Effect of testosterone therapy on migraine frequency and disability in two transgender patients: a case report

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SUMMARY

With an increasing number of patients seeking gender-affirming hormone therapy (GAHT), the clinical impact of testosterone treatments on headache needs to be determined. Our case report looks at the potential effect of testosterone on migraine among transgender patients. We present two transmasculine patients who used masculinising hormone therapy with testosterone. Both patients described their headache as moderate-to-severe pain with features that fulfilled the criteria for chronic migraine without aura. Following GAHT, one patient improved in both frequency and intensity of headache symptoms while the other noted improvement in headache intensity alone. Our report postulates that testosterone therapy may have a positive impact on headaches in individuals participating in GAHT, highlighting the need for further research on the role of testosterone therapy on headache in transmasculine individuals.

BACKGROUND

There is a growing body of evidence on the impact of hormonal changes, particularly oestrogen, on migraine, however, the role of testosterone has not been extensively explored. Findings from early studies indicate that there may be a potential clinical benefit of testosterone in the management of migraine. A recent study postulated that sex steroid exposure during the prenatal period is a potential risk factor for migraine as an adult. In women, increased testosterone levels in women is significantly correlated with the prevalence of migraine and the opposite correlation was observed in men. It is important to note that fetal hormone levels are not related to postnatal levels.[1] One study found that testosterone levels in women with migraine were lower than healthy controls,[2 3] another evaluated men with chronic headaches and determined that mean total testosterone levels were significantly lower compared with the age-matched normative population.[4] A smaller study found that men with migraine and cluster headache more frequently report symptomatology consistent with relative androgen deficiency than males without a primary headache disorder.[5] Furthermore, prophylactic use of danazol, an androgen-receptor agonist, was found to successfully control cyclical migraine headaches in women unresponsive to standard medication.[6] Testosterone therapy has been of recent clinical interest in reducing disability related to migraine and the severity of migraine attacks. Testosterone levels in postmenopausal women with migraine were negatively correlated with Migraine Disability Assessment Scores (MIDAS). MIDAS is a validated, self-administered questionnaire designed to measure headache-related disability, which can help guide treatment plans.[2] Using the MIDAS a significant improvement in migraine severity was demonstrated in premenopausal and postmenopausal women with 3 months of continuous testosterone therapy.[7]

Although the exact mechanism through which testosterone modulates migraine is unknown, there are multiple proposed fields of thought. In an in vivo study in mice with the mutation causing familial hemiplegic migraine type 1, chronic testosterone replacement prevented orchiectomy-induced cortical spreading depression (CSD) susceptibility, suggesting its role in CSD suppression.[8] Another proposed mechanism is that testosterone can induce dilation of brain blood vessels and stabilise cerebral blood flow.[9] As a neuroactive steroid, high-dose testosterone may also influence serotonin metabolism by binding to serotonin reuptake transporters.[10 11] Furthermore, effects of testosterone on migraine may be mediated by androgen-receptor modulation. Studies have shown that androgen-receptors mediate CNS depression, and activation lends to the hypothesis of testosterone-mediated analgesia in low oestrogen states.[12–14]

In recent years, increasing numbers of patients are seeking gender-affirming hormone therapy (GAHT). Given the lack of evidence of the clinical impact of testosterone treatments on migraine, clinicians are currently unable to provide evidence-based informed counselling to these patients. Our case report looks at the potential effect of testosterone on migraine among transgender patients and explores any impact on migraine disability and severity. Two patients from our clinic provided written informed consent for the writing and publication of this case report. No ethical approval was required for this study.

CASE PRESENTATION

PATIENT ONE:

A patient with history of anxiety and depression presents to clinic with a 19-year history of headaches that were predominately unilateral, severe, throbbing and pulsating with associated photophobia, phonophobia with prodromal nausea that required her to rest during the episodes. Migraine

attacks initially occurred 1–2 times per month but after a skiing accident, the patient developed postconcussive symptoms including nausea, vestibular symptoms and worsening headache frequency, 12–16 monthly migraine days (MMD) which gradually increased to daily and constant. CT head was unremarkable. Menstrual history included menarche at age of 13 with regular menses and headaches not appearing to be related to their cycle.

At the initial visit 7 years ago, the patient had a normal neurological examination and review of prior MRI brain and cervical spine imaging was unremarkable. Diagnosis of chronic migraine without aura[15] was given complicated by postconcussion syndrome. Initially propranolol and gabapentin were tried, but were discontinued shortly after due to side effects. The decision was made to start onabotulinumtoxin A (OnabotA). After five courses of OnabotA, there was some improvement in headache intensity, but headaches remained daily and constant. Due to psychiatric comorbidities, the patient was trialled on escitalopram, amitriptyline and nortriptyline over the following 2 years, but these were discontinued due to lack of efficacy from a mood perspective with little to no impact on headache.

The patient started GAHT 4 years ago with testosterone 5 mg/24 hours patches. One month prior to this, the patient was experiencing a daily and constant mild headache with superimposed more severe headaches (8 MMD). Their MIDAS was 44, with 90 days of headache, pain 4/10 in intensity with 1 ED visit. They had missed 12 days of school (over a 90-day period). At the time they were on naproxen-esomeprazole, rizatriptan and OnabotA. At a follow-up appointment, (4 months after initiation of testosterone therapy), headache frequency remained unchanged, but headache intensity had reduced. Their MIDAS decreased by >50%, now at 18, still 90 days of headache in 3 months with a pain score of 2/10 with no emergency department visits and no missed school days. There had been no changes to their acute or abortive therapies since initiation of GAHT.

There was an increase in headache intensity after breast reduction surgery later that year where oxycodone/acetaminophen was given for pain management along with increasing psychosocial stressors. Eventually, that same year, a trial of erenumab 140 mg monthly was initiated. On subsequent visits, it was noticed that headache frequency remained unchanged, but intensity decreased to low-grade (2–3/10).

They continued to do well until 2 years ago, when they had a transient worsening of headache intensity, likely correlated to the cessation of erenumab (loss of insurance coverage) along with a change from the continuous testosterone patch to intermittent dose of testosterone enanthate 200 mg/mL injection every 14 days. At that time, MIDAS was 46, 90 days of headache and pain 2/10 with no emergency department visits 3 days of missed work (over 90 days). At the next follow-up, their MIDAS was 5, with 90 days of headache, 2/10 pain and no emergency department visits and no missed days of work due to headache. Which was likely due to their double mastectomy surgery as there were no further changes in medications. Since then, they have remained stable with fluctuations in headache intensity based on life stressors, but they typically remain stable at 2 MMD on OnabotA, rizatriptan and naproxen.

Patient Two:

A patient was initially seen in clinic 11 years ago, at the time experiencing 15 MMD since adolescence. The headaches were moderate-to-severe, pulsating and pressure-like, bifrontal with associated photophobia, phonophobia and nausea. There were no symptoms of aura. Menstrual history included menarche at the age of 13 with regular menses, some of which were associated with headache.

At initial visit, the patient was given a diagnosis of chronic migraine without aura[15] complicated by a history of depression and prior medication overuse. Their MIDAS was 45, with 37 days of headache, pain was rated 6/10 with 10 days lost from school and no emergency department visits. Prior to being seen the patient was on propranolol, sumatriptan, acetaminophen/codeine, escitalopram and zopiclone. Neurological examination and neuroimaging was unremarkable. The decision at that time was to taper off propranolol, start nutraceuticals and nortriptyline. Over the ensuing years, a trial of numerous other preventative agents such as OnabotA, gabapentin, amitriptyline, verapamil and topiramate was done; all of which were minimally effective. For acute therapy, nabumetone and rizatriptan was used with good effect. Eventually, the patient was started on erenumab in 2019 at 70 mg/dose. Prior to the initiation of CGRP medications, they were experiencing 12 MMD with a MIDAS score of 17, a pain intensity of 4/10, 3 days of missed school and no emergency department visits. With no improvement after three injections, the dose was increased to 140 mg. This resulted in a reduction in headache frequency to 9 MMD.

Last year, the patient started on testosterone enanthate at a dose of 50 mg weekly. During the follow-up, the patient noted that frequency of headaches was improved to 6 MMD. Their MIDAS was 13 with pain rated as 3/10 with only 3 missed days from work and 4 missed days of school and no emergency department visits. When last seen at the end of the year, they were on 100 mg of weekly testosterone enanthate, rizatriptan and nabumetone prn, nortriptyline (with plans to decrease) and erenumab 140 mg/month and was experiencing 'scattered headaches throughout the month'. Their MIDAS was 8, with 1–2/10 pain intensity, 1 missed day of school and 3 missed days from work. With the testosterone therapy, menses had ceased resulting in resolution of perimenstrual migraine attacks.

DISCUSSION

Although data on headache prevalence in the transgender population is limited, it is accepted that headache frequency is likely to increase in individuals undergoing estrogen/antiandrogen therapy, and that androgen treatment may improve pain sensitivity in individuals who suffer from headaches prior to hormone therapy.[12 16 17] More studies are needed to look specifically at how testosterone, dosing and timing in an individual's life cycle impacts headache in those participating in GAHT. There is much to learn regarding the complexity involved in these individuals' transition and it is important to further study this population.

Both patients described headache as moderate-to-severe pain with features that fulfilled the criteria for chronic migraine without aura. Both made the decision to transition from female-to-male and used masculinising hormone therapy with testosterone. They did not have pre-existing hypertension, cardiovascular, stroke or clotting disorder risk factors, which could increase with the use of testosterone.[17]

Interestingly, one patient endorsed improvement in both frequency and intensity of headache symptoms while the other noted improvement in headache intensity alone. One study found that testosterone improved headache pain, decreased number and duration of head pain attacks,[12] suggesting that testosterone may have a possible role in management of headaches. Both patients were also started on erenumab. It was initially believed that this therapy likely played a role in the improvement of their symptoms, however, the first patient had to stop erenumab due

to insurance issues and the second patient had been on erenumab for many months with minimal benefit prior to starting testosterone. The improvement seen in the second patient could be attributed to the cessation of menstruation and the perimenstrual migraine attacks. One cannot discount the fact that there can be a substantial mental health toll on an individual contemplating transitioning and some improvement in headaches could be attributed to starting GAHT.

This case report highlights the need for further research on the role of GAHT on headache in this population. Our case report supports the idea that testosterone therapy may have a positive impact on headaches in individuals who are participating in GAHT. The authors suggest studying more patients who are using testosterone therapy to further evaluate the impact of testosterone suppression on headache in transmasculine individuals. Greater participant numbers are needed to characterise the effects of dose, duration and delivery method of testosterone therapy and to differentiate the effects of testosterone, from the psychological effects of gender transition, on migraine frequency and severity.

Learning points

- Testosterone may have an impact on headache intensity and frequency in individuals undergoing gender-affirming hormone therapy (GAHT).
- Additional studies to specifically evaluate how testosterone, dosing and timing in an individual's life cycle, impacts headache in those participating in GAHT are needed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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REFERENCES

1 Kobus M, Sitek A, Antoszewski B, *et al*. Prenatal oestrogen-testosterone balance as a risk factor of migraine in adults. *J Headache Pain* 2021;22.
2 Li W, Diao X, Chen C, *et al*. Changes in hormones of the hypothalamic-pituitary-gonadal axis in migraine patients. *J Clin Neurosci* 2018;50:165–71.
3 Calton GJ, Burnett JW. Danazol and migraine. *N Engl J Med* 1984;310:721–2.
4 Shields LBE, Seifert T, Shelton BJ, *et al*. Testosterone levels in men with chronic migraine. *Neurol Int* 2019;11.
5 Verhagen IE, Brandt RB, Kruitbosch CMA, *et al*. Clinical symptoms of androgen deficiency in men with migraine or cluster headache: a cross-sectional cohort study. *J Headache Pain* 2021;22.
6 Lichten EM, Bennett RS, Whitty AJ, *et al*. Efficacy of danazol in the control of hormonal migraine. *J Reprod Med* 1991;36:419–24.
7 Glaser R, Dimitrakakis C, Trimble N, *et al*. Testosterone pellet implants and migraine headaches: a pilot study. *Maturitas* 2012;71:385–8.
8 Eikermann-Haerter K, Baum MJ, Ferrari MD, *et al*. Androgenic suppression of spreading depression in familial hemiplegic migraine type 1 mutant mice. *Ann Neurol* 2009;66:564–8.
9 Perusquía M, Stallone JN. Do androgens play a beneficial role in the regulation of vascular tone? nongenomic vascular effects of testosterone metabolites. *Am J Physiol Heart Circ Physiol* 2010;298:H1301–7.
10 Spies M, Handschuh PA, Lanzenberger R, *et al*. Sex and the serotonergic underpinnings of depression and migraine. *Handb Clin Neurol* 2020;175:117–40.
11 Kranz GS, Wadsak W, Kaufmann U, *et al*. High-dose testosterone treatment increases serotonin transporter binding in transgender people. *Biol Psychiatry* 2015;78:525–33.
12 Aloisi AM, Bachiocco V, Costantino A, *et al*. Cross-sex hormone administration changes pain in transsexual women and men. *Pain* 2007;132 Suppl 1:S60–7.
13 Aloisi AM. Gonadal hormones and sex differences in pain reactivity. *Clin J Pain* 2003;19:168–74.
14 van der Kwast TH, Dommerholt HBR, van Vroonhoven CCJ, *et al*. Androgen receptor expression in the cervix of androgen-treated female-to-male transsexuals. *Int J Gynecol Pathol* 1994;13:133–8.
15 Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders 3rd edition (beta version). *Cephalalgia* 2013;33:629–808.
16 Hranilovich JA, Kaiser EA, Pace A, *et al*. Headache in transgender and gender-diverse patients: a narrative review. *Headache* 2021;61:1040–50.
17 Yalinay Dikmen P, Ertas M, Kosak S, *et al*. Primary headaches among gender dysphoric female-to-male individuals: a cross-sectional survey on gender transition experience. *Headache* 2021;61:1194–206.