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Case report: A case of chronic cluster headache affected by gender affirmation treatment

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Abstract

Background: Chronic cluster headache (CH) affects around one in 10,000 people, some of them are resistant to a multitude of treatments.

Case: We present a case report of a patient with treatment resistant chronic CH which has significantly improved in the setting of gender-affirming care and hormonal treatment with cyproterone acetate and estradiol.

Conclusion: The case contributes to a growing body of literature suggesting that hormonal factors may impact the clinical course of primary headache disorders, including CH. Particularly in the context of transgender patients and hormone replacement therapy, hormonal modulation may offer an adjunct or alternative approach for managing chronic and treatment-resistant headaches.

Keywords

gender change, estrogen, cyproterone acetate, refractory

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Introduction

Cluster headache (CH) is the third most common primary headache. Typically, short-lasting (15 to 180 min, untreated) unilateral attacks of excruciating periorbital pain are accompanied by autonomic symptoms and/or restlessness (ICHD-3).[1] As to its name *cluster*, the attacks typically occur in episodes, with silent intervals of months to years. But there is also a chronic form, where patients have no prolonged pain-free intervals of more than three months. Around 10–15% of CH patients suffer from the chronic form, whereof around 20% are resistant to the available treatments.[2] As in most primary headaches the pathophysiology of CH is not fully understood. Still, an involvement of the trigeminovascular system and the hypothalamus are postulated. There is a predominant incidence in men, with a ratio between 2 to 8:1, and current or past smoking, or even being a child of heavy smokers.[3]

Case description

We present a 35-year-old patient, born and raised as a boy. She reported the first headache attacks at the age 9, but only 17 years later, she was diagnosed with CH. At that time, the CH was already chronic, with an exacerbation of the attack frequency at around 30 years of age. The frequency varied between two and up to more than 10 attacks per day. The patient reported typical half-sided attacks with accompanying autonomic features, such as conjectival injection and nasal congestion. The attacks lasted around 15 min, when treated, and they were occurring during day and sometimes at night, without any additional seasonal variation. The patient was treated by different headache specialists and had multiple emergency room visits.

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Other relevant diagnoses included: Attention deficit hyperactivity disorder (ADHD), asthma, gastritis, chronic sinusitis, depression, sleep disorder (insomnia), hormone-inactive microadenoma of the pituitary gland (this was checked before and after treatment), and bladder disorder with forced micturition plus fecal incontinence of unclear etiology. The patient had never smoked. In the family there was neither CH nor migraine. The neurological examination was normal and so was a magnetic resonance imaging of the brain, except for the before mentioned microadenoma. There were no signs of chronic sinus disease.

The acute treatment consisted of oxygen (15 L/min), sumatriptan 6 mg sc, ketamine 7.5 mg intranasally and/or lidocaine 4% intranasally, with varying efficacy. For many years the patient was treated with verapamil, without much effect. In the last five years before gender affirmation from male to female, the patient was treated with the following therapies: verapamil (up to 720 mg/d, no effect), lithium (up to 1200 mg/d, no effect), topiramate (up to 100 mg/day, no effect), galcanezumab (360 mg/m, no effect), LSD (once 100 µg po, not tolerated), Gammacore® (no effect), and also magnesium (300 mg/d, no effect), candensartan (8 mg/d, no effect), memantine (10 mg/d, no effect), lamotrigine (up to 150 mg/d, no effect), and gabapentin (up to 800 mg/d, no effect). Each one of these therapies was tried for at least three months before stopping. There were no tolerability issues reported. Only greater occipital nerve infiltration (GONI) had reduced the frequency of the attacks partially for a few days.

Also, other medications were initiated for anxiety disorder, such as trazodone, lorazepam, sertraline, quetiapine, midazolam, and methylphenidate for the ADHD. These drugs did not have any impact on the CH disease course. In addition, she/her had several intravenous treatments, such as high dose steroids, ketamine and fentanyl; none with any effect. Furthermore, other interventions were tried: sphenopalatine and stellate ganglion blocks. At the age of 33 years an occipital neurostimulator was implanted. Due to lack of effect regarding frequency and intensity of the attacks, it was explanted again one year later. The patient was in continuous psychotherapy over at least two years.

The patient felt not comfortable in her own body for many years. At age 34, she decided to have a gender affirmation (male to female). Hormone therapy with cyproterone acetate (an antiandrogene) 50 mg/d and estradiol 10 mg/d was initiated by the endocrinologists end of January 2023 and the dose was slowly increased. After two weeks, the cluster attacks were less frequent and milder. Another six weeks later, with another increase in the hormone dose, the patient was free of attacks until mid of October 2023, with one exception (two attacks/day for a week) in August 2023, when she developed pancreatitis of unknown etiology.

For the first time in eight years of chronic CH, the patient was totally free of attacks for six months. The urinary and fecal problems normalized. Also, depressive symptoms were reduced and the patient's quality of life improved. Some of the medications could be reduced. The patient remained on lamotrigine (150 mg/d), methylphenidate, benzodiazepines prn and GONI was performed once again in October 2023. After that the patient had experienced again a few attacks in a setting of stress situations (e.g. she was attacked at the street parade), these only lasted for a few days and then resolved. Two esthetic operations (forehead and jaw surgery) were performed, the goal was to render the face more feminine. Gender-affirming surgery was planned for 2025. Overall, the gender-affirming hormonal treatment had a significant impact on the CH history of this patient.

Discussion

There are clearly differences in gender prevalences of primary headaches. Whereas there are more women suffering from migraine or paroxysmal hemicrania, there is a predominance of men in CH.[4,5] The effect of sexual hormones is not fully understood. The current case of a patient with chronic CH who experienced significant improvement in both the frequency and intensity of attacks following gender affirmation highlights the potential influence of sex hormones on the course of CH. Interestingly, men with CH typically report more severe attacks, but women may experience attacks of longer duration or greater variability in intensity, which can lead to misclassification or delayed diagnosis.[6] The patient in this case had suffered from chronic CH for years and was resistant to a wide range of conventional treatments, including high doses of verapamil, CGRP monoclonal antibodies, and nerve stimulation therapies. This long-standing refractoriness to treatment suggests that the drastic improvement seen after starting hormone therapy could be linked to the hormonal changes associated with the gender affirmation.[7] The introduction of cyproterone acetate, an antiandrogen, and estradiol appeared to coincide with a marked reduction in headache attacks and an improvement in quality of life, suggesting a potential role of sex hormones, particularly estrogen, in modulating the trigeminovascular system and the hypothalamic mechanisms implicated in CH. There have been small case series before, where hormonal treatment has been used, but not in the setting of gender affirmation treatment.[8–10] In the case series by Stillman et al., as in an older Italian study in episodic CH, low testosterone have been reported.[8,11] Interestingly, Verhagen et al. found in a cross-sectional questionnaire study symptoms of androgen deficiency in men with CH. While the above-mentioned study by Petersen et al. measured hormone levels in two larger groups of episodic and chronic CH and found an altered endocrine system in male patients with CH towards a state of compensated hypogonadism.[7]

Recent studies support the notion that sex hormones can significantly influence pain modulation and headache

disorders.[12] Estrogen, in particular, plays a complex role in women's headache patterns, such as menstrual migraines, which fluctuate with hormonal changes during the menstrual cycle. CH, although not directly associated with the menstrual cycle, may be similarly influenced by changes in testosterone and estrogen levels. Testosterone, generally higher in men, has been linked to decreased pain thresholds, whereas fluctuating estrogen levels in women have been associated with both increases and decreases in pain sensitivity.[13] The patient's initiation of hormone therapy, which decreased testosterone levels and increased estradiol, may have contributed to changes in the regulation of pain pathways, resulting in the suppression of CH attacks. The hypothalamus, a region known to be involved in both the circadian rhythms and the autonomic symptoms of CH, is also a key regulator of hormonal cycles, further suggesting that changes in the hormonal milieu could directly impact CH pathophysiology.[14] This is particularly relevant in the context of this patient's transition, where the stabilization of estrogen levels could have a modulating effect on the hypothalamic dysfunction thought to play a role in CH.

Moreover, the improvement in other symptoms such as bladder dysfunction, fecal incontinence, and depressive symptoms following hormone therapy suggests a broader systemic effect of sex hormones beyond CH management. This raises the question of whether other neurological and autonomic systems, may also be responsive to hormonal changes. The patient's prior resistance to the full spectrum of pharmacologic treatments for CH, such as calcium channel blockers, anticonvulsants, and antidepressants, along with the transient and incomplete relief provided by GONI and neurostimulation, highlights the limitations of current CH management in refractory cases. Hormone therapy may have provided a therapeutic avenue in this case. Although the exact mechanism remains unclear, it is plausible that the antiinflammatory properties of estradiol and its potential to modulate central nervous system excitability and neurovascular responses play a role in the observed reduction of CH attacks.

Conclusion

This case contributes to a growing body of literature suggesting that hormonal factors may significantly impact the clinical course of primary headache disorders, including CH. While more research is needed, particularly in the context of transgender patients and hormone replacement therapy, this case suggests that hormonal modulation may offer an adjunct or alternative approach for managing chronic and treatment-resistant CH. Transgender individuals, especially those undergoing hormone therapy, represent an understudied population in headache research. Given the profound improvement in this patient's headache pattern following gender-affirming hormone therapy, further investigation into the role of sex hormones in CH pathophysiology is warranted. Prospective studies should explore whether hormonal fluctuations or therapy may serve as a therapeutic target in refractory CH, potentially leading to more personalized and effective treatment strategies.

Clinical implications

- A case of refractory CH presented, where there was a clear reduction of attacks after gender-affirming treatment.
- Possible mechanisms and their implications for further studies in gender medicine are discussed.

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Ethical approval and patient consent

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