Brief Report

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–4

DOI: 10.1177/0333102414527647
cep.sagepub.com

SAGE

Complete alleviation of treatment refractory primary SUNCT syndrome with clomiphene citrate (a medicinal deep brain hypothalamic modulator)

Todd D Rozen

Abstract

Objective: To report the first ever case of primary short-lasting unilateral neuralgiform headache attacks (SUNCT) syndrome completely responsive to clomiphene citrate.
Methods: Case report.
Results: SUNCT is a primary headache disorder marked by frequent attacks of one-sided headache with cranial autonomic associated symptoms. When SUNCT is deemed medicinally treatment refractory, it can cause tremendous patient-related disability. Surgical treatment options are available including hypothalamic deep brain stimulation, occipital nerve stimulator placement or arterial decompression surgery, but these procedures carry significant morbidity. A patient presented with a 10 month complaint of multiple, daily short-lasting, right-sided headaches each lasting from 60 to 120 seconds in duration and occurring from 100 to 200 times per day. The head pain was associated with ipsilateral eyelid ptosis and conjunctival injection. The patient was diagnosed with SUNCT but was unresponsive to multiple recognized medicinal treatments. He had complete alleviation of his attacks with clomiphene citrate, a synthetic, non-steroidal, ovulatory stimulant that directly binds to hypothalamic estrogen receptors. The clomiphene was tolerated without any adverse events. A putative mechanism of action for clomiphene in the prevention of SUNCT will be presented.
Conclusion: Clomiphene citrate is a unique treatment for SUNCT and appears to be very safe and effective.

Keywords

Clomiphene citrate, cluster headache, estrogen, hypocretin, hypothalamus, orexin, SUNCT

Date received: 28 January 2014; accepted: 16 February 2014

Short-lasting unilateral neuralgiform headache attacks (SUNCT) is a unique headache disorder marked by short-lived bouts (1–600 seconds) of very frequent (sometimes 100 or more attacks per day), one-sided head pain of moderate to severe intensity with associated conjunctival injection and tearing (1). For a period of time SUNCT was recognized as the most difficult to treat primary headache syndrome (2). If, however, a patient does not respond to one of the main recognized therapies (lamotrigine, gabapentin, topiramate), this condition can still cause tremendous disability and require heroic maneuvers by the physician to establish an effective treatment program. In many instances this involves invasive procedures such as hypothalamic deep brain stimulation (DBS), occipital nerve stimulator placement or arterial decompression surgery, all of which carry the possibility of significant morbidity and even the chance of mortality (3–6). Clomiphene citrate is a synthetic, non-steroidal ovulatory stimulant that directly binds to hypothalamic estrogen receptors and has both estrogenic and anti-estrogenic functions. Its unique hypothalamic tissue-binding properties make it a promising treatment for the trigeminal autonomic cephalalgias (TACs), which are hypothalamic modulated syndromes of which SUNCT is a recognized subform (1). Previously the

Geisinger Health System, Department of Neurology, Geisinger Headache Clinic, PA, USA

Corresponding author:
Todd D Rozen, Geisinger Specialty Clinic, MC 37-32, 1000 East Mountain Blvd, Wilkes-Barre, PA 18711, USA.
Email: tdrozmigraine@yahoo.com

author described one medicinally refractory SUNCT patient who had significant but not complete alleviation of his attacks with clomiphene citrate, but that patient ended up having a secondary SUNCT syndrome from a growth hormone secreting pituitary tumor (7). The present case is the first to report a complete alleviation of primary SUNCT syndrome utilizing clomiphene citrate, while also hypothesizing on its preventive mechanism of action.

Case report

A 65-year-old man presented to a dedicated headache specialty clinic with a 10 month complaint of multiple, daily, short-lasting, right-sided headaches. Each headache would last from 60 to 120 seconds and would occur from 100 to 200 times per day. Just while doing his intake history, the patient had 20 attacks in a 30-minute time period. Head pain location was right supraorbital and right temple but it would radiate to his right cheek and lip. Associated symptoms during each and every attack included right eyelid ptosis, conjunctival injection, lacrimation and nasal rhinorrhea. Pain quality was described as burning. He also suffered agitation during each attack such that he would rock back and forth and rub his eye. There were definite trigger zones that when altered would elicit attacks including touching his temple, forehead and lip, as well as talking and eating. He had lost a considerable amount of weight during the pain cycle to guard against triggering headaches and basically had stayed almost mute to avoid talking. His past medical history was significant for hypertension, diabetes and hyperlipidemia. On examination, after touching the patient's right cheek or palpating his supraorbital notch or after cervical rotation, he would immediately develop conjunctival injection as well as a ptosis in addition to head pain. The remainder of his exam including neurovascular examination was normal.

Prior to this cycle for the last 9 years, he would have similar cycles of pain but they always would occur in the fall around the time of the clock change and end in the spring again at the time of the clock change, and his attack frequency was much less prevalent at two to five attacks per day with the same duration and associated symptoms. He had also experienced 1 year without a cycle. Only one other cycle had lasted an entire year with daily attacks, which was reminiscent of the present pain cycle, but the attacks were not nearly as frequent or as severe. During this present cycle he had tried various preventive medications before coming to the headache specialist, including topiramate (increased his attack frequency), oxcarbazepine (increased attack frequency), pregabalin (no change in headache frequency) and indomethacin up to 150 mg per day with no change in headache frequency. Previous neuroimaging included MRI brain with and without gadolinium, which was normal.

The patient was given a diagnosis of episodic and now probable chronic SUNCT syndrome meeting the ICHD 3 beta criteria (1). He never had heard of this diagnosis as previously he was told he had cluster headache. However, prior to this cycle he was not really bothered by the syndrome as his attacks were brief and only occurred several times per day. To complete his evaluation, neurohormonal laboratory testing (growth hormone, IGF1, prolactin, free and total testosterone) and a dedicated MRI pituitary study to rule out a pituitary tumor as well as imaging of his intra and extracranial circulation (MRA brain and neck) to exclude dissection and aneurysms were completed, and these investigations were normal. A high volume right suboccipital nerve block (9 cc 1% lidocaine with 1 cc triamcinolone 40 mg/ml) was done to try to break or modulate his cycle of pain but this offered no relief. He was then tried on gabapentin, but at 1200 mg per day he felt this increased the frequency of attacks (actually the third anti-epileptic medication to do so). He was also tried on melatonin (9 mg) and baclofen 60 mg without any benefit. Lamotrigine was considered, but as almost every other anti-epileptic medication had made his condition worse it was decided to try clomiphene citrate which the author had previously tried in a medicinally refractory SUNCT patient with some success (7). The patient was started on 50 mg per day for the first 2 weeks. Within 4 days of initiation he started to see a reduction in headache frequency especially during his sleep time as he was now getting hours of sleep on clomiphene, whereas, previously, he was being awoken every 15 minutes with attacks. After being on 75 mg for 5 days he became pain-free, and was sleeping throughout the night without any awakening, and there was now an inability to trigger attacks from his trigger zones. He did well for 1.5 months at this dose but then had a slight recurrence of attacks (one to two per day) with a re-occurrence of his trigger zones. His clomiphene dose was increased to 100 mg per day and he became pain-free again and this continued for another 3 months, at which time he felt he was out of cycle and was able to taper off clomiphene and has continued pain-free at 4 months off clomiphene. The patient had absolutely no adverse events on clomiphene treatment. He also was able to talk and eat, and able to regain the weight he had lost previously, which pleased him.

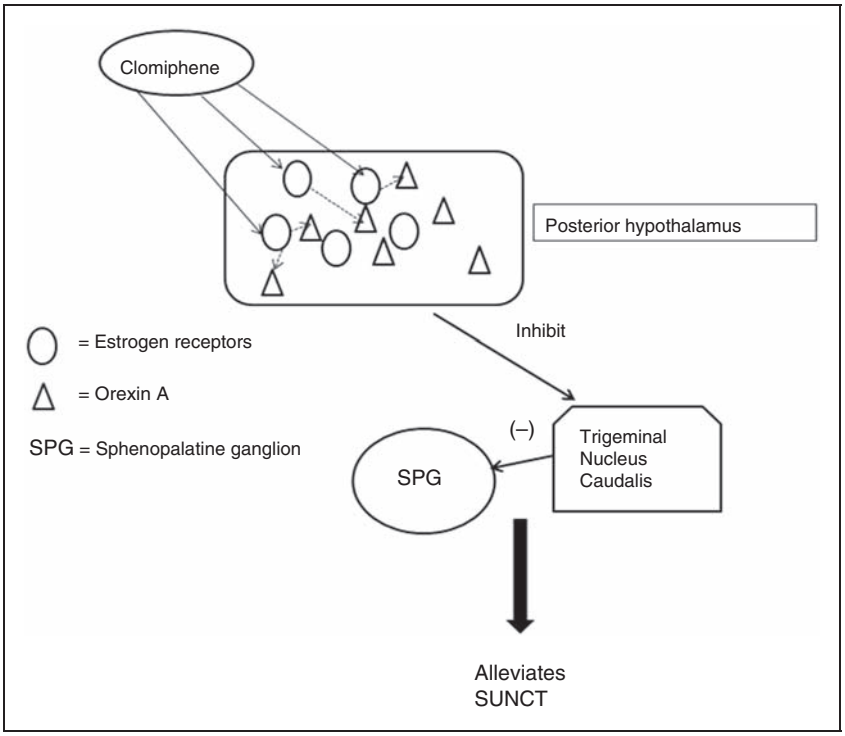

Figure 1. Proposed mechanism of clomiphene citrate in the preventive treatment of SUNCT syndrome.

Discussion

The presumed pathologic generator of SUNCT appears to be in the posterior hypothalamus based on functional imaging studies during ictal attacks, the same region noted to be active in other TACs including cluster headache (8). One of the most effective non-medicinal treatments for these syndromes has been hypothalamic DBS targeting this region (3). The mechanism by which hypothalamic DBS works to suppress TACs is not yet known. Clomiphene citrate would seem to work in the same location as DBS as it directly binds to the hypothalamus, thus is a type of medicinal 'hypothalamic deep brain modulator'. How clomiphene effectively alleviates SUNCT and also cluster headache (previously reported by the author) can only be hypothesized (9). Recently, there has been an interest in the hypothalamic neuropeptides orexin A and B, and their role in the pathogenesis of the TACs, as both can modulate trigeminal afferent activity, although orexin A appears to have antinociceptive effects whereas orexin B is pronociceptive (8). Newly documented is that gonadal steroids also influence orexin expression (10). In male rats there is estrogenic regulation of orexin, and in castrated males estradiol is required to restore hypothalamic orexin protein levels to baseline, whereas testosterone administration has no effect on restoring orexin activity (9). Estrogen receptors co-localize and are coextensive with hypothalamic orexin neurons, and also influence orexin expression from non-hypothalamic CNS structures. Thus, as clomiphene has a direct effect on hypothalamic estrogen receptors and estrogen modulates hypothalamic orexin expression plus hypothalamic estrogen receptors co-localize to orexin neurons, the author can then hypothesize that clomiphene citrate works to prevent SUNCT and cluster headache attacks by upregulating orexin A levels, which then act by inhibiting trigeminal nucleus caudalis activity and secondarily suppressing the trigemino-autonomic reflex preventing hypothalamic driven head pain (Fig. 1).

Irrespective of its mechanism of action, one of the clear benefits of clomiphene is that it appears to work without any significant side effects, at least in the SUNCT patients who have used it so far and the cluster headache patient who has been previously reported (7,9). Clomiphene citrate is also effective when other established SUNCT treatments fail, and thus it seems to be a welcome addition to the SUNCT armament. This unique treatment for SUNCT should be considered for all patients before any surgical procedure is suggested, as these invasive techniques have a much higher potential morbidity. The recommended starting dose of clomiphene citrate is 50 mg per day, increasing by 25 mg every 2 weeks if necessary with a maximum dose of 100 mg per day.

Clinical implications

- Clomiphene citrate is effective for medicinally refractory primary SUNCT syndrome.
- Clomiphene citrate may work preventively in SUNCT by binding to hypothalamic estrogen receptors with a secondary modulation of orexin leading to an inhibitory influence on the trigeminal autonomic reflex.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

References

1. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 1–808.
2. Leone M, Rigamonti A, Usai S, et al. Two new SUNCT cases responsive to lamotrigine. *Cephalalgia* 2000; 20: 845–847.
3. Bartsch T, Falk D, Knudsen K, et al. Deep brain stimulation of the posterior hypothalamic area in intractable short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). *Cephalalgia* 2011; 31: 1405–1408.
4. Matharu M, Watkins L and Shanahan P. Treatment of medically intractable SUNCT and SUNA with occipital nerve stimulation. *J Neurol Neurosurg Psychiatry* 2010; 81: e51–e52.
5. Favoni V, Grimaldi D, Pierangeli G, et al. SUNCT/SUNA and neurovascular compression: New cases and critical literature review. *Cephalalgia* 2013; 33: 1337–1348.
6. Black DF and Dodick DW. Two cases of medically and surgically intractable SUNCT: A reason for caution and an argument for a central mechanism. *Cephalalgia* 2002; 22: 201–204.
7. Rozen TD, Saper JR, Sheftell FD and Dodick DW. Clomiphene citrate as a new treatment for SUNCT (hormonal manipulation for hypothalamic influenced trigeminal autonomic cephalalgias). *Headache* 2005; 45: 754–756.
8. Holland P and Goadsby PJ. The hypothalamic orexinergic system: Pain and primary headaches. *Headache* 2007; 47: 951–962.
9. Rozen T. Clomiphene Citrate for Treatment Refractory Chronic Cluster Headache. *Headache* 2008; 48: 286–290.
10. Muschamp JW, Dominguez JM, Sato SM, et al. A role for hypocretin (orexin) in male sexual behavior. *J Neurosci* 2007; 27: 2837–2845.