Efficacy of bone marrow transplantation for adolescent/adult-onset cerebral/cerebellar-brainstem ALD

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Objective There are accumulating evidences on the efficacy of hematopoietic stem cell transplantation (HSCT) for child-onset cerebral adrenaloleukodystrophy (ALD) at early stages to stop disease progression. The aim of this retrospective study is to estimate the efficacy of BSCT for adult cerebral ALD. To evaluate the efficacy, we compared clinical outcomes of adolescent/adult-onset ALD patients who underwent bone marrow transplantation (BMT) with those of patients who did not receive BMT from the same institution.

Methods Eight adult ALD patients with cerebral/cerebellar/brainstem lesions at early stages were followed up to determine survival, treatment progression, cerebral/cerebellar/brainstem lesions. Survival probability was significantly higher in group 1 than in group 2 (P<0.001). Conclusion BMT for adolescent/adult-onset ALD was effective to stop disease progression. Clinical course after BMT was better than patients who did not undergo BMT.

Serum GFAP and neurofilament light as biomarkers of disease activity and disability in NMOSD and MS

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Objective: Gliarial fibillary acidic protein (GFAP) and neurofilament light chain (NFL) are intermediate filaments of astrocytes and neurons, respectively. The aim of this study is to examine the potential role of serum GFAP and NFL levels in the disease activity and disability in neuromyelitis optica spectrum disorders (NMOSD) and Japanese multiple sclerosis (MS) patients. Methods: (1) Serum GFAP and NFL levels in CSF and sera were measured in healthy controls (HC, n=49; 49 sera) and NMOSD (n=33; 42 CSF and 31 sera), multiple sclerosis (MS) (n=33; 33 sera), and healthy controls (HC, n=49; 49 sera) and MS (n=33; 33 sera). (2) The associations of GFAP and NFL levels with clinical parameters were assessed. Results: CSF and serum GFAP and NFL were strongly associated and correlated with clinical parameters. In NMOSD, GFAP and NFL were increased by recent relapse (540.9 versus 340.9 pg/ml, p<0.001) and MS patients had higher serum GFAP and NFL than HC patients (p<0.001). Conclusion Serum GFAP and NFL are biomarkers of disease activity and disability in NMOSD and MS, and can serve as potential diagnostic and monitoring biomarkers for NMOSD.

Voxel-based QSM analysis as an imaging biomarker

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Objective Brain iron accumulation has been proposed as one of the pathomechanisms in Parkinson disease (PD). This study aimed to examine the whole-brain pattern of iron accumulation associated with cognitive impairment in patients with PD, using voxel-based quantitative susceptibility mapping (QSM) analysis. Methods: We enrolled 24 patients with PD (PD-MCI, 22 patients with PD and PD-related dementia (PDRD), 2 patients with PD and normal cognition (PD-CN), and 20 age-matched healthy controls (HC) in this case-control study. All participants underwent global cognitive and physical assessments and brain MRI. The PD-MCI group had lower MMSE scores than the PD-CN and HC groups. There were no gray matter volumetric differences between the groups. In contrast, the voxel-based QSM analysis showed that the PD-MCI group had significantly higher QSM values in the left insula, the left superolateral temporal gyrus and anterior cingulate cortex (ACC) than the PD-CN group. These QSM values were negatively correlated with MoCA scores in all participants (precuneus: r = -0.406 p < 0.01, caudate head: r = -0.432 p < 0.01, left insula: r = -0.476 p < 0.01, left ACC: r = -0.476 p < 0.01). Conclusion Voxel-based QSM analysis can be used as an auxiliary biomarker associated with cerebral iron burden and highlights the potential of QSM as an auxiliary biomarker for early evaluation of cognitive decline in patients with PD.
AO-02-1 Alpha-synuclein propagation via olfactory pathway in non-human primate model

Objective: Parkinson’s disease (PD) is a neurodegenerative disease characterized by α-synuclein (α-Syn) aggregates, called Lewy bodies. The α-Syn aggregates are believed to play a role in two major pathways of the olfactory system. In this study, we analyzed pathological progression by α-Syn fibrils injected into the olfactory bulb (OB) of common marmosets and measured regional brain activity by MRI. 

Method: We prepared α-Syn fibrils from wild-type marmosets. Under anaesthesia, five female and two male marmosets (about two years old) were injected with α-Syn fibrils in the left OB. The injection site at the OB was confirmed by histological examination. The MRI was performed 3 days after the injection. 

Results: In all the animals, α-Syn aggregates were detected mainly in the ipsilateral OB, amygdala and entorhinal cortex. The MRI showed a progressive spreading of p-α-Syn positive aggregates, which were also positive for Ub and p62. 

Conclusion: Our data suggest that α-Syn fibrils injected into the OB of common marmoset could induce a progressive spread of α-Syn aggregates, which might represent a potential model for PD in non-human primate.

AO-02-2 BBB-crossing drug delivery system by modulating tight junction at brain microvascular endothelium

Objective: Antisense oligonucleotide (ASO)-based therapeutics are now a powerful means of treating intractable neurological diseases. However, safe and efficient methods of delivering ASOs across the blood-brain barrier (BBB) to the central nervous system remains to be clarified. Therefore, we examined the effects of angubindin-1 on the delivery of ASO across the BBB in mice by magnetic and biochemical analyses

Method: We examined the effects of angubindin-1 on the delivery of ASO across the BBB in mice by magnetic and biochemical analyses.

Result: The BBB permeability was improved by angubindin-1 treatment.

Conclusion: Our data suggest that angubindin-1 could be a promising strategy for delivering ASOs to the central nervous system.

AO-02-3 Targeting Tyro3 ameliorates a model of PGRN-mutant FTLD-TDP via tau-mediated synaptic pathology

Objective: In FTLD, PGRN-linked FTLD, we newly generated a knock-in mouse carrying the R504X mutation to investigate the molecular mechanism of PGRN-linked FTLD. Using this new model, we identified the novel phosphorylation site of tau that is linked to the initiation of synapse pathology prior to TDP43 aggregation. Furthermore, we also demonstrated that targeting of early-stage tau signaling represents a promising therapeutic strategy for FTLD.

Method: To investigate the molecular mechanism of PGRN-linked FTLD, we newly generated a knock-in mouse carrying the R504X mutation (PGRN-KI). Using this new model, we identified the novel phosphorylation site of tau that is linked to the initiation of synapse pathology prior to TDP43 aggregation. Furthermore, we demonstrated that targeting of early-stage tau signaling represents a promising therapeutic strategy for FTLD.

Result: The mammalian expression cassette for scFv-X was constructed and was subcloned into the BoDV vector. The scFv-X-OPC secreted scFv-X, which recognized misfolded SOD1 specifically. The BoDV vector carrying scFv-X (BoDV-scFv-X) infected OPCs expressing scFv recognizing misfolded SOD1.

Conclusion: Our data suggest that targeting of early-stage tau signaling represents a promising therapeutic strategy for FTLD.

AO-02-4 A novel cell transplantation therapy for ALS using OPCS expressing scFv recognizing misfolded SOD1

Objective: Various studies have demonstrated that the misfolded forms of SOD1 could spread from cell to cell via extracellular mechanisms. Recently, the dysregulated extracellular SOD1 forms are considered to induce neuronal death. Therefore, it is necessary to establish a cell-based therapeutic strategy to prevent the spread of misfolded SOD1 in ALS.

Method: We generated a monoclonal antibody (clone X) specific to misfolded SOD1. 

Result: The mammalian expression cassette for scFv-X was constructed and was subcloned into the BoDV vector. The scFv-X-OPC secreted scFv-X, which recognized misfolded SOD1 specifically.

Conclusion: Our data suggest that targeting of early-stage tau signaling represents a promising therapeutic strategy for FTLD.
【目的】 慢性炎症性脱髓性多発根ニューロパチー(CIDP)はtypical CIDPとatypical CIDPに大別される。タウオパチーには、大脳皮質基底核症候群(CBS)、進行性核上性麻痺(PSP)、アルツハイマー病(AD)を含む非アルツハイマー型認知症(NA-AD)への類似が見られ、これらと差別する指標として開発された。一方、pure motorは多巣性運動ニューロパチーとの異同が問題と考えられた。

【方法】 2015年の1年間にCIDP病名で抗糖脂質抗体測定の依頼があったもので、追加調査で153例においてCIDPの最終診断を確定したものを対象とした。NSE(ニューロン特有のサグレノイドタンパク質)、GM1抗体陽性例の多くがtypical CIDPであり液性因子としてtypical CIDPの病態への関与が示唆された。なかでも、典型メタボリック脳症(MDS-UPDRS)の解析で右背外側運動前野に(p=0.04)機能的結合の低下がみられた。基底核ネットワークの解析では、MDS-UPDRS partⅠのスコアと右前頭極との間に負の相関が見られた(p=0.04)。【結果】 RBD群では、基底核ネットワークの解析で右背外側運動前野に(p=0.04)機能的結合の低下がみられた。基底核ネットワークの解析では、MDS-UPDRS partⅠのスコアと右前頭極との間に負の相関が見られた(p=0.04)。【結論】 稼業性睡眠障害誘発睡眠とバイタル総合症の診断基準を確立し、さらに臨床神経学における異常を抽出し、さらに新たな知見として感覚運動ニューロパチーの診断基準を確立する。

【目的】 NfL, tau, and TDP-43 levels in cerebrospinal fluid (CSF) and in plasma may be useful diagnostic biomarkers of ALS. The level of TDP-43 in CSF can serve as a diagnostic and prognostic biomarker in ALS. The level of TDP-43 in CSF and in plasma in may be useful diagnostic biomarkers of the disease.

【目的】 tauopathyには、大脳皮質基底核症候群(CBS)、進行性核上性麻痺(PSP)、アルツハイマー病(AD)を含む非アルツハイマー型認知症(NA-AD)への類似が見られ、これらと差別する指標として開発された。なかでも、典型メタボリック脳症(MDS-UPDRS)の解析で右背外側運動前野に(p=0.04)機能的結合の低下がみられた。基底核ネットワークの解析では、MDS-UPDRS partⅠのスコアと右前頭極との間に負の相関が見られた(p=0.04)。【結果】 RBD群では、基底核ネットワークの解析で右背外側運動前野に(p=0.04)機能的結合の低下がみられた。基底核ネットワークの解析では、MDS-UPDRS partⅠのスコアと右前頭極との間に負の相関が見られた(p=0.04)。【結論】 稼業性睡眠障害誘発睡眠とバイタル総合症の診断基準を確立し、さらに臨床神経学における異常を抽出し、さらに新たな知見として感覚運動ニューロパチーの診断基準を確立する。

【目的】 在発症を示すBRAINの前部領域における感覚運動ニューロパチーの変化を明らかにするため、感覚運動ニューロパチーを対象に、特に下髄、中脳、環境を対象にしたPETを用いた評価を行った。

【目的】 通常において、F-THK5351の集積パターンは異なり、適切な関心領域を選択すると鑑別可能である。脳幹、前頭葉、丘頭葉、基底核の集積を高集積部位としているが、これらの解析において基底核の集積が特徴的であることから、基底核に特异的な関心領域Integral Region of Interest (IRI)を設定した。

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Elucidation of early pathophysiology of spinal-bulbar muscular atrophy using disease specific iPSCs

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Objective: Spinal and bulbar muscular atrophy (SBMA) is an adult onset neuromuscular degenerative disease caused by the expansion of a CAG repeat in androgen receptor (AR) gene. So far, the findings from mice models indicated that testosterone-dependent mutant AR aggregations play important roles in neuronal dysfunctions and degeneration. We generated induced pluripotent stem cells (iPSCs) from SBMA patients to establish more accurate disease models, and investigated the pathogenesis of SBMA. Method We established iPSCs from fibroblasts of 4 SBMA patients and 3 age-matched controls. iPSCs were differentiated into motor neurons (MNs) to study the pathophysiological effects of SBMA. Results: Mutant AR aggregations were not detected in 4-week SBMA-MN culture by immunocytochemistry. AR aggregations were robustly observed in 4-week control-MN culture. We identified several molecules which induced similar neurodegenerative phenotypes in control-MNs to SBMA-MNs. Using this early disease model we performed microarray analysis, and identified AR aggregations play important roles in neuronal dysfunction and degeneration. We generated iPSCs from fibroblasts of 4 patients with SBMA, and differentiated them into motor neurons (MNs) for the pathophysiological analysis of SBMA. We established an early disease model of SBMA, and identified several molecules which induced similar neurodegenerative phenotypes in control-MNs to SBMA-MNs. Using this early disease model we performed microarray analysis, and identified AR aggregations were not detected in 4-week SBMA-MN culture by immunocytochemistry.

Transplantation of human iPS cell-derived dopamine neural progenitor cells for Parkinson's disease

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Objective: To examine the efficacy and safety of midbrain dopaminergic progenitor cells derived from patients with Parkinson's disease (PD) and transplanted in a rodent model of PD. To establish unilateral Parkinsonian model mice, we injected 6-OHDA into the striatum of immunodeficient model mice. Severity of model mice were evaluated by rotation behavior of the mice after subcutaneous injection of dopamine. We differentiated human iPSCs from healthy subjects into neuropheres containing dopamine neural precursor cells, using a neural differentiation protocol we recently established. After transplanting these cells, we evaluated the rotation behavior of model mice continuously. Six months after transplantation, we sacrificed the sacrificed animals and analyzed their brain sections to evaluate the detection of transplanted cells in that. Result We established 36 6-OHDA injected PD model mice that met the criteria of PD symptoms. Then dopaminergic progenitor were transplanted into 18 of them and saline was injected into 18 of them as a sham group. No tumor formation was observed in the brain section at four months after transplantation. From the early stage after transplantation, transplantation group showed a decrease in rotation behavior and after 3 months it decreased significantly compared to the sham group. Conclusions Highly enriched dopaminergic neural progenitor cells differentiated from human iPSCs by our neural induction protocol could be transplanted safely even without purification by cell sorting and improved symptoms of PD model mice.
A Rapid Molecular Diagnostic Method for Spinal Muscular Atrophy

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Purpose: Spinal muscular atrophy (SMA) is a common autosomal recessive disorder with an estimated prevalence of 1 in 10,000 live births. The disorder is caused by survival motor neuron 1 gene (SMN1) deficiency leading to dysfunction of limb movement and even dyspnea. A novel method for SMA detection has been used for the comparison to the present method. Method: A novel method for SMA detection has been developed, Genomic DNA from whole blood, amniotic fluid, or dried blood spots were analyzed by the newly designed SMA Detection Kitin ClarityTM Digital PCR (dPCR) System and MLFA (Multiplex ligation-dependent probe amplification). The current testing golden standard for SMA for determining copy numbers of SMN1 and SMN2 genes. All study subjects signed with the consent agreement form approved by local ethical committee. Results: 272 clinical samples were enrolled and used to establish the cut-off ranges for unaffected individual, SMA carrier and SMA patient categories. After setting the cut-off range for each group, we further analyzed 12 samples by both dPCR-based method and MLFA. One hundred percent concordant results were obtained between the two methods. Conclusion: The newly designed SMA Detection Kit provides a robust and precise approach to distinguish unaffected individuals, SMA carrier and SMA patients. It enables high-throughput screening without sophisticated protocols, low costs but powerful.

AHCN channel inhibitor benefits a mouse model of spinal muscular atrophy

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Objective: We previously demonstrated that increased hyperpolarization-activated cyclic nucleotide-gated (HCN) current underlies the aberrant excitability of motor axons in spinal muscular atrophy (SMA). This study investigated the effect of HCN inhibitors in a mouse model of SMA. Methods: Neonatal SMA mice and control littermates were treated with three different HCN inhibitors, including ZD2888, ivabradine, and zatebradine at different dosage via daily intraperitoneal injection (n=16-21 in each group). Mice with or without treatment were subjected to survival analysis, motor functional tests (righting test, hanging test, and tilting test), and pathological studies (spinal cord and neuromuscular junction). The expression of SMN1 was analyzed using Western blotting. Results: SMA mice treated with ZD2888 (1 and 2 mg/kg) showed significantly less early mortality and better motor function than untreated SMA control. On the other hand, ivabradine and zatebradine did not benefit SMA mice in lifespan or motor behaviors. Treatment with both ZD2888 did not reduce spinal motor neuronal death. However, SMA mice receiving ZD2888 treatment (2 mg/kg) showed significantly higher percentage of innervated neuromuscular junction than untreated SMA mice at postnatal day 8. Notably, ZD2888 treatment did not alter SMN expression in spinal cord of SMA mice. Conclusions: ZD2888, an HCN channel inhibitor, benefits a mouse model of SMA in early survival and functional behaviors via restoration of neuromuscular junction.