment and neuropathology in offspring mice. Here, we investigate the chronic hypoxia-induced epigenetic modifications in AD.MethodsThe 3-month-old APPswe/PS1dE9 mice were exposed to hypoxic environment 6 hour/day for 30 days, followed by learning and memory tests and biochemical and neuropathology measurement at the age of 4, 6, and 9 months.ResultsWe found hypoxia exaggerated the neuropathology and cognitive impairment in AD mice. Chronic hypoxia induced demethylation on genomic DNA and decreased the expression of DNA methyltransferase 3b (DNMT3b) in vivo. We further found that DNMTs inhibition elevated the protein levels of amyloid precursor protein, β- and γ-secretases, whereas overexpression of DNMT3b suppressed the levels of them in vitro.ConclusionsOur study suggests chronic hypoxia can aggravate AD progression through demethylation of genes encoding γ-secretase components by downregulation of DNMT3b.

O-46-2

BMP-4 expression by pericytes after ischemia aggravates white matter damage

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[Objective] The aim of this study was to characterize signaling abnormalities of transforming growth factor β (TGF β) superfamily members in vascular cognitive impairment (VCI). **[Methods]** To investigate the role of BMPs in VCI, we performed an immunohistochemical study using post-mortem frontal lobe tissues from 6-7 cases of VCI, Alzheimer's disease, and age-matched controls, using antibodies against TGF β1, BMPs (BMP-2/4/6/7/9), as well as two pericyte markers and an oligodendrocyte precursor cell (OPC) marker. We subsequently tested oxygen-glucose deprivation (OGD) in cultured pericytes to simulate ischemia, and also investigated effects of BMP-4 on cultured vascular cells and myelin related cells. **[Results]** Among the TGF β superfamily members, BMP-4 was highly expressed in pericytes in the white matter of VCI, and its expression correlated with the degree of myelin loss. Continuous OGD induced BMP-4 expression in cultured pericytes. Furthermore, BMP-4 induced tube formation of endothelial cells and proliferation of pericytes. BMP-4 suppressed maturation of OPCs and strongly induced conversion of OPCs to astrocytes. **[Conclusions]** Our findings suggest that ischemic myelin damage evolves in parallel with BMP-4 upregulation in pericytes. BMP-4 expression promotes angiogenesis but induces astrogenesis at the expense of OPC maturation and proliferation, which may aggravate myelin damage. These results may explain why white matter is particularly vulnerable to chronic hypoperfusion. Regulation of BMP-4 signaling has the potential as treatment strategy for VCI.

O-46-3

The twenty-four kDa C-terminal tau fragment associates with propagation and calpain digestion

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Purpose＞ The truncated tau protein is a component of the neurofibrillary tangles. Two years ago, in this meeting, we reported that 24-kDa C-terminal tau fragment (Tau-CTF24), cleaved behind R242, increased with aging in tauopathy model mice (Tg601). In this paper, we examined whether or not calpain I is a responsible enzyme and Tau-CTF24 shows high propagation activity.Methods＞ SH-SY5Y cells were transfected with human tau and were digested with calpain-I. The western blotting of Tg601 mice brain extracts (N = 3) were done using antibodies against P35 , calpastatin , calpain-cleaved spectrin (136kf) and post-calpain-1. To analyze propagation activity, SH-SY5Y cells were cultured and transfected with the expression vector. Aggregated tau filaments or detergent-insoluble fractions from human brains were added to SH-SY5Y cells expressing Tau-FL or Tau-CTF24 and the culture continued for 48 h. Detergent-insoluble fractions were prepared and cells were stained with phosphorylated Tau antibodies.Results＞ The digestion of Tau-FL by calpain-I produced Tau-CTF24 in vitro. In old Tg601 mice, the amount of P35, P25 and 136kf increased and calpastatin decreased. When insoluble tau from diseased brains or aggregated recombinant tau was introduced as seeds into SH-SY5Y cells, a larger amount of insoluble tau was formed in cells overexpressing Tau-CTF24 than in those overexpressing Tau-FL. Immunoblot and confocal microscopic analyses revealed the aggregated Tau-CTF24 bound to cells more rapidly.Conclusion＞ Tau-CTF24 could be generated by calpain 1 and showed high propagation activity.

O-46-4

Loss of FUS causes phosphorylated tau accumulation in aged mice

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Aim: To investigate whether loss of FUS causes phosphorylated tau accumulation in aged mice. **Methods:** We generated hippocampus specific FUS-knocked down mice by injecting AAV expressing shRNA against FUS. The mice exhibited abnormal behaviors including aberrant anxiety, disinhibition, and hyper activity which mimicked FTLD-like behavioral impairments. Using this mouse model, we investigated the effect of FUS-silencing and subsequent change of Tau isoform ratio on phosphorylated tau accumulation in the hippocampus. **Results:** To investigate if FUS silencing followed by a change in the tau isoform ratio leads to deposition of tau phosphorylation, we examined aged mice with hippocampal-specific knock-down of FUS at 12, 18, and 24 months post-injection. Immunohistostaining with MC1, AT8, and PHF1 antibodies revealed inclusion-like phosphorylated tau signals as well as neuronal loss in aged shFUS mice. The phosphorylated tau levels were significantly increased in shFUS mice at 18 and 24 months, which was rescued by 4R-T specific co-suppression in shFUS mice. **Conclusion:** A pathophysiological link between FUS and the regulation of 4R-T/3R-T isoforms might be involved in the pathogenesis of FTLD/ALS and 4R-tauopathies.

O-46-5

Role of Complement Receptor 1 Mediated Mechanisms in Alzheimer Disease Related Tau Pathology

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Purpose: Complement component (3b/4b) receptor 1 (CR1), an important ingredient of complement system, was a newly identified locus which has close connections with Alzheimer's disease (AD). However, the mechanism of CR1 on AD-related taupathy remains unclear. Cr1-related protein Y (*Crry*), a rodent specific gene, which encodes an important cell-surface regulator of complement that shares great similar protein sequences and functions to human CR1, and Crry in murine model has been widely accepted as the replace of CR1 in human. **Methods**: In this study, we aim to explore the potential mechanism of CR1 on AD-related taupathy via testing the role of Crry in a murine AD transgenic model. **Results**: Finally, we discovered that Crry protein was mainly located in microglia and upregulated in brain of P301s mice during aging process. When down-regulating the expressions of Crry, tau phosphorylation and cognitive functions deficiency were significantly alleviated via modulating neuroinflammation and complement system in AD context. **Conclusions**: These findings highlight the role of CR1 in AD-related taupathy and suggest that modulating CR1 may be promising therapeutic targets for AD.

O-47-1

Door-to-Imaging時間，Imaging-to-Needle時間，Door-to-Needle時間の関係

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【目的】急性期脳梗塞に対するtPA治療では，door-to-imaging時間（DTI time）はdoor-to-needle時間（DTN time）に強く関係しており，DTN 60分以内，DTI 25分以内が推奨されている．しかし，DTN timeとimaging-to-needle時間（ITN time）との関係についてはほとんど報告されていない．DTN time 60分以内を達成するためには，画像診断の前と後の両方の過程が重要と推察される．我々は，tPA治療を行った症例において，DTI time，ITN time，DTN timeの関係を調べた．【方法】日本，豪州それぞれ1施設ずつにおいて，tPA治療の可能性があり緊急治療体制をとった症例を前向きに登録した．本研究では，発症から4.5時間以内にtPA治療を行った122例を評価した．DTN time，DTI time，ITN timeを解析し，また，近年米国から報告されているデータと比較した．【結果】平均年齢72±14歳，治療前NIHSSスコア中央値16，男性50%であった．DTN timeは中央値56分，DTI time 26分，ITN time 29分であった．72%の症例でDTI timeが25分以内，59%の症例でDTN time 60分以内であった．DTI time（スピアマン相関係数 0.68, p＜0.01），ITN time（0.67, p＜0.01）は，それぞれDTN timeと相関関係がみられた．一方，米国の報告では，ITN timeとDTN timeとの間に強い相関関係（相関係数 0.90）がみられ，本研究に比してITN timeが有意に長かった（DTN time 76分，DTI time 19分，ITN time 54分）．【結論】DTI timeとITN timeは，いずれもDTN timeに寄与する．画像診断後に治療開始が遅れることはDTN timeに影響する可能性がある．

O-47-2

主幹動脈閉塞を予測するプレホスピタル脳卒中スケール：FACE2-ADスケール

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【目的】主幹動脈閉塞（Large Vessel Occlusion，以下LVO）による脳梗塞は迅速に血管内治療が可能な施設へ搬送する必要がある．救急隊が簡便にLVOを予測するスケールを考案した．【方法】対象は，2012年4月～2015年2月に脳卒中疑いまたは意識障害のため当院へ救急搬送された5504例のうち，発症24時間以内に受診し，画像検査で頭頸部の血管評価を行った患者．データ欠損例は除外した．LVO（内頚動脈，中大脳動脈［M1またはM2］，脳底動脈）に関連する因子を抽出し，予測スケールを考案した．【結果】解析対象となった1444例（男性876例，年齢71.2±14.2歳）のうち，脳梗塞を436例に認め，そのうちLVOは130例であった．脳梗塞以外に脳出血233例，てんかん126例，一過性脳虚血発作58例，くも膜下出血45例などが含まれていた．救急隊搬送記録でLVOに関連した因子は，高齢，顔面麻痺，上肢麻痺，言語の障害，意識障害（JCS≧3），眼球共同偏倚，心房細動（Atrial fibrillation，以下Af），拡張期血圧低値であり，ロジスティック回帰分析では，顔面麻痺（オッズ比[OR] 2.04, 95%信頼区間[CI]1.28-3.26），上肢麻痺（OR 1.65, 95%CI 1.02-2.66），JCS≧I-3（OR 1.71, 95%CI 1.08-2.72），共同偏倚（OR 12.61, 95%CI 7.54-21.50），Af（OR 2.54, 95%CI 1.57-4.48），拡張期血圧≦85mmHg（OR 2.47, 95%CI 1.60-3.88）が関係していた．そこで顔面麻痺（Face），上肢麻痺（Arm），JCS≧I-3（Consciousness），Af，拡張期血圧≦85mmHg（Diastolic blood pressure）を各1点，共同偏倚（Eye deviation）を2点としてFACE2-ADスケールを作成した．FACE2-ADスケールが3点以上の場合，LVOの検出率は感度88%，特異度76%，陽性的中率27%，陰性的中率98%，Area Under Curve 0.88（p<0.001）であった．【結論】FACE2-ADスケールは，救急隊による簡便な評価でLVOによる脳梗塞患者のトリアージに有用と考えられる．今後，前向きの検証研究が必要である．

O-47-3

塞栓源不明の脳梗塞患者の臨床的特徴

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【目的】近年，塞栓源不明の脳梗塞をESUS（Embolic strokes of undetermined source）と診断する新しい概念が提唱されているが，その診断には右左シャントの有無，深部静脈血栓や大動脈弓部粥腫病変の検索は必須ではないとされている．当院におけるESUS患者の臨床的特徴を検討した．【方法】2014年9月から2015年8月に当院の脳卒中科に入院した発症7日以内の急性期脳梗塞患者284例中，MRI施行可能であった280例（男性156例，75±12歳）を対象とした．ESUSの割合，入院後に行った各種検査施行率を後方視的に調査した．また，TOAST分類におけるsmall vessel occlusion（SVO），large artery atherosclerosis（LAA）と背景因子を比較検討した．【結果】ESUSの診断にはホルター心電図や経胸壁心エコーの検査を必須とし，診断基準に合致した症例は69例（24.6%）であった．ESUS患者における各種検査施行率は経頭蓋超音波における右左シャント検出（87.0%），経食道心エコー検査（46.4%），下肢エコー検査（36.2%）であり，69例中8例が大動脈原性，7例が奇異性，5例が活動性悪性腫瘍合併，4例が原因複数の脳塞栓症，44例（64.7%）が原因不明の脳塞栓症であった．原因不明の脳塞栓症の退院時の抗血栓療法は37例（84.1%）で抗血小板薬を，6例（13.6%）で抗凝固薬を選択していた．TOAST分類でのSVO患者（41例），LAA患者（39例）と比較して，ESUS患者は年齢，性，脳卒中の既往，高血圧，脂質異常症には差がなかったが，糖尿病を有する率が有意に低かった（14.5% vs. 33.8%，P=0.008）．また，入院時BNP値（92.2±105.9 vs. 63.9±63.9 pg/ml, P=0.047）やD-dimer値（中央値[4分位], 1.3 [0.6-2.8] vs. 0.8 [0.5-1.8] μg/ml, P=0.007）が有意に高値であった．【結論】ESUS患者の半数以上が各種検査施行後も原因不明の脳塞栓症患者であった．ESUS患者はSVO患者やLAA患者に比べてBNPやD-dimerが高値であった．

O-47-4

一過性黒内障を呈した一過性脳虚血発作の特徴と予後の検討-Fukuoka Stroke Registry-

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【目的】一過性黒内障（transient monocular blindness：TMB）は虚血に由来する一過性の視力障害であり，一過性脳虚血発作（transient ischemic attack：TIA）の一症状である．TMBを主訴として発症したTIAの臨床的特徴と，その後の脳虚血イベント（脳梗塞発症またはTIA再発）発症率について検討する．**【方法】**2007年6月から2015年7月までにFukuoka Stroke Registry（FSR）に登録された発症7日以内の急性期脳卒中連続10,586症例のうち，TIA連続1,392症例（男性 872例，女性 520例，年齢 70±13歳）を対象とした．TMBにて発症したTIA群（TMB群）とそれ以外のTIA群（非TMB群）の2群に分け，背景因子，脳虚血イベント発症率について比較検討した．**【結果】**92症例（6.6%）がTMB群に，1,300症例（93.4%）が非TMB群に分類された．TMB群は非TMB群と比較して高血圧（66% vs 76%, p=0.039），2型糖尿病（16% vs 28%, p=0.017），心房細動（11% vs 19%, p=0.049）の合併頻度が有意に低く，症状持続時間が10分未満と短い症例が多く（54% vs 19%, p<.0001），ABCD^{2}スコアは有意に低かった（2［1-3］vs 4［4-5］, p<.0001）．来院時の血圧は収縮期血圧（138±23 vs 156±28, p<.0001），拡張期血圧（78±13 vs 85±18, p<.001）ともにTMB群が有意に低く，またDWI陽性率もTMB群が有意に低かったが（13% vs 44%），先行するTIAの既往（30% vs 19%，p=0.006），主幹動脈病変を有する頻度（37% vs 20%，p<.001）はTMB群が有意に高かった．TIA発症後の脳虚血イベント発症率は，3ヶ月，6ヶ月の時点では非TMB群が有意に高かったが（Log-rank test; p=0.029, p=0.014）が，1年後の時点では両群に有意差を認めなかった（Log-rank test; p=0.124）．**【結論】**TMB症例ではその他のTIA症例と比較して発症後早期の脳虚血イベント発生率は低いが，長期的には両者に有意差は認めなかった．

O-47-5

日本国内の都市部と地方におけるTIAの臨床的特徴と急性期診療：PROMISE TIA研究班

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【目的】日本の都市部と地方における，一過性脳虚血発作（TIA）の診療内容や予後の違いを明らかにする．【方法】Promise TIA registryは2011年6月から2013年12月の期間に発症から7日以内のTIAを登録し，登録後1年間の追跡を行った多施設共同前向き研究である．参加57施設の所在地の人口密度を求め，その中央値である1350/km^2（IQR：814-4450）を基準とし，それ以下を地方，より上を都市部と定義し2群間の臨床的特徴を比較した．【結果】1年後のフォローアップを完了した1226例が対象となった．都市部は18施設588例（女性212例，69±12歳），地方は39施設638例（女性217例，70±12歳）であった．都市部において糖尿病の既往（26%対19%，p=0.002）や脳卒中の家族歴（21% vs 13%，p<0.001）をもつ症例が多く，発症前のアスピリン内服が多かった（21% vs 15%，p= 0.011）．ABCD^{2}スコアは都市部で高く（median 5 [IQR 4-6] vs 4 [3.75-5], p=0.007），都市部ではより多くが入院治療を受け（96% vs 89%，p<0.001），ホルター心電図（43% vs 17%，p<0.001），経胸壁心エコー（75% vs 54%，p<0.001），経食道心エコー（32% vs 7%，p<0.001），頸動脈エコー（86% vs 51%，p<0.001）の施行率が高かった．これらの違いは，性別，年齢，入院の有無で調整した多変量解析でも有意であった．病型診断では，都市部において，TOAST分類におけるその他の病型が多かったが（8% vs 4%，p=0.014），3か月後および12か月後の虚血性脳卒中の発症率には差がなかった．【結論】都市部と地方とでは，TIA患者の臨床像や急性期診療の内容に，いくつかの違いがみられた．

O-48-1 **海外最優秀候補演題**

Greater progression of Parkinson disease in patients carrying LRRK2 risk variants

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Objectives: To characterize clinical characteristics and progression in patients with LRRK2 variants, G2385R, R1628P and S1647T, which are associated with increased risk for Parkinson Disease（PD）in Asian population.**Methods:** A total of 202 patients with PD, including 133 patients with risk variants and 69 patients without these variants, were followed up and evaluated using Modified Hoehn and Yahr（H&Y）staging scale, Unified Parkinson's Disease Rating Scale（UPDRS）part III, Non-Motor Symptom Scale（NMSS）, Parkinson's disease Questionnaire-39 item version（PDQ-39）and Elderly Cognitive Assessment Questionnaire（ECAQ）. Means of generalized estimating equation（GEE）model was performed to compare the differences from baseline between LRRK2 risk variant carriers and non-carriers.**Results:** At baseline, patients with risk variants exhibited significantly worse ECAQ score（P=0.0202）and PDQ-39 domain 1（mobility）（P=0.0253）, domain 2（activities of daily living）score（P = 0.0154）than control patients. Our longitudinal analysis revealed greater progression from 3 year of PD onwards by using Modified Hoehn and Yahr（H&Y）staging scale（P=0.041）.**Conclusions:** PD patients with Asian specific risk variants（G2385R, R1628P and S1647T）in LRRK2 may experience severe disease progression in the long-term follow up.

O-48-2

Consistency of asymmetry between on IMP-SPECT and on DAT scan in multiple system atrophy

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Object Multiple system atrophy（MSA）usually shows symmetrical, levodopa unresponsive parkinsonism. It has been reported that only 20% of patients with pathological definite MSA have asymmetrical parkinsonian features as rigidity and akinesia. It has been also reported, however, that higher incidence of asymmetry of signal changes in nuclear medical studies such as DAT scan on striatum and IMP-SPECT on cerebellum than of clinical symptoms. On the other, the study about consistency of asymmetry between on IMP-SPECT and on DAT scan has never been reported. **Patients and Method** We retrospectively reviewed 26 MSA patients（11 MSA-C, 15 MSA-P）and 11 Parkinson's disease patients who underwent both DAT scan and IMP-SPECT. The normal ranges were defined as 10% of difference of specific binding ratio（SBR）on DAT scan and the mean + 2SD of asymmetrical property of signals in cerebellum of PD patients on IMP-SPECT. **Results** Asymmetry was observed in 19 MSA patients（15 MSA-C, 4 MSA-P）on SBR of DAT scan and in 7 MSA patients（5 MSA-C, 2 MSA-P）on cerebellar blood flow of IMP-SPECT. In terms of consistency of asymmetry of signal changes, ipsilateral asymmetry between on DAT scan and on IMP-SPECT was seen in 5 of 7 MSA patients. **Conclusion** Ipsilateral asymmetry between on DAT scan and on IMP-SPECT was more frequently observed in this study. Because cerebellum is strongly connected with contralateral cerebral hemisphere functionally and anatomically, the results may provide suggestions to the hypothesis about molecular mechanism of propagation of pathology in MSA.

O-48-3

Usefulness of electrogastrography for the diagnosis of Parkinson's disease in early stage

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[目的]未治療・早期パーキンソン病（PD）の診断における胃電図の感度と特異度を嗅覚検査，MIBG心筋シンチグラフィーと比較する．[方法]未治療PD37名(年齢66±8.1歳，罹病期間17±7.2か月)，健常対照23名(年齢69±7.0歳)で胃電図（胃電計EG，ニプロ社），嗅覚検査（OSIT-J，第一薬品産業）を測定した．PD群ではMIBG心筋シンチグラフィーも行った．胃電図記録を流動食負荷前後で行い，空腹時20分，食後20分（食後1），食後20～40分（食後2）の3区画でスペクトル解析を行い，それぞれの主要周波数（DF），DF変動係数(ICDF)，全積算パワーに対する徐波領域（1.6-2.0回/分），正常波領域（2.0-4.0回/分），速波領域（4.0-9.0回/分）の%比を算出した．[結果]胃電図所見では，空腹時のICDFは対照群（3.7±3.7%）と比べてPD群（9.5±6.3%）で有意に高かった（p=0.001）．空腹時および食後2の正常波%比はPD群で有意に低かった．OSIT-Jは対照群（7.2±3.8）と比べPD群（4.6±3.3）で有意に低かった（p=0.01）．PD群のMIBG集積の心縦隔比は早期相2.10±0.69，後期相1.96±0.92，wash out比率50.9±16.9%であった．空腹時ICDFは基準値を4.55とすると感度67.6%，特異度82.6%であり，OSIT-Jは基準値を5.5とすると感度59.5%，特異度73.9%であった．当施設での基準値を用いるとMIBG筋シンチグラフィーの感度は後期相新縦隔比で70.3%，wash out比率で81.1%であった．空腹時ICDFはOSIT-J，MIBGの各指標と相関しなかったが，MIBGの各指標と嗅覚検査は相関した．[結論]胃電図の空腹時ICDFはPDに対して嗅覚検査よりも優れた特異度と感度を，MIBG心筋シンチグラフィーと同等の感度を示し，PDの早期診断に有効である可能性がある．PDの胃電図異常はMIBG心筋集積低下や嗅覚異常と相関がなく，心交感神経節後障害や嗅覚低下とは異なる病態背景を反映している可能性がある．

O-48-4

Analysis of the Differential Diagnosis between Parkinson's disease and vascular parkinsonism

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【目的】パーキンソン病(PD)と脳血管性パーキンソン症候群との鑑別は進行期では比較的容易ではあるが，パーキンソン病の初期や軽度の脳梗塞によるパーキンソン症候群との鑑別は困難なことが多々ある．最近はDaT scanやMIBG心筋シンチで，パーキンソン病において特徴的所見を示すが，病初期では有意差がでないことがある．早期にこの両疾患を鑑別できることは今後の治療方針にも寄与することになる．【方法】PDと脳血管性パーキンソン症候群のMRI所見の差異，臨床症状の特徴の相違点，臨床検査所見で鑑別に寄与する点を比較検討する．PDでは血清中のmonoamine oxidaseが上昇するとの報告があるが，我々は今までの解析ではパーキンソン病の初期から血清中の内因性のmonoamine oxdase阻害物質であるisatinが低下する傾向にあることを示した．採血後，血清に分離し，-80℃で保存，酢酸エチルでisatinを抽出後，固相カラム精製後，HPLV-UVを用いて定量した．血清isatin濃度をPDと脳血管性パーキンソン症候群で測定し，臨床画像と比較した．症例はPD症例数85例，脳血管性パーキンソン症候群症例数は8例で少ないが，純粋に脳血管障害のみによる症例を選んだ．コントロール症例数58例．【結果】臨床的には両群とも動作緩慢，小刻み歩行はよくみれる所見であった．安静時振戦は主にPDでみられ，歯車様筋固縮はPDでは高率に認められたが，脳血管性では比較的固縮の軽度なものが多かった．投薬の反応はPDではよかったが，予想に反し，脳血管性でも反応例は半数以上認められた．脳血管性パーキンソン症候群ではisatinはコントロールに比べ，同じか上昇傾向であったが，PDでは有意に低下した．【結論】isatinの測定は鑑別に有効性が示唆されたが，特にPDの病初期や比較的軽い脳血管性パーキンソン症候群の鑑別に役立つと考えれる．今後脳血管性パーキンソン症候群の症例解析数を増やし，臨床所見や画像所見の相関性を比較する必要がある．

O-48-5

Clinical evaluation for SWEDDs patients using 123I- MIBG myocardial scintigraphy

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目的：パーキンソン病(PD)では臨床症状出現以前から黒質線条体ドパミン神経終末に変性が起こっているため，^{123}I-FP-CITドパミントランスポーターSPECT（DAT-SPECT）は発症早期から異常を示すとされている．しかし，その異常がない症例もあり，SWEDDsと称される．本研究ではSWEDDsの臨床的特徴を明らかにする目的で，^{123}I- MIBG心筋シンチグラフィー(MIBG)を一緒に施行した症例を対象として，MIBGの異常の有無でSWEDDsを2群に分け，各群の特徴について検討した．**対象と方法**：対象は2年以内の間隔でDAT-SPECTとMIBGをともに行い，臨床症状からはPDが疑われる145例（男性73例，女性72例）．DAT-SPECTは^{123}I-イオフルパン静注後30分で撮像，画像評価は左右の線条体のSBRで行い，左右差(SAI)も計算した．MIBGは早期像(E)，後期像(D)のH/M比およびWRを算出し，施設基準係数で補正した標準化値を用いた．DATのSBRは4.5以下，MIBGはE, Dともに2.2以下を異常とした．また，症候から振戦優位型（T型），固縮・寡動型（RA型）に分類した．**結果**：145例中，SWEDDs症例は30例（20.7%）であった．このうちMIBGのH/M(E)で異常を示したAN群は11例（男性7例，女性4例，平均年齢67±9歳），正常(N群)は19例（男性8例，女性11例，平均年齢67±10歳）であった．MRI画像，抗パーキンソン病薬の反応性，臨床経過を考慮した結果，AN群で最終的にPDと診断したのは9例(81.8%)であったのに対し，N群では11例(57.9%)であった．その2群について年齢，Hoehn & Yahr stage，罹病期間，SBR，SAI，WR及び症候型で比較した結果，両群に有意差は認めなかった．**結論**：SWEDDsでもMIBG心筋シンチのH/M比の異常があると，PD以外の疾患を区別できる確率が高まるが，H/M比の異常の有無により分類される2群のSWEDDsの臨床背景，運動症候，SBR，SAI，WRには有意差はなく，今後，非運動症候の違いなどが検討課題となる．

O-49-1

Clinical profiles of orbital inflammatory pseudotumors with neurological involvement

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Background: Orbital inflammatory pseudotumor（OIP）is a non-infectious and non-neoplastic clinical syndrome characterized by the presence of an inflammatory mass at orbital level. The disease often shows neurological signs including cranial nerve palsies. **Objective:** To elucidate clinical, radiological and immunological features of OIP with neurological signs. **Methods:** We retrospectively investigated clinical profiles in 14 patients（7 females, 7 males）having OIP with neurological sings between 2010 and 2015. **Results:** Among the 14 Japanese patients having OIP with neurological signs, 7 patients（50%）had idiopathic OIP, 2 patients（14%）had OIP with IgG4-related disorders, 2 patients（14%）had SAPHO syndrome with OIP, 1 patients（7%）had PR3-ANCA$^+$ OIP, 1 patients（7%）with MPO-ANCA$^+$ OIP, and 1 patients（7%）had sarcoidosis with OIP. The median age onset was 63 years（interquartile range, 44-84）. Cranial nerves（CN）involvement was shown in CN II（50%）, III（71%）, IV（21%）, V（14%）, and VI（36%）. Twenty-one percent of patients had involvement of orbital muscles. MRI findings indicated that pseudotumors were located in orbital cavity（43%）and orbital apex（57%）, and 7% of pseudotumors extended in cavernous sinus. Sixty-four percent of patients had great efficacy of prednisolone monotherapy, but 7% of patients needed combination therapy of prednisolone and immunosuppressive drugs during disease courses. **Discussion/conclusion:** Our findings are consistent with a concept that OIP with neurological involvement is a unique immune-mediated syndrome.

O-49-2

Clinical, radiological and immunological features of idiopathic hypertrophic pachymeningitis

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Background: Hypertrophic pachymeningitis（HP）is thought to be associated with granulomatous disorders including autoimmune diseases and the 'idiopathic' variety. **Objective:** To confirm characteristic features and explore immunological factors of idiopathic HP. **Methods:** We retrospectively investigated clinical profiles of 36 patients with immune-mediated or idiopathic HP. All patients with idiopathic HP had seronegative status of MPO/PR3-ANCA, and normal value of serum IgG4. **Results:** Among the 36 Japanese patients with immune-mediated or idiopathic HP, 17 patients（47%）had MPO-ANCA$^+$ HP, 9（25%）had idiopathic HP, 4（11%）had PR3-ANCA$^+$ HP, and 6（17%）had other immune-mediated disorders including IgG4-related disorders. Idiopathic HP was characterized by: (i) a high frequency of patients with lesions limited to the dura mater; (ii) a high frequency of patients with otitis media; (iii) a high frequency of patients with involvement of cranial nerves II, VIII, IX and X; (iv) no patients with the classical form of granulomatosis with polyangiitis in contrast to PR3-ANCA$^+$ HP; (v) less severe neurological damage in contrast to PR3-ANCA$^+$ HP; and (vi) a high frequency of patients with good response of immunotherapy. **Discussion/conclusion:** Most of features in idiopathic HP were equivalent to those in MPO-ANCA$^+$ HP. These findings support that most of idiopathic HP may be potentially explained by pathogenesis with similarity to MPO-ANCA$^+$ HP. More sensitive assays of ANCA and more specific markers of IgG4-associated disorders are needed to further characterize the phenotype of patients.

O-49-3

Bedside three-step-diagnosis in 104 cases with neuroendocrinological disorders after HPV vaccination

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【目的】過去の疾患・症候群の診断基準に該当しない**HPVワクチン接種後副反応**の新規症候群を神経内科臨床診断の基本手法である**三段階診断**に即して解析する．【方法】対象は上記副反応疑いで登録された104例の女性（発症年齢16±4歳），ベッドサイドの三段階診断の基本に即して**解剖学的診断**，**病因学的診断**，**臨床診断**の順序で検討した．補助的情報を担う臨床検査結果（SPECT，　内分泌負荷検査，FDG－PETなど）と照合した．【結果】104例の中核障害は概日リズム障害，体温異常，記憶障害，計算障害，疲労，歩行障害，光・音過敏，疼痛などの特徴的スペクトラムで（1）自律神経・内分泌症候（2）情動・認知症候（3）視・聴・嗅・味覚・体性感覚症候（4）ロコモーション症候の4カテゴリーに分類できた．【考察】視床下部は自律神経調節，内分泌調節，神経炎症反射，認知・情動・行動機能，光・音過敏に関与することが動物実験並びに臨床研究で知られている．視索前野，外側視床下部，脳弓周辺部は生理的ロコモーションに，内側視床下部はロコモーション・ジャンプに，後部視床下部と外側視床下部は疼痛制御回路にそれぞれ関与する．病像スペクトラムは大脳皮質，錐体路，基底核，小脳，視床，辺縁系の単独病変による旧来の神経症候学では説明できず，**視床下部の単独障害と考えれば一元的に説明できる**．ワクチン接種から症状発現までの期間は，30日以内，30日～60日，1年以上2年未満のそれぞれに症状発現のピークを認め，多彩な症状が重層的に進展する**臨床経過は既知の自己免疫性チャネルパチーに類似していた**．補助的臨床検査では内分泌負荷試験が視床下部障害を示唆，SPECTは視床下部とネットワークを持つ前部帯状回の機能低下を示し，全身FDG－PETで免疫臓器の集積増加を認め，上記臨床診断と矛盾しない結果であった．【結論】**HPVワクチン副反応は心因反応ではなく**，視床下部を介する広範なストレス応答障害が主病態と考えた．

O-49-4

Gene expression profile of activated HTLV-1-infected cells from HAM patients

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[Objective] Although HTLV-1-infected cells rarely express HTLV-1 viral proteins in the peripheral blood, migrating infected cells into the spinal cords are activated and express the proteins in HAM patients, causing an HTLV-1-specific inflammation. It suggests that, if the cells were not activated, the inflammation may not occur. Here, we investigated gene expression profile of activated HTLV-1-infected cells compared with non-active infected cells to identify molecules for controlling HTLV-1-infected cells. [Methods] To enrich fresh HTLV-1-infected cells, we collected CD4+CADM1+ cells from peripheral blood lymphocytes of 4 HAM patients using a cell sorter. To obtain activated HTLV-1-infected cells, we cultured peripheral blood lymphocytes from 2 HAM patients for 18 hours, then collected CD4+Env+ cells. Total RNA extracted from these cells was subjected to microarray analysis using a 60k-formatted slide（Agilent Technologies）. [Results] After normalization of raw signal data, we performed statistical analysis. Based on the criteria of p-value ＜0.05 and fold change ＞2, 2344 genes of activated HTLV-1-infected cells showed significant changes in gene expression levels by the Welch T-test. [Conclusions] Activated HTLV-1-infected cells from HAM patients showed altered expression levels in a lot of host genes compared with fresh infected cells. We are further performing pathway and gene ontology analysis.

O-49-5

Molecular analysis of HTLV-1 subgroups associated with the risk of developing HAM

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[Objective] Among HTLV-1-infected individuals, the lifetime risk of developing HTLV-1-associated myelopathy（HAM）is associated with the HTLV-1 gene subgroups（i.e., subgroup-A or -B）. The purpose of this study is to understand the molecular mechanism responsible for this association. [Methods] We studied the functional difference in the viral transcriptional regulator Tax and HBZ between each subgroup by nucleotide sequencing, reporter gene assays and microarray analysis. [Results] （1）the distinct nucleotide substitutions corresponding to each subgroup are also associated with the nucleotide substitutions in other parts of the viral genes;（1）mRNA expression of HBZ in HTLV-1-infected cells was significantly higher in HAM patients with subgroup-B than those with subgroup-A;（2）transcriptional changes in inducible cells that express each subgroup of Tax or HBZ protein under the control of an inducible promoter showed different target gene profiles;（3）there was a positive correlation between HBZ and the expression of its target FoxP3 in HAM patients with subgroup-B but not in patients with subgroup-A; however,（4）there were no functional differences in Tax and HBZ between each subgroup evaluated by reporter gene assays. [Conclusions] These results indicate that different HTLV-1 subgroups cause different patterns of viral and host gene expression in HAM patients via independent mechanisms of direct transcriptional regulation, thereby associated with the onset of HAM.

O-50-1

A mutation in CACNA1G causes autosomal dominant spinocerebellar ataxia

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【目的】脊髄小脳変性症は遺伝的に多様性のある疾患である．これまでに優性遺伝性の遺伝子座はSCA1-41とDRPLAの36病型が報告されており，そのうち32病型で原因遺伝子が同定されている．今回，われわれは新規の原因遺伝子を同定するために，優性遺伝性脊髄小脳変性症の大家系を遺伝学的に解析した．【方法】原因遺伝子の同定には高密度SNPタイピングに基づく連鎖解析とエクソームシーケンスを用いた．電気生理学的検討として，培養細胞に野生型および変異型の*CACNA1G*を導入し，パッチクランプ法により電気生理学的特性の変化を解析した．また，患者由来iPS細胞を用いて小脳プルキンエ細胞への分化誘導を行った．【結果】新規原因遺伝子として電位依存性カルシウムチャネルの1つであるCav3.1をエンコードする*CACNA1G*を同定した．同一の変異を優性遺伝性脊髄小脳変性症の別の1家系でも認めた．Cav3.1は低電位活性型のT型カルシウムチャネルに分類され，小脳を含む中枢神経系にも豊富に発現している．われわれが同定した変異はカルシウムチャネルのリピートIVのS4に存在した．各リピートのS4は電圧センサーとして非常に重要なドメインであった．カルシウムチャネルの生理学的特性の変化を調べた結果，変異型ではプレパルスによる電流変化が陽性電位方向にシフトしていた．プルキンエ細胞への分化誘導には形態学的・免疫細胞化学的に変化を認めなかった．【結論】脊髄小脳変性症の多くは繰返し配列の異常伸長に起因して発症にいたるが，これまでにも，原因遺伝子としてカルシウムチャネルを含むいくつかのチャネル遺伝子が報告されており，今回の研究によって本症のチャネル病としての病態解明が一層進むものと期待される．

O-50-2

The clinical and pathological features of autosomal-dominant SCA with CACNA1G mutation

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[Introduction] Autosomal dominant cerebellar ataxias（SCAs）are clinically and genetically heterogeneous neurological disorders. Mutations in 29 different genes have been identified for SCAs. We describe the clinical phenotype and the pathological findings of a large Japanese family exhibiting a young adulthood onset SCA with several other symptoms, and having a mutation in *CACNA1G*, which was very recently reported as the cause of SCA. [Methods] To identify the disease locus, genome-wide single nucleotide polymorphism genotyping and linkage analysis were performed. To find a gene mutation, whole exome sequencing was performed on the family members. The genomic DNAs were processed using the SureSelect Human All Exon Kit, and sequenced by HiSeq 2500. Postmortem evaluations were conducted in one patient. [Results] The age onset of motor symptom was concentrated in young adulthood. Among nine affected members, one had learning disability, one had severe psychiatric problem, and three had truncal myoclonus. Otherwise, principal feature of the affected members was pure cerebellar syndrome with slight pyramidal signs. Linkage analysis and exome sequencing successfully identified the *CACNA1G* missense mutation. Pathologically, severe loss of Purkinje cells and ubiquitin-positive deposits of cerebral and cerebellar white matter were detected. [Conclusion] We reported the SCA family with *CACNA1G* mutation. Our findings will strongly consolidate *CACNA1G* mutation as the cause of SCA, and broaden the knowledge of clinical and pathological characteristics of the disease.

O-50-3

Mutational analysis of causative genes for autosomal recessive SCD in early-onset patients

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Objective:To elucidate the molecular epidemiology of early onset spinocerebellar degeneration（SCD）excluding AD-SCD by the mutational analysis of causative genes for AR-SCD.Methods:SCD patients with the age of onset under age 40 excluding SCA1, 2, 3, 6, 8, 12, 17,or 31, DRPLA, AOA2,or ataxia with vitamin E deficiency（AVED）were enrolled in this study. We also excluded patients with affected pedigree members in multiple generations. DNA samples were subjected to the mutational analysis of the whole exons of *APTX*, *SACS* and *SPG7* employing direct nucleotide sequencing method.Results:Among 139 patients with the diagnosis of SCD registered in our cohort, 26 patients consisting of 16 males and 10 females fulfilled the enrollment criteria. The mean age of onset was 17.4 years old（ranges: 0 - 39）. Three had positive family history with affected siblings. Novel heterozygous non-synonymous variants p.V540L in exon 12 in *SPG7* and p.M3551L in exon 10 in *SACS*, and heterozygous synonymous variants c.151C＞T in exon 3 and c.7074G＞T in exon 10 in *SACS* were identified, respectively. 31 known variants were identified including 2 homozygous and 7 heterozygous non-synonymous variants and 6 homozygous and 16 heterozygous synonymous variants in *SPG7* or *SACS*. No homozygous or compound heterozygous pathogenic mutations were identified.Conclusion:This study revealed that AOA1, AR-SACS, or SPG7 is not frequent in the early-onset SCD in the Japanese population. Considering the genetic heterogeneity of AR-SCD, exome-first approach would be efficient for genetic diagnosis of early-onset SCD.

O-50-4

Two Japanese families of hereditary spastic paraplegia (SPG9) probably caused by ALDH18A1 mutations

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[目的] 本邦の遺伝性痙性対麻痺家系においてRare variantの検索から*ALDH18A1*変異の症例を検討した．[対象と方法] エクソーム解析を行ったJASPAC症例の中で，コントロールのアリル頻度が2/922以下となる*ALDH18A1*のrare variantを検索した．[結果] 今回，*ALDH18A1*変異が原因であると考えられた2家系を見出した．第一家系は近親婚のある兄妹例で，発端者は*ALDH18A1*のホモ接合性変異を2つ有していた（p.F10L/p.R128H）．第二家系は近親婚のない兄弟例であり，発端者と弟は，複合ヘテロ接合性変異を有していた(p.R441*/p.R665Q)．両家系とも精神発達遅延を伴っていた．ミスセンス変異は，SIFT, PROVEAN, Polyphen2においてそれぞれp.F10L: tolerated, neutral, neutral, p.R128H: damaging, neutral, deleterious, p.R665Q: tolerated, neutral, probably damagingの判定であった．p.F10はマウスと象，p.R128とp.R665はヤツメウナギで保存されていなかった．HGVDではこれらのvariationの報告はなかった．[考察と結論] *ALDH18A1*はSPG9の原因遺伝子として報告された（2015年）が，今回我々は，本邦ではじめてのSPG9家系を見出した．その臨床像は，精神発達遅滞を伴うHSPであった．*ALDH18A1*変異は常染色体優性遺伝性と劣性遺伝性の両方の遺伝型式を取りうるので，遺伝形式にかかわらずHSPの原因遺伝子として検索すべきである．さらに，第二家系の母は高齢発症のALSであり，*ALDH18A1*とALSとの関連についても検討を行う必要があると考えられた．

O-50-5　**海外最優秀候補演題**

EPIDEMIOLOGICAL, CLINICAL, AND GENETIC STUDY IN A LARGE COHORT OF PATIENTS WITH SPASTIC PARAPLEGIA

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Purpose: This study includes the evaluation of a comprehensive spectrum of clinical features and the mutational screening of the SPG4/*SPAST* gene in patients with hereditary spastic paraplegia (HSP). **Method:** A large cohort of patients were recruited from Italian, Brazilian, and Japanese populations in a period from 2008 to 2015. Clinical and instrumental functional analyses consist of neurological assessment and neuroimaging. Mutational screening was carried out by Sanger sequencing and MLPA analysis. Haplotype studies were also performed. **Results:** Our study highlights clinical and epidemiological differences among populations, showing unique genotype-phenotype correlations. Genetic analysis revealed a total of 52 different pathogenic nucleotide changes in 284 HSP patients: 21 sporadic cases and 263 cases from 96 families. Among them, six nucleotide changes were novel and pathogenic. The analysis revealed a great portion of private mutations worldwide and confirmed the founder effect for one recurrent variant in the Italian population. Interestingly, mutations were detected in 21% of sporadic cases and in a range from 16% to 100% of families, depending on the number of affected in the family. **Conclusion:** This study represents the first worldwide SPG4/*SPAST* genetic screening on HSP patients. Epidemiological and clinical results broaden the spectrum of the clinical presentations of HSP associated with mutations in SPG4/*SPAST*. Finally, our findings provide evidence that the chance to detect SPG4/*SPAST* mutations varies proportionally to the number of affected in the family.