Idiopathic intracranial hypertension in a pediatric transgender patient

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A R T I C L E   I N F O
Keywords:
Idiopathic intracranial hypertension
Pediatric Transgender Androgens Papilledema

A B S T R A C T
Purpose: Androgens given for gender affirmation have been implicated in the pathophysiology of idiopathic intracranial hypertension (IIH) in transgender patients. 10 cases of transgender adults with IIH have been published but this association has not been described in younger patients. Herein we describe the first case of IIH in an adolescent transgender patient.

Observations: A 17-year-old non-obese female-to-male transgender patient on subcutaneous testosterone since age 13 presented with a two-month history of transient visual obscuration and frontal headaches. Ophthalmological examination revealed Frisen grade 2 papilledema with preserved visual function. Lumbar puncture confirmed elevated opening pressure. Papilledema resolved with oral acetazolamide and reduction of testosterone therapy.

Conclusions and Importance: The use of cross-sex hormone therapy (CSH) for gender affirmation may increase the risk of IIH. Awareness of this association is important as the number of younger transgender patients seeking CSH is increasing significantly.

1. Introduction

Idiopathic intracranial hypertension (IIH) in adults is strongly associated with obesity and its incidence is four times higher in women than in men, at 7.7 versus 1.6 per 100,000, respectively. The etiology of IIH is unknown and likely multifactorial. Even though the role of sex hormones in the pathophysiology of IIH is not completely understood, androgen excess in women is associated with IIH. Specifically, women with IIH have increased serum testosterone and increased cerebrospinal fluid (CSF) testosterone and androstenedione. This pattern of androgen excess differs from the one seen in isolated obesity or obesity related to polycystic ovary syndrome, which shares many features with IIH, suggesting that androgen excess may be an independent risk factor for IIH. Cross-sex hormone therapy (CSH), estrogen for transgender women and testosterone for transgender men, is used for gender affirmation. IIH has been reported in at least 16 adult transgender patients treated with CSH (Table 1), whereas no cases have been reported in younger patients. Herein we describe the case of an adolescent who developed IIH while being treated with testosterone for a female-to-male (FTM) transition.

2. Case report

A 17-year-old non-obese female-to-male (FTM) transgender patient was referred to the pediatric neuro-ophthalmology clinic for evaluation of possible IIH because of a two-month history of transient visual obstructions and frequent generalised and frontal headaches that worsened with physical activity. He had no diplopia, tinnitus, nausea, or other symptoms of intracranial hypertension. He had undergone mastectomy at a younger age and had been treated with subcutaneous testosterone injections since age 13, which resulted in adequate masculinisation. His testosterone dose had been adjusted for age gradually, and 1 month before our exam it had been increased to 70 mg per week. The patient’s body mass index was 25.8 kg/m², and he denied any recent weight gain. He was on no other medication. Ophthalmological examination revealed normal visual acuity of 20/20 in both eyes and normal color vision on Hardy-Rand-Rittler (HRR) plate test. The pupils reacted normally to light with no relative afferent pupillary defect (RAPD) and there was no sixth nerve palsy. The anterior segments looked normal on the slit lamp and fundoscopy revealed bilateral Frisen grade 2 papilledema. Optical coherence tomography (OCT) showed thickening of the peripapillary retinal nerve fiber layer (116 μm OD and 184 μm OS) and Humphrey 24-2 visual fields were normal. A head computed

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https://doi.org/10.1016/j.joc.2021.101208
Received 18 February 2021; Received in revised form 9 June 2021; Accepted 20 September 2021
Available online 22 September 2021
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Table 1
Reported cases in the literature of idiopathic intracranial hypertension (IIH) in transgender patients.

| Case | Age | Gender | BMI  | Hormone tx                        | Symptoms start | Treatment of IIH                                                                 | Evolution                                                                 |
|------|-----|--------|------|-----------------------------------|----------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 1    | 28  | MTF    | 30.13| Estrogens, spironolactone         | 8 M post-tx start | Hold estrogen; change to sublingual estrogen + DMX 1 g/day                       | Resolved at 5 M                                                          |
| 2    | 31  | FTM    | 56.5 | Testosterone                      | 1Y post-tx cessation | DMX 1 g/day + resume testosterone                                                | Resolved at 6 M                                                          |
| 3    | 22  | FTM    | 27.9 | Testosterone, progestin           | Rapid onset post-tx start | Shunt; DMX 3 g/day → 1.5 g/day, furosemide 20 mg/day, topiramate 25 mg/day, endovascular stent | Resolved at 18 M; atrophy without edema at 6 M                          |
| 4    | 36  | FTM    | 25.0 | Testosterone                      | 50 M post-tx start | DMX 0.5 g/day + 50% decrease testosterone                                        | Resolved at 5 M                                                          |
| 5    | 23  | FTM    | 27.05| Testosterone                      | 2W post-tx start   | DMX 1.5 g/day + furosemide 80 mg/day, topiramate 150 mg/day; fenestration OD     | Improved at 1 M                                                          |
| 6    | 22  | FTM    | <30  | Testosterone                      | 3W post-tx start   | DMX 1 g/day with taper + change to long-action testosterone                      | Improved subjectively at 1D, lost to follow-up                          |
| 7    | 33  | FTM    | NA   | Testosterone                      | <10 M post-tx cessation | DMX 2.5 g/day + fenestration OD                                                  | No symptoms at 2W; resolved + 50 lbs loss at 2 M                         |
| 8    | 39  | FTM    | >40  | Estrogens, spironolactone         | 2.5Y post-tx cessation | DMX 1 g/day → 2 g/day → 2.5 g/day, topiramate 50 mg/day, therapeutic LP, fenestration OS | Resolved + increase testosterone at 2 M                                 |
| 9    | 34  | MTF    | 41.9 | Estrogens, progestin              | 2.5Y post-tx start; 1 M post-op | DMX 1 g/day → 50% decrease testosterone                                          | Improved at 5 M                                                          |
| 10   | 24  | FTM    | NA   | NA                                | NA              | DMX 500 mg/day                                                                  | Persistence at 2 M                                                       |
| 11   | 23  | FTM    | 29.1 | Testosterone                      | 11 M post-tx start | DMX 325 mg/day + topiramate                                                      | Persistence at 2 M                                                       |
| 12   | 19  | FTM    | 31.9 | Testosterone                      | 2Y tx, many months of symptoms | Topiramate                                                                       | Improvement at 6 M                                                       |
| 13   | 36  | FTM    | 35.0 | Testosterone                      | 19 M post-tx start | DMX 325 mg/day + topiramate                                                      | Improvement at 6 M                                                       |
| 14   | 22  | FTM    | 36.1 | Testosterone                      | 13 M post-tx start | DMX 1 g/day + nortriptyline 75 mg/day                                            | Improved over 2Y                                                        |
| 15   | 23  | FTM    | 44.0 | Testosterone                      | 15 M post-tx start | DMX 1 g/day + nortriptyline 75 mg/day                                            | Improved over 2Y                                                        |
| 16   | 25  | FTM    | NA  | Estrogens                         | No symptoms, referral after 4Y tx                                               | None                                                                       | Stable at 3 M and 1Y                                                     |

FTM = female-to-male transition, MTF = male-to-female transition, BMI = body mass index, tx = therapy, g = grams, mg = milligrams, lbs = pounds, OU = oculus uterque, OD = oculus dextrus, OS = oculus sinister, DMX = acetazolamide, D = day, M = months, Y = years, NA = not available/unknown.
tomography (CT) and angio-CT were also normal. A lumbar puncture confirmed elevated opening intracranial pressure (37.5 cm of water). The patient was diagnosed with IIH and started on oral acetazolamide 250 mg twice daily. Endocrinology was involved for management of hormone therapy. Testosterone was withheld the week of initial presentation and was subsequently tapered to 50 mg weekly. The headaches and optic nerve swelling improved progressively, allowing for cessation of acetazolamide 3.5 months later. On last follow-up, 10 months after initial presentation, the patient continued to receive 50 mg of testosterone per week and remained asymptomatic with no recurrence of papilledema.

3. Discussion

In recent years, the number of transgender adolescents seeking endocrine care has increased significantly. This is paralleled with societal acceptance of gender diversity and the ample evidence that gender-affirmation treatment improves the mental health of patients with gender dysphoria, or distress caused by the incongruence between gender identity and gender assigned at birth.15–17

Our patient developed IIH while being treated with testosterone for FTM transition, like 70% of reported adults who developed IIH while undergoing affirming therapy (Table 1: cases 2–7, 10–15).4–6,9,11,13 His IIH symptoms manifested 4 years after beginning testosterone treatment, which is in keeping with a widely variable duration between start of hormone therapy and onset of IIH symptoms in previously published adult cases, between a few weeks and 5 years (Table 1).4–12 Of the previously reported adult cases, 8 were obese (Table 1: cases 1, 2, 8, 9, 12–15).10–13 Our patient was not obese but was overweight. Even though androgen excess seems to contribute to IIH independently from obesity, the latter remains an important confounding factor when analyzing the role of CSH in transgender patients with IIH.18

The exact role of testosterone in the development of IIH is unknown. However, given that men with androgen deficiency may have a higher risk of developing IIH, it has been proposed that IIH occurs at a level of circulating serum testosterone shared by women with androgen excess and men with androgen deficiency.18 The presence of androgen receptors in the choroid plexus has been demonstrated in animal models.19 Stimulation of those receptors by excess testosterone would result in increased CSF secretion in IIH.2,4,10,20 Reflecting a trend that is likely to continue in years to come, monthly referrals to a pediatric transgender clinic in Northern California increased by over 500% between 2015 and 2018.21 Awareness and reporting of the possible causal association between CSH and IIH, a potentially blinding condition, are important in view of the increasing number of young transgender patients seeking hormone-affirmation therapy.

Patient consent

Written informed consent for publication was obtained from the patient’s legal guardian.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for

Declaration of competing interest

The following authors have no financial disclosures: T.N., M.H., and L.H.O.

Acknowledgments

None.

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