IV

Trigeminal autonomic cephalalgias

CQ IV-1

How are trigeminal autonomic cephalalgias classified and typed?

Recommendation

The International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta) classifies cluster headache together with related diseases under "*Trigeminal autonomic cephalalgias*". Furthermore, "*Trigeminal autonomic cephalalgias*" is further divided into five subtypes: cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua and probable trigeminal autonomic cephalalgia. **Grade A**

Background and Objective

The objective of this section is to classify "*Trigeminal autonomic cephalalgias*" according to the International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta).[1)2)]

Comments and Evidence

Cluster headache and related diseases are characterized by short-lasting, unilateral headache attacks accompanied by cranial parasympathetic autonomic symptoms including conjunctival injection, lacrimation, and rhinorrhea. These syndromes support the involvement of trigeminal-parasympathetic reflex activation, and ICHD-3 beta introduces the concept of trigeminal autonomic cephalalgias (TACs) (**Table 1**). TACs comprise the following subtypes: 3.1 *cluster headache*, 3.2 *paroxysmal hemicrania*, 3.3 *short-lasting unilateral neuralgiform headache attacks*, 3.4 *hemicrania continua,* and 3.5 *probable trigeminal-autonomic cephalalgia*.

Table 1. Classification of "3. *Trigeminal autonomic cephalalgias*"

3.1 Cluster headache
3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache
3.2 Paroxysmal hemicrania
3.2.1 Episodic paroxysmal hemicrania
3.2.2 Chronic paroxysmal hemicrania (CPH)
3.3 Short-lasting unilateral neuralgiform headache attacks
3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
3.3.1.1 Episodic SUNCT
3.3.1.2 Chronic SUNCT
3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
3.3.2.1 Episodic SUNA
3.3.2.2 Chronic SUNA
3.4 Hemicrania continua
3.4.1 Hemicrania continua, remitting subtype
3.4.2 Hemicrania continua, unremitting subtype
3.5 Probable trigeminal autonomic cephalalgia
3.5.1 Probable cluster headache

• References

1) Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629-808.
2) International Headache Classification Promotion Committee of Japanese Headache Society (translator): International Classification of Headache Disorders 3rd Edition (beta version). Igakushoin, 2014. (In Japanese)

• Search terms and secondary sources

- Search database: Ichushi Web for articles published in Japan (2011/12/21)
  Cluster headache 585
  Cluster headache and classification 98
- Search database: PubMed (2011/12/21)
  Cluster headache 2865
  Cluster headache and classification 307

CQ IV-2

How are trigeminal autonomic cephalalgias diagnosed?

Recommendation

Trigeminal autonomic cephalalgias are diagnosed according to the International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta). **Grade A**

Background and Objective

This section describes the diagnostic criteria of the various diseases included in "*trigeminal autonomic cephalalgias*" as provided by the International Classification of Headache Disorders 3rd edition (beta version; ICHD-3 beta).

Comments and Evidence

The International Classification of Headache Disorders 3rd edition (beta version; ICHD-3 beta)[1)2)] provides the diagnostic criteria for the headache types included in "3. *Trigeminal autonomic cephalalgias*" as follows:

3.1 *Cluster headache*
• Diagnostic criteria
A. At least five attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 min (when untreated)[1)]
C. Either or both of the following:
1. at least one of the following symptoms or signs, ipsilateral to the headache:
a) conjunctival injection and/or lacrimation
b) nasal congestion and/or rhinorrhoea
c) eyelid oedema
d) forehead and facial sweating
e) forehead and facial flushing
f) sensation of fullness in the ear
g) miosis and/or ptosis
2. a sense of restlessness or agitation
D. Attacks have a frequency between one every other day and 8 per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis.
Note:
1. During part (but less than half) of the time-course of 3.1 *Cluster headache*, attacks may be less severe and/or of shorter or longer duration.

3.1.1 *Episodic cluster headache*
• Diagnostic criteria
A. Attacks fulfilling criteria for 3.1 *Cluster headache* and occurring in bouts (cluster periods)
B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥1 month.

3.1.2 *Chronic cluster headache*
• Diagnostic criteria
A. Attacks fulfilling criteria for 3.1 *Cluster headache*, and criterion B below
B. Occurring without a remission period or with remissions lasting <1 month, for at least 1 year.

3.2 *Paroxysmal hemicrania*

• Diagnostic criteria

A. At least 20 attacks fulfilling criteria B-E

B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 min

C. At least one of the following symptoms or signs, ipsilateral to the pain:

1. conjunctival injection and/or lacrimation
2. nasal congestion and/or rhinorrhea
3. eyelid edema
4. forehead and facial sweating
5. forehead and facial flushing
6. sensation of fullness in the ear
7. miosis and/or ptosis

D. Attacks have a frequency above five per day for more than half of the time

E. Attacks are prevented absolutely by therapeutic doses of indomethacin[1)]

F. Not better accounted for by another ICHD-3 diagnosis.

• Note:

1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.
   [In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case can be evaluated as nonresponsive.]

3.3 *Short-lasting unilateral neuralgiform headache attacks*

• Diagnostic criteria

A. At least 20 attacks fulfilling criteria B-D

B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern

C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:

1. conjunctival injection and/or lacrimation
2. nasal congestion and/or rhinorrhoea
3. eyelid edema
4. forehead and facial sweating
5. forehead and facial flushing
6. sensation of fullness in the ear
7. miosis and/or ptosis

D. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active

E. Not better accounted for by another ICHD-3 diagnosis.

3.3.1 *Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)*

• Diagnostic criteria

A. Attacks fulfilling criteria for 3.3 *Short-lasting unilateral neuralgiform headache attacks*

B. Both of conjunctival injection and lacrimation (tearing).

3.3.2 *Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)*

• Diagnostic criteria

A. Attacks fulfilling criteria for 3.3 *Short-lasting unilateral neuralgiform headache attacks*, and criterion B below

B. Only one or neither of conjunctival injection and lacrimation (tearing).

3.4 *Hemicrania continua*

• Diagnostic criteria:

A. Unilateral headache fulfilling criteria B-D

B. Present for >3months, with exacerbations of moderate or greater intensity

C. Either or both of the following:
1. at least one of the following symptoms or signs, ipsilateral to the headache:
   a) conjunctival injection and/or lacrimation
   b) nasal congestion and/or rhinorrhoea
   c) eyelid edema
   d) forehead and facial sweating
   e) forehead and facial flushing
   f) sensation of fullness in the ear
   g) miosis and/or ptosis
2. a sense of restlessness or agitation, or aggravation of the pain by movement

D. Responds absolutely to therapeutic doses of indomethacin[1)]

E. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.
   [In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case can be evaluated as nonresponsive.]

3.5 *Probable trigeminal autonomic cephalalgia*

• Diagnostic criteria:

A. Headache attacks fulfilling all but one of criteria A-D for 3.1 *Cluster headache*, criteria A-E for 3.2 *Paroxysmal hemicrania*, criteria A-D for 3.3 *Short-lasting unilateral neuralgiform headache attacks* or criteria A-D for 3.4 *Hemicrania continua*

B. Not fulfilling ICHD-3 criteria for any other headache disorder

C. Not better accounted for by another ICHD-3 diagnosis.

• References

1) Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629-808.
2) International Headache Classification Promotion Committee of Japanese Headache Society (translator): International Classification of Headache Disorders 3rd Edition (beta version). Igakushoin, 2014.

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  Cluster headache 585
  Cluster headache and classification 23
- Search database: PubMed (2011/12/21)
  Cluster headache 2865
  Cluster headache and classification 1469

CQ IV-3

How big is the population of patients with trigeminal autonomic cephalalgias? What are the risk factors and aggravating factors? What is the prognosis?

Recommendation

The prevalence of cluster headache has been reported to be around 56 to 401 per 100,000 population, and is lower than that of migraine. The onset age of cluster headache is usually from the twenties to the forties. The prevalence is 3 to 5 times higher in men than in women. During the cluster period, attacks occur regularly and may be provoked by alcohol, histamine or nitroglycerin. **Grade B**

Background and Objective

Cluster headache is characterized by severe headache from the periorbital region spreading to the frontal and temporal regions, occurring in clusters lasting several weeks to several months. Headache attacks occur commonly at nighttime and during sleep. Male preponderance has been reported. It usually takes a long time before a diagnosis of cluster headache is finally made. Describing its clinical characteristic is important.

Comments and Evidence

The incidence of cluster headache varies among reports, and range from 56 to 401 per 100,000 population (Table 1).[1)-9)]

Previous studies have reported a male: female ratio of 5-6.7 : 1, showing male preponderance. However, Manzoni[10)] investigated the time of onset of cluster headache by decade and found a gradual decrease in male preponderance (male to female ratio of 6.2 : 1 in patients with onset before 1960, and 3.5 : 1 in patients with onset in 1990-1995). This report also showed a relationship with change in lifestyle, especially smoking. Likewise, Ekbom et al.[11)] also reported a trend of decreasing male preponderance as the year of onset became more recent.

The age of onset is commonly between 20 to 40 years. A report from Japan indicated mean onset ages of 29-40 years in men and 24-40 years in women, with no significant difference.[12)]

Various triggering and aggravating factors have been reported, including alcoholic drink, nitroglycerin, and histamine. Cluster headache has been reported to be common in heavy alcohol drinkers and heavy smokers.[13)]

Sjöstrand et al.[14)] conducted long-term follow-up of 60 patients, and reported that 26.5% had only one cluster period during follow-up. This report also showed that 83% had a second period of cluster headache within 3 years. In another study that followed 189 patients for over 10 years, 13% of the patients with an initial diagnosis of episodic cluster headache shifted to chronic cluster headache, while 33% of the patients with an initial diagnosis of chronic cluster headache shifted to episodic cluster headache.[15)]

Table 1. Studies on the prevalence of cluster headache

	Age of subjects	Prevalence per 100,000 population (95% confidence interval)
Sweden[1)]	18 year	92 (42-174)
San Marino[2)]	All ages	69 (39-114)
USA[3)]	All ages	401 (262-588)
San Marino[4)]	All ages	56 (31-92)
Norway[5)]	18-65 years	381 (153-254)
Italy[6)]	18-65 years	200 (146-254)
Sweden[7)]	All ages (twins)	151 (108-194)
Italy[8)]	≥14 years	279 (173-427)
Georgia[9)]	≥18 years	87 (no data-258)

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• Search terms and secondary sources

- Search database: PubMed (2011/12/29)
  Cluster headache 2614
  and prevalence 297
  and gender 38
  and clinical findings 473
  and prognosis 205

CQ IV-4

What is the proposed pathophysiology for trigeminal autonomic cephalalgias?

Recommendation

The hypotheses of the pathophysiology for cluster headache and other trigeminal autonomic cephalalgias are classified as follows:

1. Generator in the hypothalamus
2. Explanation by the association of trigeminal nerve activity with vascular response based on changes in serum neuropeptide concentrations
3. Pain generation around the internal carotid artery
4. Parasympathetic activation due to hyperexcitation of trigeminal nerve

Grade B

Background and Objective

Studies to elucidate the pathophysiology of cluster headache have proposed the hypothesis of headache arising from around the internal carotid artery and the hypothesis of headache originating from a hypothalamic generator based on the abnormal circadian rhythm in patients. Furthermore, it has also been hypothesized that cluster headache is caused by parasympathetic activation due to hyperexcitation of trigeminal nerve, and this is included in the category of trigeminal autonomic cephalalgias (TACs).

Comments and Evidence

The hypotheses of the pathophysiology for trigeminal autonomic cephalalgias are classified as follows:

1. Generator in the hypothalamus

Observation of changes in melatonin related to circadian rhythm in cluster headache patients has suggested a possibility that central changes in circadian rhythm may be involved in cluster headache.[1] In addition, PET study has demonstrated that the posterior hypothalamus is activated during cluster headache attacks.[2] Also, MRI (T1-weighted image) with voxel-based morphometry has demonstrated high cell density in posterior hypothalamus gray matter.[3] Moreover, studies using MR spectroscopy (MRS) in patients with cluster headache have shown a decrease in N-acetylaspartate (NAA)/creatinine ratio, an indicator of neuronal damage, suggesting the presence of organic abnormalities in the hypothalamus.[4][5] Other reports have suggested a possible association of neural orexin (hypocretin) distributed in the lateral hypothalamus area with the onset of cluster headache.[6][7]

2. Explanation by the association of trigeminal nerve activity with vascular response based on changes in serum neuropeptide concentrations

During headache attacks in cluster headache patients, external jugular vein blood levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are increased while substance P (SP) and neuropeptide Y are unchanged. In addition, oxygen inhalation and subcutaneous injection of sumatriptan reduce the augmented CGRP levels to those of normal subjects. These findings thus provide *in vivo* evidence for trigeminovascular activation during cluster headache attacks in patients.[8] Another study has reported that levels of nitric oxide (NO) metabolites in cerebrospinal fluid are increased during attacks compared to remission, and that NO metabolite levels are increased during remission in cluster headache patients compared to healthy controls.[9] These findings suggest that changes in neuropeptides in the trigeminovascular system may trigger cluster headache.

3. Pain generation around the internal carotid artery

At present, three candidate culprit lesions have been proposed for the generation of pain and diverse autonomic symptoms.

(1) Cavernous sinus

This is the hypothesis that dilatation of the internal carotid artery inside the cavernous sinus increases blood flow to the orbit and increases venous inflow to the sinus, but dilatation of the internal carotid artery also reduces the venous outflow from the sinus causing congestion in the sinus, resulting in unilateral periorbital pain and associated symptoms.[10]

(2) Proximity to cavernous sinus

Parasympathetic fibers from the sphenopalatine ganglion, pain fibers from the trigeminal nerve, and sympathetic fibers from the superior cervical ganglion join in the cavernous sinus. It has been hypothesized that when these fibers are excited, dilatation of the internal carotid artery occurs in addition to autonomic symptoms.[11]

(3) Proximity to foramen lacerum

When the internal carotid artery inside the carotid canal in the temporal bone is dilated for some reason, the compression may inhibit sympathetic functions and at the same time induce inflammation in the surrounding area to stimulate the parasympathetic nerves, thereby causing autonomic symptoms characteristic of cluster headache. Especially, the presence of a small ganglion (internal carotid ganglion), located where the greater superficial petrosal nerve (parasympathetic nerve) joins the internal carotid nerve (cervical sympathetic nerve) on the wall of the internal carotid artery, has been demonstrated in humans. This ganglion, which contains parasympathetic and sensory neurotransmitters, has been suggested to be associated with the onset of cluster headache.[12]

4. Parasympathetic activation due to hyperexcitation of trigeminal nerve

Because cluster headache is characterized by severe unilateral headache (first and second branches of the trigeminal nerve) accompanied by ipsilateral autonomic symptoms including Horner sign, lacrimation, conjunctival injection, nasal congestion and rhinorrhea, this headache belongs to the category of trigeminal-autonomic cephalalgias (TACs).[13] Regarding the mechanism of how over-excitation of the trigeminal nerve causes parasympathetic activation, the following hypothesis has been proposed. When the trigeminal system becomes highly activated, the excitation spreads to the superior salivary nucleus, resulting in excitation from the sphenopalatine ganglion to parasympathetic nerves of intracranial large blood vessels, lacrimal glands and nasal mucosa. As a result, autonomic symptoms such as lacrimation and nasal congestion are manifested.[13)-15)] Furthermore, Goadsby et al.[13] have shown that stimulation of the trigeminal ganglion leads to release of CGRP, SP and VIP from trigeminal nerve endings in cats, and increases in CGRP and VIP in blood of jugular vein during attacks in patients with cluster headache and paroxysmal hemicrania.[13] In addition to the above proposed pathophysiology, there is also a possibility that hypothalamus in the central nervous system acts as the generator, inducing cluster headache and the associated autonomic symptoms.[14]

5. Others

Other reports have suggested the involvement of hormonal abnormalities such as estrogen,[16] polymorphism of the orexin (hypocretin) receptor (present in hypothalamus) gene,[17] and genetic background, but these factors have not been studied as much as in migraine.

• References

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- Search database: PubMed (2011/12/29)
  Cluster Headache and Pathophysiology 922

CQ IV-5

What kinds of acute treatments are available for cluster headache, and how effective are they?

Recommendation

1. For triptans, subcutaneous injection of sumatriptan 3 mg (up to 6 mg/day) is recommended (covered by health insurance in Japan). The effectiveness of sumatriptan nasal spray 20 mg/dose and oral zolmitriptan 5 to 10 mg has been reported, but evidence has not been established, and they are currently not covered by health insurance in Japan.
2. Pure oxygen delivered via a side tube of a face mask at 7 L/minute for 15 minutes has been reported to be useful.
3. The somatostatin analog octreotide has been reported to be effective in overseas countries, but clinical trials have not been conducted in Japan. Lidocaine, cocaine, ergotamine, general analgesics [nonsteroidal anti-inflammatory drugs (NSAIDs)] have no effect.

Grades A-C (1. triptans: sumatriptan subcutaneous injection; A, sumatriptan nasal spray, oral zolmitriptan; B. 2. oxygen inhalation; A. 3. somatostatin, lidocaine, cocaine, ergotamine, NSAIDs; C)

Background and Objective

Before the development of triptans, there was no effective treatment for acute attacks of cluster headache, and various treatment methods were used based on experience. The section aims to consolidate the evidence-based acute treatments for cluster headache and to develop guidelines.

Comments and Evidence

1. Triptans

Studies conducted overseas have reported that subcutaneous sumatriptan 6 mg has few adverse effects and shows no decline in efficacy on long-term use.[1)2)] Reports showed that headache was improved at 15 min after subcutaneous injection in 74% of the patients, and was completely relieved at 30 min in 77% of the patients, and the effectiveness was also demonstrated in Japan.[3)-5)] A study overseas has reported that subcutaneous sumatriptan at doses lower than 6 mg is also effective (headache improvement rate was 98% with 6 mg subcutaneous injection, 74% with 3 mg, and 8% with 2 mg)[6)] (grade A recommendation).

Randomized controlled double-blind trials have reported that intranasal sumatriptan (20 mg/dose) using nasal spray is effective, with headache improvement rate of 57% at 30 min,[7)-9)] but this formulation is currently not available in Japan (grade B recommendation).

Oral zolmitriptan has been reported to be highly effective,[10)] but this drug is currently not covered by health insurance in Japan (grade B recommendation). Recently zolmitriptan nasal spray has been developed overseas and is being used as an acute treatment for cluster headache. Randomized controlled double-blind trials have reported that intranasal zolmitriptan nasal spray 5 mg and 10 mg significantly improved headache compared to placebo.[11)-13)] The European Federation of Neurological Societies (EFNS) guidelines for cluster headache and other trigeminal autonomic headaches rates zolmitriptan 5 and 10 mg/dose as grade A/B recommendation.[14)]

2. Oxygen inhalation[15)]

Randomized double-blind trials comparing pure oxygen inhalation and room air inhalation have found approximately 8% improvement with pure oxygen inhalation. In a recent randomized controlled double-blind trial on high-flow oxygen (12 L/min), approximately 78% of the patients inhaling oxygen became pain free, compared to 20% of the patients inhaling room air[16)] (grade A recommendation).

3. Others

Use of lidocaine,[17)] cocaine, ergotamine,[18)] and NSAIDs has been reported but effectiveness has not been confirmed (grade

C recommendation). Somatostatin was reported in the past to be effective,[19] and a recent randomized placebo-controlled double-blind trial has reported the effectiveness of octreotide, a somatostatin analog[20] (grade C recommendation).

• References

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• Search terms and secondary sources

"Cluster Headache/therapy" [MeSH] 875
"cluster""headache""acute""treatment" 173
"cluster""headache""acute""treatment", Limits Activated: Clinical Trial, Randomized Controlled Trial 30

CQ IV-6

What kinds of medications for prophylactic therapy are available for cluster headache, and how effective are they?

Recommendation

1. Prophylactic therapy for episodic cluster headache
   (1) Among calcium channel blockers, verapamil 360 mg/day has been shown overseas to have prophylactic effect but the adverse effect of delayed cardiac conduction causing bradycardia and heart failure is a concern. For lomerizine, some prophylactic effect is expected in the clinical trial stage, but this drug is not covered by health insurance in Japan (as of March 2013).
   (2) Ergotamine tartrate (1 to 2 mg) taken orally before bedtime may be effective as prophylaxis.
   (3) Civamide (a structural analog of capsaicin) nasal spray has been reported overseas to be effective, but clinical trial has not been conducted in Japan.
   (4) Corticosteroids are considered effective, but there is no clear evidence.
   (5) The prophylactic effects of triptans and melatonin are not known.
2. Prophylactic therapy for chronic cluster headache
   Lithium carbonate, valproic acid, gabapentin, topiramate, divalproex sodium, and baclofen have been reported to be effective, but the effects have not been established.
3. Treatments other than pharmacotherapy
   Patients who do not respond to pharmacotherapy are sometimes treated with nerve block therapies (including trigeminal nerve block, stellate ganglion block, sphenopalatine ganglion block, and greater occipital nerve block), trigeminal rhizotomy, and sphenopalatine ganglion resection. Gamma knife treatment and deep brain stimulation have also been conducted, but the effect has not been established.

Grades B and C [1. Prophylactic therapy for episodic cluster headache: (1) verapamil; B (off-label use approved in Japan), lomerizine; C, (2) ergotamine tartrate; C, (3) civamide; C, (4) corticosteroids (off-label use approved in Japan); B, (5) others (triptans, melatonin); C. 2. Prophylactic therapy for chronic cluster headache: lithium carbonate, valproic acid, gabapentin, topiramate, divalproex sodium, baclofen; C. 3. Treatments other than pharmacotherapy: nerve block therapies, others; C]

Background and Objective

Because there are few therapies that are effective for the prevention of cluster headache, this section aims to consolidate the prophylactic therapies for cluster headache based on evidence and develop guidelines.

Comments and Evidence

1. Prophylaxis for episodic cluster headache

(1) Calcium channel blockers

The prophylactic effect of verapamil 360 mg/day has been proven overseas in placebo-controlled double-blind trials, but attention is required regarding the adverse event of cardiac conduction delay causing bradycardia and heart failure.[1] In Japan, verapamil was approved for off-label use for migraine and cluster headache from September 28, 2011 (http://www.hospital.or.jp/pdf/14_20110928_01.pdf) (grade B recommendation). Lomerizine is expected to have some prophylactic effect in the clinical trial stage (currently not covered by health insurance in Japan (grade C recommendation).

(2) Ergotamine tartrate

Many cases responding to prophylactic therapy with oral ergotamine tartrate have been reported, but stringent placebo-controlled double-blind trials have not been conducted (grade C recommendation).

(3) Civamide

Civamide is a structural analog of capsaicin. Use of civamide nasal spray [100 μL of 0.025% civamide (25 μg)] for 7 consecutive days reduces the frequency of headache[2] (grade C recommendation)

(4) Corticosteroids

For corticosteroids, although a report has indicated the effectiveness of intravenous bolus of high-dose methylprednisolone,[3] randomized controlled double-blind trials have not been conducted. On the other hand, another open-label study suggests that methylprednisolone alone does not provide any advantage above prednisone.[4] Use of prednisolone 40 to 60 mg/day or dexamethasone 8 mg has also been reported.[5] The 2006 European Federation of Neurological Societies (EFNS) guideline recommends a protocol to start with 60-100 mg of prednisone once daily for at least 5 days, then taper by 10 mg/day.[6] In this guideline, steroids are ranked grade A even though appropriate randomized controlled double-blind trials have not been conducted.[6] In Japan, steroids have been approved for off-label use for cluster headache on September 28, 2011 (grade B recommendation).

(5) Others

Beta blockers are usually not effective for cluster headache, and they are not used. Among triptans, a study has concluded that sumatriptan 300 mg/day is not effective as prophylactic treatment.[7] More recently, eletriptan (80 mg/day) has been reported to be effective, [8] but controlled double-blind studies have not been conducted. Melatonin 10 mg was reported to be effective, [9] but a recent controlled double-blind study has reported no difference compared to placebo.[10] (grade C recommendation).

2. Prophylactic therapy for chronic cluster headache

Lithium carbonate was reported to be effective in approximately 40% of the patients with chronic cluster headache, [11] but recent reports raise doubt about its effectiveness. The effectiveness of valproic acid,[12] gabapetin,[13][14] topiramate,[15] baclofen,[16] and divalproex sodium[17] has been reported, but controlled double-blind trials have not been conducted and the effects are yet to be established (grade C recommendation).

3. Treatments other than pharmacotherapy

Nerve block therapies including trigeminal nerve block, stellate ganglion block, greater occipital nerve block,[18] and sphenopalatine ganglion block[19]; trigeminal rhizotomy; and sphenopalatine ganglion resection have been conducted. Gamma knife treatment[20] and deep brain stimulation[21][22] have also been attempted, and reported to be effective in some patients. Because of the high rate of failure and adverse effects associated with gamma knife treatment, recent reports conclude that this modality cannot be recommended actively.[23][24] Furthermore, greater occipital nerve electrical stimulation[25] and suboccipital steroid injection[26] have been reported to be effective in some patients. (grade C recommendation).

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• Search terms and secondary sources

"Cluster Headache/prevention and control" [MeSH] 95
Cluster Headache prevention treatment 180
"prevention""cluster headache"Limits: Clinical Trial, Randomized Controlled Trial 27

CQ IV-7

What kinds of medications are available for the treatment of paroxysmal hemicrania, and how effective are they?

Recommendation

Paroxysmal hemicrania responds absolutely to indomethacin, and indomethacin is therefore recommended as a treatment drug for paroxysmal hemicrania [highest dose up to 75 mg for oral formulation, and up to 100 mg for rectal administration (suppository) in Japan]. Other drugs such as verapamil, nonsteroidal anti-inflammatory drugs (NSAIDs) and topiramate have been reported to be effective, but clear evidence is yet to be established.

Grade A (indomethacin: A; verapamil, NSAIDs and topiramate: C)

Background and Objective

Paroxysmal hemicrania manifests pain and associated symptoms similar to those of cluster headache. However the duration of attack is 2 to 30 min, which is shorter than that of cluster headache, and the frequency of headache attack is high. Paroxysmal hemicrania occurs more commonly in women than in men, and responds absolutely to indomethacin. This section reviews the literature on indomethacin and other drugs for the treatment of paroxysmal hemicrania.

Comments and Evidence

Based on the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta),[1] the diagnostic criteria for paroxysmal hemicrania are as follows:

Diagnostic criteria:

A. At least 20 attacks fulfilling criteria B-E

B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes

C. At least one of the following symptoms or signs, ipsilateral to the pain:

1. conjunctival injection and/or lacrimation
2. nasal congestion and/or rhinorrhea
3. eyelid oedema
4. forehead and facial sweating
5. forehead and facial flushing
6. sensation of fullness in the ear
7. miosis and/or ptosis

D. Attacks have a frequency above five per day for more than half of the time

E. Attacks are prevented absolutely by therapeutic doses of indomethacin

F. Not better accounted for by another ICHD-3 diagnosis.

The ICHD-3β provides the above diagnostic criteria. Among them, criterion "E. Attacks are prevented absolutely by therapeutic doses of indomethacin" clearly states the absolute therapeutic effect of indomethacin (grade A recommendation). The 2006 European Federation of Neurological Societies (EFNS) guideline[2] also describes the treatment for paroxysmal hemicrania, noting that indomethacin is the most effective prophylactic drug according to many reports.[3-6] Furthermore, in a prospective study reported in 2008 on the administration of indomethacin in 31 patients with paroxysmal hemicrania, all patients responded to indomethacin.[7] Regarding the dose of indomethacin, *Note 1* of the ICHD-II diagnostic criteria states "In order to rule out incomplete response, indomethacin should be used in a dose of ≥150 mg daily orally or rectally, or ≥100 mg by injection, but for maintenance, smaller doses are often sufficient." On the other hand, the Japanese Edition of the International Classification of Headache Disorders 3rd edition (beta version)[8] gives the dose of indomethacin that can be used in Japan as follows.

"In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case

can be evaluated as nonresponsive".

Other drugs such as verapamil, NSAIDs and topiramate have been reported to be effective,[9)-13)] but clear evidence is yet to be established (grade C recommendation).

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• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  Paroxysmal hemicrania & treatment & Clinical trial Results 14

CQ IV-8

What kinds of medications are available for the treatment of SUNCT and SUNA, and how effective are they?

Recommendation

The prevalence of SUNCT and SUNA is low, and no controlled trial has been conducted. However, case studies have suggested that lamotrigine is the most effective, while gabapentin and topiramate are also effective. During headaches that severely impact daily living, intravenous lidocaine has been reported to be effective. Grade C

Background and Objective

Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is characterized by short-lasting attacks of unilateral pain accompanied by ipsilateral lacrimation and congestion in the eye. On the other hand, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) is accompanied by either conjunctival injection or lacrimation, and SUNCT is considered possibly a subform of SUNA. This section reviews the literature on the treatments SUNCT and SUNA.

Comments and Evidence

Few headache guidelines in European and American countries describe the treatments for SUNCT and SUNA. The 2006 European Federation of Neurological Societies (EFNS) guideline has the following description, "No controlled trials have been published, and the rareness of the syndrome makes this a difficult task".[1] Among the treatments tried, lamotrigine is considered the most effective from case reports, while gabapentin and topiramate are also regarded to be effective. For headaches that severely impact daily living, intravenous lidocaine has been reported to be effective. A small-scale prospective study on treatments of SUNCT reported that SUNCT attacks did not respond to oxygen inhalation or intramuscular indomethacin in all patients.[2] This report also indicated that lamotrigine (up to 400 mg/day) was effective in 68% of SUNCT and 25% of SUNA patients, topiramate (up to 400 mg/day) was effective in 52% of SUNCT patients, and gabapentin (up to 3,600 mg/day) was effective in 45% of SUNCT and 60% of SUNA patients.[2]

A review on case reports of treatment of SUNCT by lamotrigine was reported.[3] While the doses used were variable, in 5 patients started with 25 mg/day and titrated at 25 mg/week to a maintenance dose of 125 to 200 mg/day, 3 patients achieved complete remission and 2 patients showed 80% or greater reduction in attack frequency.[4]

For gabapentin, among 8 patients who received a starting dose of 600 mg/day divided in 2 doses, increasing when attack occurred in one week up to a dose of 900/day divided in 3 doses, 5 patients (62.5%) achieved complete relief and 3 patients showed marked improvement in headache duration, frequency and severity.[5] In Japan, there is a case report of SUNCT in which gabapentin 800 mg/day achieved resolution of headache attack and autonomic symptoms.[6]

In a prospective study of lidocaine used with lamotrigine, intravenous or subcutaneous infusion of lidocaine (2 g dissolved in 100 mL of saline) at a rate of 6 mL/hour (2 mg/min) for 5 to 14 days was effective in 11 of 14 patients.[7]

In a case report, oral zonisamide was started at 100 mg/day and titrated from day 3 to a dose of 300 mg/day. Since attack did not occur, zonisamide was tapered and discontinued. Attack recurred on day 3 after discontinuation, and the drug was restarted with no more attack thereafter.[8]

In addition to pharmacotherapy, cases of response to deep brain stimulation and gamma knife radiosurgery have been reported.[9][10] However, cases showing no response to gamma knife radiosurgery of the trigeminal nerve, but occurrence of adverse effects including anesthesia dolorosa, deafness, vertigo, and dysequilibrium were also reported,[11] indicating that gamma knife radiosurgery of the trigeminal nerve is not necessarily an appropriate treatment for SUNCT.

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• Search terms and secondary sources

Sunct and treatment Limits Activated: Clinical Trial Results 6
Sunct and treatment Limits Activated: meta-analysis Results 1
sunct and radiosurgery Results 2

CQ IV-9

How do trigeminal autonomic cephalalgias impact the patients' heathy life expectancy and QOL?

Recommendation

In patients with cluster headache, disability in daily living and economic loss during the headache attack period have been reported. Furthermore, the pain and disability in daily living in patients with cluster headache are at least as severe as those in migraine patients. **Grade B**

Background and Objective

This section reviews the literature and discusses the degree of disability in daily living caused by pain during the attack period in patients with cluster headache.

Comments and Evidence

Various instruments such as Short Form-36 (SF-36) and Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ 2.1) have been used to investigate the degree of disability in daily life of patients with cluster headache. The SF-36 is a scientific scale used to assess health-related quality of life (QOL). It consists of a number of questions, and the responses are scored and calculated to measure eight health concepts: (1) physical functioning, (2) role physical, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role emotional, and (8) mental health. In the MSQ, patients are asked to provide response to questions related to headache-related impact on daily and social life during the past 4 weeks, rated on a six-point scale from "none of the time" to "all of the time", and the total score is used to measure the degree of QOL impairment.

A study comparing SF-36 scores between 56 patients with cluster headache and 1,636 healthy persons found significant differences in six items, and a study comparing SF-36 and MSQ 2.1 scores between 35 patients with cluster headache and 62 healthy persons also reported significant differences in both scores.[1)2)] Furthermore, comparison between cluster headache patients and migraine patients revealed significant differences in the SF-36 subscales of "physical pain" and "social functioning", indicating that the degree of disability in daily living caused by cluster headache is as severe as or more severe than that caused by migraine.[2)] In addition, a study comparing 13 patients with cluster headache and 79 patients with migraine using SF-20 reported significantly higher pain score as well as poorer health associated with social functioning in cluster headache patients compared to migraine patients.[3)]

Regarding the consumption habits, cigarette-smoking has been reported to be significantly more frequent in cluster headache patients than in the general population, suggesting an issue in lifestyle among cluster headache patients.[4)] Regarding the economic loss for cluster headache patients, a study comparing the treatment costs due to healthcare utilization (direct costs) and loss due to headache-related absence from work (indirect costs) over a 6-month period between 72 patients with chronic cluster headache and 107 patients with episodic cluster headache reported direct/indirect economic loss of €5,963 per person.[5)]

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• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  (Cluster Headache) & (Quality of Life) 53
  (Cluster Headache) & (burden) 18