Cluster headache (CH) is a rare trigeminal autonomic cephalalgia. Although its pathophysiology is not entirely understood, the hypothalamus and trigeminal nociceptive and autonomic pathways seem to play a key role in its pathology. In the majority of cases, CH begins at a young age and affects mainly men. This article presents a case of a 76-year-old woman with CH that developed at the age of 74. This is one of the first documented reports of CH with such atypical features from an epidemiologic point of view. A possibility of symptomatic cluster-like headache (CLH) attributed to cerebrovascular disease in the patient is also discussed.

**Keywords:** age at onset, cluster headache, primary headache, secondary headache, trigeminal autonomic cephalalgia

Cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC) that is defined in the latest version of the International Classification of Headache Disorders (ICHD) as unilateral, severe pain localized in the orbital, supraorbital, or temporal area lasting 15 to 180 minutes and occurring at a frequency of one every other day to eight times a day. Like other TACs, it is accompanied by lateralized, cranial parasympathetic symptoms ipsilateral to the headache, such as conjunctival injection; lacrimation; nasal congestion or rhinorrhea; forehead and facial sweating; Horner syndrome; eyelid edema; and characteristic behavioral features (eg, restlessness or agitation).

Episodic CH (ECH) is characterized by headache attacks grouped in periods lasting from 7 days to 1 year and separated by pain-free periods lasting at least 1 month, while chronic CH (CCH) occurs when the headache attacks last more than 1 year with remission periods that are shorter than 1 month. Chronic CH can be primary (ie, from the onset of CH) or secondary (ie, evolving from ECH).

The pathophysiology of CH is not completely understood. It is postulated to be associated with the trigeminal nociceptive and autonomic pathways and with the biologic clock driven by the hypothalamus. Dysfunction of posterior hypothalamic gray matter is probably a factor that strongly contributes to the development of the attacks. Moreover, the trigeminal autonomic reflex plays a key role in the pathophysiology of CH attacks.

CH is a rare disorder according to several studies based only on clinically confirmed diagnoses conducted in various countries. The prevalence of CH ranges from 0.056% (San Marino) to 0.38% (Norway) of the general population. Male preponderance is another characteristic feature of CH, with male (M:F) ratios in the groups examined in the above-mentioned studies of 15:0, 14:1, 12:9, and 6:1. In a large analysis based on observation for over three decades, the M:F ratio with respect to age at onset varied from 2.3:1 (age at onset range: 50–59 years) to 8.4:1 (age at onset range: 40–49 years) for ECH and from 0:3 (age at onset range: 60–69 years) to 14.0:1 (age at onset range: 30–39 years) for CCH. The onset of CH usually occurs at about 30 years old. A recently published large analysis including over 800 patients revealed the mean age at onset to be 30.1 ± 13.0 years in men and 30.4 ± 15.7 years in women.
noting that CH patients smoke more often than migraine patients.\textsuperscript{14}

According to the latest guidelines of the American Headache Society, high-flow oxygen is a Level A recommendation for acute treatment of CH.\textsuperscript{15} Sodium valproate is one of the most frequently used agents for prophylactic treatment. In an open clinical trial, this treatment was effective in 73.3\% of patients, with headache completely disappearing in 60\% and markedly decreasing in 13.3\% of enrolled individuals, leading the authors to state that sodium valproate seems to be effective for the treatment of CH.\textsuperscript{16}

This article reports the case of a 76-year-old woman who presented CH that had begun at the age of 74.

Case Report
The patient has given written informed consent for the publication of this case report.

The 76-year-old retired woman was admitted to the Department of Neurology of Poznan University of Medical Sciences in July 2015 complaining of a right-sided unilateral attack of headache associated with ipsilateral conjunctival injection, lacrimation, rhinorrhea, and redness; the episodes lasted up to 40 minutes. The pain was severe (sometimes excruciating), described as stabbing, burning, deep, non-fluctuating, and accompanied by photophobia and phonophobia. The frequency of the episodes had increased within the preceding 3 weeks, achieving three to four episodes a day. The symptoms occurred for the first time in June 2013, and the patient was admitted to the department, where the diagnosis was established. In addition, she suffered from diabetes mellitus, permanent atrial fibrillation, and glaucoma. In 2002 and 2009, she had suffered ischemic stroke that caused left-sided hemiparesis. The patient smoked approximately six to seven cigarettes a day. Upon admission to the emergency room, the patient had an attack of CH. Oxygen at 15 L/minute flow was administered immediately, and the attack ceased. The neurologic examination showed spastic, left-sided hemiparesis (4 on the Lovett scale) with an ipsilateral Babinski sign. Head computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) were performed precisely (including pericavernous areas) by an experienced radiologist. Apart from the large area of ischemic changes in the right hemisphere, no clinically relevant disturbances (including neurovascular conflict, aneurysm, etc) were present. Doppler ultrasound examination showed 30\% to 40\% occlusion of the internal carotid artery bilaterally. An ophthalmologic consultation did not reveal any features of an exacerbation of glaucoma. During hospitalization, the patient had several CH attacks, all of which were successfully treated with oxygen. Prior to hospitalization in 2015, the patient was taking 2 × 300 mg of sodium valproate (Depakine Chrono 300, Sanofi–Aventis) a day. After increasing the daily dosage to 2 × 500 mg (Depakine Chrono 500, Sanofi–Aventis), the CH attacks became less frequent and severe; thus, the patient was discharged with the recommendation of taking sodium valproate at that dose.

Discussion

There have been many reports of patients with unusual CH in the literature. Some have focused on the coexistence or relationship between CH and other conditions; eg, Flavia and Chiara described a patient with CH with probable paroxysmal hemicrania,\textsuperscript{17} while Edvardsson presented a case of CH associated with a clinically nonfunctioning pituitary adenoma.\textsuperscript{18} Other reports pertain to therapy of the disease.\textsuperscript{19,20} Finally, there have been several descriptions of patients with symptomatic cluster-like headache (CLH), a condition that can be associated with internal carotid artery dissection or prolactinoma.\textsuperscript{21,22} However, there are only single reports of CH with unusual features from an epidemiologic point of view, especially with onset at an age atypical for CH and in a female individual, which is also rare.\textsuperscript{6–12} CH in a woman with age at onset of 89 years has been reported,\textsuperscript{23} and Evers et al have also described CH with age at onset of over 80 in a woman,\textsuperscript{24} but these are the only reports of CH in a woman at an older age of onset than in the present case. Interestingly, Evers et al also presented a case of a man with CH onset at the age of 75.\textsuperscript{24} A retrospective review on the occurrence of CH in middle-aged and elderly women demonstrated seven women with an age at onset of 52 to 72 years.\textsuperscript{25} It is worth noting that, according to a large study by Manzoni et al,\textsuperscript{13} age at onset of CH can be considered atypical if it is higher than 58 years in women and 50 years in men. There is also a report of a patient who developed CLH at an older age; however, the headache might have been secondary to other disorders.\textsuperscript{26}

The present case seems to be a primary chronic form of the disease. The fact that CCH tends to begin at an older age was noted by Horton in 1964.\textsuperscript{27} Ekbo et al found a higher mean age at onset of CH in women with CCH compared to women with ECH and men with ECH or CCH.\textsuperscript{10} In addition, the range of age at onset in women with CCH is wider than in the other groups mentioned above.\textsuperscript{10} Primary CCH seems to occur in women later than secondary CCH.\textsuperscript{10,13} In adults, the M:F ratio is the lowest and can even be inverted in patients with CH and age at onset of over 50 years old.\textsuperscript{10,13} Similarly, the ECH:CCH ratio in adults is the lowest in women who are older than 50 years at onset.\textsuperscript{12} Therefore, it
has been stated that CH with late onset in women is likely to be chronic.\textsuperscript{12} A possible primary CCH in an 83-year-old woman has also been previously shown in a case report by Evers et al.\textsuperscript{24}

According to the third edition of ICHD (beta version), the diagnostic process for any type of headache should always include the differentiation between primary and symptomatic headache attributed to other disorders.\textsuperscript{1} A symptomatic headache can be diagnosed if there is a temporal and causal relation between its first episode and another condition known to manifest headache or if the headache fulfills other criteria for causation by that disorder. However, due to the very high prevalence of headache, there has to be good evidence that this disorder is associated with headache. This evidence can result from large clinical observational studies or from smaller studies based on advanced methods. Moreover, a symptomatic headache can be diagnosed if it worsens or improves in parallel with respective worsening or improvement of the causative condition.\textsuperscript{1}

The most common pathologies causing symptomatic CLH are vascular ones,\textsuperscript{28} including mainly aneurysm,\textsuperscript{29} neurovascular conflict,\textsuperscript{26} and artery dissection.\textsuperscript{21} Interestingly, CLH seems to always be ipsilateral to the pathology. According to the diagnostic process in the present case, these pathologies and other conditions able to cause CLH could be excluded; nonetheless, in anamnesis, a large right-sided ischemic area was revealed in head CT and MR due to two ischemic strokes. A possible causal association between an ischemic cerebrovascular accident (ICVA) and headache (but not CH) has been well-documented.\textsuperscript{1,30,31} Headaches associated with ICVA are thought to be caused by edema, disturbances in the trigeminovascular system, and hemorrhagic transformation\textsuperscript{21} and are also postulated to have vascular causes and to come from either intracranial or extracranial vessels.\textsuperscript{30} Their suspected pathophysiology explains their frequent location ipsilateral to the ICVA. These headaches occur in up to one-third of patients with ICVA\textsuperscript{1}; however, they almost never resemble CH. They are usually nonspecific, of moderate intensity, bilateral or unilateral and ipsilateral (in 68% of patients) to the ischemic area, and can be either stabbing, throbbing, pulsating, or continuous.\textsuperscript{1,30,31} Such headaches usually accompany ICVA in the acute phase (onset headaches), but they can also occur later (late-onset headaches). According to Medina et al, late-onset headaches might begin within a year after transient ischemic attack (TIA).\textsuperscript{32}

Headaches related to ICVA substantially differ from the present case of reported headache. First, this case was severe and met the third edition of ICHD (beta version) diagnostic criteria of CH.\textsuperscript{1} Second, it appeared 4 years after the latest ICVA, so there was no temporal relation between the headache and ICVA. Third, a causal relation is doubtful due to lack of large observational studies and case reports showing a pathogenetic association between ICVA and CH; as mentioned above, only occurrence of nonspecific headache in ICVA has been sufficiently documented.\textsuperscript{1,30,31} Fourth, the headache was effectively treated with oxygen and sodium valproate; therefore, the reported headache seemed to be a case of a primary chronic CH. Its location ipsilateral to the ischemic area was probably coincidental. While it is certainly possible that it was a case of symptomatic CLH, this is unlikely and cannot be proven.

There are very few reports of symptomatic chronic paroxysmal headaches associated with ICVA. Trucco and Badino presented a case of chronic, left-sided CLH that developed in a 70-year-old man who had suffered from several episodes of left middle cerebral artery and vertebro-basilar TIAs and strokes since the age of 64.\textsuperscript{33} The present authors share the opinion that temporal relation between two different diseases is an important condition that allows one to suspect a pathogenetic connection between them; however, it was difficult to assess such a relation in their patient, because the authors did not specify what temporal interval had occurred between the last ICVA and the onset of CLH—it is known only that CLH appeared approximately 6 years after the first ICVA. This information is not sufficient to diagnose symptomatic CLH due to such a long time interval, and the authors state that a pathogenetic association in their case report is not proven. It is also worth noting that Newman et al presented a case of chronic paroxysmal headache attributed to ICVA in a 56-year-old woman.\textsuperscript{34} Similar to the present case, in which the headache was ipsilateral to the ischemic area, she had suffered from right-sided ischemic stroke with left-sided hemiparesis. Nonetheless, there are several essential differences between these two patients. First, the headache reported by Newman et al resembled chronic paroxysmal hemicrania (CPH), not CH. Second, it had begun only a week after the stroke, so a temporal relation between the headache and ICVA was evident. Therefore, the authors could easily diagnose a symptomatic CPH in their patient.

Conclusions

CH rarely affects women, and in the majority of cases it begins at a young age. This is one of very few case reports of CH in a woman with onset at an older age. Reports of epidemiologically unique headaches are needed because they bring very helpful knowledge to science and daily clinical practice. The present case report points to the need to diagnose primary CH or
symptomatic CLH very carefully after precise consideration of diagnostic criteria; this is extremely important for appropriate diagnosis and effective treatment. Caution should be exercised when considering whether patients are affected by CH because of its possible occurrence at an older age.

Since in the present case there were no apparent temporal or causal relations between the reported headache and ICVA, a diagnosis of symptomatic CLH attributed to cerebrovascular disease was considered unlikely, although theoretically possible. There is a strong need for large clinical observational studies based on high-quality neuroimaging, as well as case reports exploring a possible pathogenetic association between ICVA and CLH.

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