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【 CASE REPORT 】

Chronic Cluster Headache with a Pediatric Onset: The First Japanese Case Report

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Abstract:
A 9-year-old female reported left-sided, excruciatingly severe, stabbing orbital pain with cranial autonomic symptoms. The attacks continued for 1 year with a remission period of 2 months. Each attack duration was approximately 120 minutes with a frequency of two to three times a day. The patient was diagnosed with chronic cluster headache (CCH) according to the third edition of the International Classification of Headache Disorders. A combination of low-dose verapamil and lomerizine once a week decreased the frequency of the attacks, and oral sumatriptan became an effective abortive therapy. No case reports of pediatric CCH have been previously published in Japan.

Key words: chronic cluster headache, verapamil, lomerizine, prophylactic therapy, pediatric onset, oral sumatriptan

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Introduction

Cluster headache (CH) is the most common of the trigeminal autonomic cephalalgias and the most painful of the primary headache disorders (1). CH is characterized by attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal, or occurs in any combination of these sites, lasts from 15-180 minutes and occurs from once every other day to eight times a day (2). The pain of CH is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis or eyelid edema, and restlessness or agitation (2). CH attacks have both circadian and circannual rhythmicity (3). Experimental and human functional imaging suggests that these syndromes activate a normal human trigeminal parasympathetic reflex and produce secondary clinical signs of cranial sympathetic dysfunction (2). The prevalence of CH is estimated to be 0.05-3% (3). The age at onset of CH is usually 20-40 years of age. For some unknown reasons, males are affected approximately three times more often than females (2). The onset of CH may occur as early as 1 year of age (4-6), although the number of cases that occur before the age of 10 years is very low (6). CH can be divided into episodic CH (ECH) and chronic CH (CCH) subforms, distinguished based on the presence or absence of a remission period lasting at least 3 months on an annual basis (2). A low prevalence of CCH has been previously reported in Asian countries, contrary to that in European and North American countries (7-10). To the best of our knowledge, this report represents the first clinical case report of CCH with a pediatric onset in Japan.

Case Report

The patient was a 9-year-old pure Japanese female who presented to our headache center with a 1-year history of left-sided, excruciatingly severe, stabbing pain located in her orbit. The attacks were associated with nasal obstruction, conjunctival injection, tearing, flushing, and eyelid edema and presented with restless and migrainous features such as nausea and vomiting. The duration of the attacks was approximately 120 minutes, with a frequency of two to three times a day. Regarding the patient's family history, her mother reported the presence of migraine. Her parents were never smokers. The patient had throbbing pain of the left temple that lasted approximately 4 hours with nausea once a month from 5 years of age. These headaches improved by

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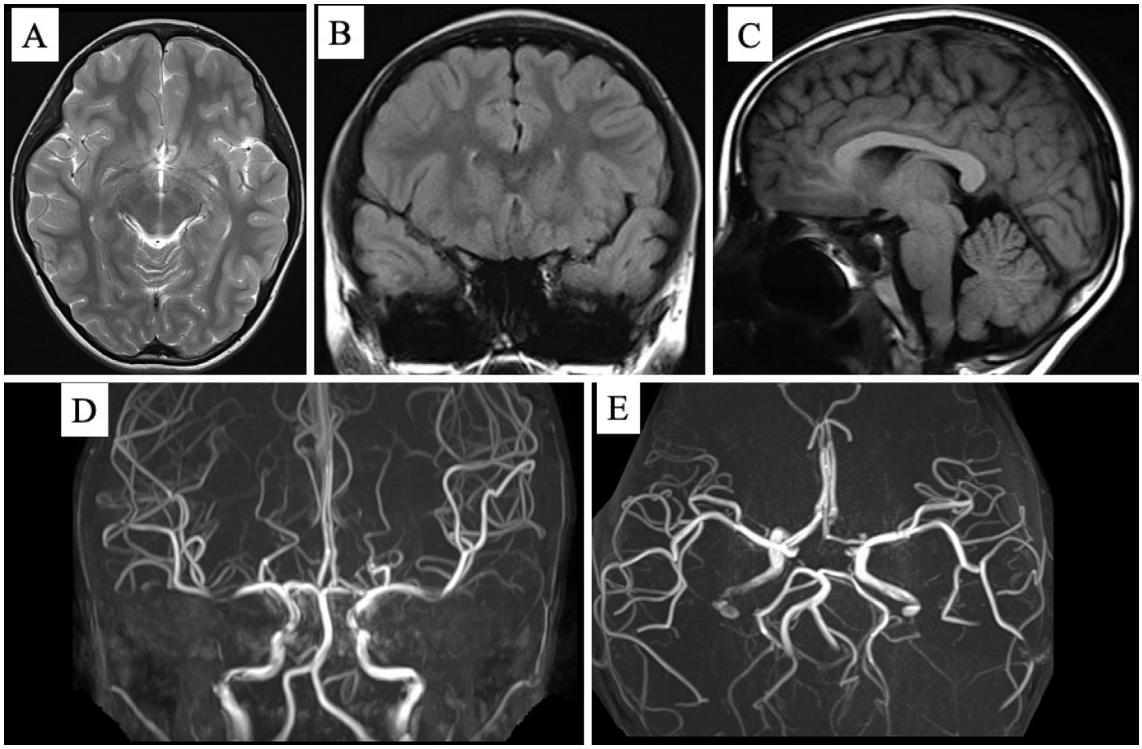

Figure. **Brain magnetic resonance imaging and magnetic resonance angiography showing normal results. A: T2 sequence, axial view. B: Fluid attenuated inversion recovery sequence (FLAIR), coronal view. C: T1 sequence, sagittal view. D, E: Magnetic resonance angiography.**

resting or taking over-the-counter (OTC) medications and were suggested to be migraine. However, taking OTC medications had no effect on new headache attacks. Initially, in the pediatrics department, the patient was suspected of having sinusitis and was referred to the otolaryngology department. The patient was given antibiotics, which had no effect on the headaches. The headaches continued for 3 months; then, she visited the neurosurgery department and was diagnosed with CH. The CH attacks improved by subcutaneous sumatriptan (1.5 mg) in 5-10 minutes. Considering her weight (28 kg) and age, the dose of subcutaneous sumatriptan was half of that listed for Japanese insurance coverage (3 mg). However, sumatriptan nasal spray (20 mg), oral sumatriptan (50 mg), and pure oxygen inhalation (7 L/min) were ineffective. After verapamil was started at 80 mg/day and increased to 120 mg/day, the attacks decreased to approximately 3 times a week. When attacks occurred, the patient visited a general physician or an emergency room at a general hospital and received subcutaneous sumatriptan. The CH attacks continued for 1 year with a headache free period of 2 months. Her vital signs, physical examination, and neurological examination results were normal. Electrocardiogram and laboratory testing results were also normal. Brain magnetic resonance imaging and magnetic resonance angiography (Figure) showed normal results. We diagnosed the patient with CCH according to the third edition of the International Classification of Headache Disorders (ICHD-3) (2). In our headache center, the patient was able to tolerate 3 mg of subcutaneous sumatriptan. Self-injection of subcutaneous sumatriptan was introduced; however, the patient was unable to self-inject because of severe pain and restlessness during the attacks. An increase in verapamil from 120 mg/day caused malaise. Although the frequency of the attacks did not change with the concomitant use of topiramate (25 mg/day), the subjective intensity of the attacks was reduced by approximately 30%. Furthermore, oral sumatriptan (50 mg) became effective at the time of attacks within 20 minutes. However, continuation of topiramate use caused anorexia and weight loss. Therefore, the patient was administered lomerizine (5 mg/day), which has been used for migraine prophylaxis in Japan, and no side effects were reported. Finally, lomerizine was increased to 10 mg/day. Three months later, the attack frequency was reduced to once a week.

Discussion

CH is a very rare disorder among children; in 18-year-old Swedish Army recruits, the prevalence was 0.09% (11), while in an Italian multicenter study of patients <18 years old, the prevalence of CH was 0.03% (12). The clinical presentation described for CH in children seems to be very similar to that observed in adults (6, 13). However, there are some differences between children and adults with CH (14). CH with a pediatric onset tends to be associated with less restlessness, less prominent autonomic features, a lower frequency of the clusters, and a shorter duration of the cluster attack but a trend toward a gradual increase in frequency and duration of symptoms as patients reach adulthood (15).

Females develop CH at an earlier age of onset, which may reduce the typical male to female ratio in younger patients (6). In CH patients with pediatric onset, it is more often females who tend to have chronic courses (6). This particular pattern of the gender ratio in relation to onset in different age groups suggests that hormonal factors may actually play a role in the pathogenesis of CH. CCH is defined as CH attacks that typically occur for 1 year or longer without remission or with remission periods lasting less than 3 months, and the criterion for the remission period of CCH was recently revised in the ICHD-3 from <1 month to <3 months (2). Imai et al. (9) reported a clinical profile of Japanese patients that included 86 consecutive new CH patients (68 males, 18 females; mean age, 38.4±12.2 years; range 17-73 years). In this report, the overall rate of onset at 10-19 years was 22% (19/86) with rates of 19% (13/68) in males and 33.3% (6/18) in females. There were no patients younger than 10 years of age. The average diagnostic delay was reported to be 5.3±6.4 years because the clinical features of CH were not recognized (16). A pediatric onset and pain that does not reach the maximum intensity within the first 5 minutes were also features that contributed to diagnostic delay (17). A diagnosis of CH with a pediatric onset is rare because of the difficulties of children in describing their symptoms. Migraine is the most common misdiagnosis; other reported erroneous diagnoses include psychogenic headaches, parasomnias, pseudo seizure, and ethmoiditis (5, 18, 19). CH can have migrainous features, such as nausea, vomiting, photophobia, and phonophobia, in both adult and pediatric patients; among the latter, the occurrence of migrainous features is a major source of misdiagnosis as migraine, which is far more common than CH among pediatric patients (20). In a Korean study, the CCH subtype appeared more often with comorbid migraine, which may increase the speed and ease of diagnosis (21). The lower prevalence of CCH in Asian patients may be due to racial, lifestyle, or cultural factors. Neurologists and pediatricians should consider diagnoses of rare headache syndromes in pediatric patients. The subcutaneous injection of sumatriptan and pure oxygen inhalation are first-line treatments for acute CH attacks (22). Verapamil is an agent of choice for preventing CH (22), and it is the drug of choice for the prophylaxis of both ECH and CCH. The best evidence supporting its effectiveness was obtained from a randomized controlled trial that compared verapamil at 360 mg/day in three divided doses with a placebo (23). Verapamil is generally well tolerated and can be used in combination with corticosteroids, sumatriptan, and ergotamine in children (20). Other prophylactic agents that may be effective include glucocorticoids, lithium, topiramate, lomerizine, baclofen, and melatonin (22). According to a report from an Italian pediatric headache center, all 11 pediatric patients with ECH showed a good clinical response to 2 mg/kg/day of prednisone, which was effective in interrupting attack recurrence after an interval ranging from 2 to 5 days (24). However, continuous corticosteroid therapy for CCH is problematic given the deleterious side effects of prolonged systemic use. Lithium is not recommended for children because of its potential for many side effects and its narrow therapeutic window, although it is recommended for CCH (19). Lomerizine belongs to the same class of diphenylpiperazine-type calcium channel blockers as flunarizine. ln the assessment of overall improvement in an open-label trial with 38 CH patients, the proportion of patients who rated the effect as improved to markedly improved was 65.0% in the 10 mg/day lomerizine group and 53.3% in the 20 mg/day lomerizine group (25). Lomerizine is recommended for the oral prophylaxis of not only migraine but also CH (22). The treatment of pediatric CH is mainly extrapolated from experience in adult CH patients, and no clear guidelines are available. Several treatments have been attempted in cases reported in the literature (19, 24, 26).

In our case, by adding lomerizine to verapamil treatment, the frequency and intensity of the CH attacks decreased, and oral sumatriptan became effective. The oral route of administration is not usually recommended in CH, because of the delayed effect compared to subcutaneous or intranasal administration. Barha et al. reported that oral zolmitriptan 5 mg and 10 mg doses were effective in the acute treatment of adult ECH (27). The 5 mg and 10 mg doses, which were higher than the recommended initial dose for the treatment of migraine (2.5 mg), were chosen for assessment in this study to provide a rapid attainment of clinically effective plasma concentrations of zolmitriptan (27). Adequate prophylactic therapy not only reduces the frequency, but also increases the pain threshold for CH. Therefore, oral sumatriptan 50 mg may have made it possible for our patient to reach effective plasma concentrations since her weight is 28 kg. Although the patient was unable to self-inject the drug because of severe pain and restlessness during the attacks, her quality of life was significantly improved. Drugs and doses are limited in children.

The present case indicated that it may be useful to try combinations of low doses of some drugs for prophylactic therapy and the effectiveness of oral triptans brings good news for the acute treatment of CCH with a pediatric onset. There have been no previous case reports of CCH with a pediatric onset in Japan. Further cases need to be accumulated to determine the characteristics and treatments of CCH in Japanese patients.

The authors state that they have no Conflict of Interest (COI).

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