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Single Case – Headache

Cerebrospinal Fluid Leak and Idiopathic Intracranial Hypertension in a Transgender Male: Is Intracranial Hypertension Hormonally Mediated?

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Keywords

Idiopathic intracranial hypertension · Cerebrospinal fluid · Cerebrospinal fluid leak · Female-to-male · Male-to-female · Hormone replacement therapy · Testosterone · Arachnoid granulations · Papilledema

Abstract

Introduction: The pathophysiology of idiopathic intracranial hypertension (IIH) is not fully characterized, and less is known about its development in transgender patients. Several cases of IIH in transgender patients have been reported, but fewer cases have been published that identify a cerebrospinal fluid (CSF) leak as a complication of IIH in this population. These patients can serve as an important study population, as an association between exogenous testosterone use in karyotypical females and development of IIH may support a hormonally mediated mechanism of development of this disease. ***Case Presentation:*** We describe the case of a 33-year-old obese (BMI: 30.58 kg/m^2) female-to-male transgender patient on exogenous testosterone for 15 years who presented with 1 month of acute or chronic headache with profuse rhinorrhea. Fundoscopic exam revealed disk pallor and edema consistent with a Frisen grade 3 papilledema. Nasal secretion was positive for beta-2 transferrin, consistent with CSF. Computed tomography head demonstrated a 5-mm defect in the medial left middle cranial fossa, bilateral optic nerve prominence and tortuosity, and abnormal arachnoid granulations concerning for IIH. After a successful endoscopic endonasal repair of the left lateral sphenoid recess leak, our patient continued to report headaches, was started on acetazolamide, and noted improvement in symptoms. ***Conclusion:*** The case described herein further supports the growing body of evidence that implicates a hormonal mechanism of action in the development of IIH. Importantly, it also addresses the need for increased study and conversation about rare neurologic diseases in transgender patients.

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Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a disorder characterized by signs and symptoms of increased intracranial pressure without an isolated cause [1]. IIH is a clinical diagnosis with support drawn from patient history, semiology of headache, physical exam, fundoscopic exam, lumbar puncture, and neuroimaging findings. The most common presenting features of increased intracranial pressure are headache, vision changes, and pulsatile tinnitus. As in other causes of increased intracranial pressure (neoplasm, cerebral venous sinus thrombosis, intracranial hemorrhage, etc.), the headache semiology in IIH is positionally worse while supine and upon waking. Imaging and laboratory evaluation are helpful in the diagnosis of IIH, but no single finding is sensitive to rule out IIH in its absence. However, a good fundoscopic exam in these patients is critical to establishing a diagnosis, as it is exceedingly rare for patients to develop IIH without papilledema [2].

Although the symptoms of IIH are often similar to those seen in secondary causes of increased intracranial pressure, the pathophysiologic mechanism underlying its development is not fully understood. Even less is known about the development of IIH in transgender patients on exogenous testosterone. These patients can serve as an important study population, as an association between exogenous testosterone use in karyotypical females and development of IIH may support a hormonally mediated mechanism of development of this disease. Furthermore, cerebrospinal fluid (CSF) leak is a known complication of IIH, but has only been rarely described in the literature among transgender patients. As healthcare access for transgender patients continues to improve, so must physician recognition of important medical complications among this population. The case described herein addresses the need for increased study and conversation about the development of IIH and subsequent CSF leak in a vulnerable segment of our population.

Case Presentation

A 33-year-old obese (BMI: 30.58 kg/m^2) female-to-male (FTM) transgender patient on exogenous testosterone 200 mg/mL every 2 weeks since 2009 presented with 1 month of acute or chronic headache with rhinorrhea. Our patient described chronic paroxysmal headaches with a pounding character, occasionally retro-orbital, worse on the left, worse in the morning, worse positionally while supine, and associated with photophobia and dizziness. Approximately 1 month prior to assessment, our patient developed sudden onset, 10/10 headache in the left temporal region with clear and profound rhinorrhea. The acute onset headache was different in character and more severe than our patient's typical headache. Associated symptoms included new-onset blurry vision on the left, lightheadedness, subjective gait abnormality, nausea, and left ear fullness. He denied hearing whooshing sounds, heartbeat, or ringing in the ear. The pain, when severe, occurred throughout the entire day and frequently prevented him from working and sleeping. There was development of rhinorrhea onset at the same time as the acute headache. When leaning forward or in the lateral decubitus position, the rhinorrhea was present at the nares and would drench the pillow at night. When supine, the rhinorrhea would trickle down the back of the throat and cause gagging which would prevent restful sleep. Of note, our patient denied recent physical trauma, change in medication, recent nasal instrumentation, or usage of vitamin A containing supplements or skincare products.

On physical exam, our patient was noted to have hyperemic and edematous nasal mucosa bilaterally, visual acuity of 20/25 bilaterally, and a fundoscopic examination notable for disk

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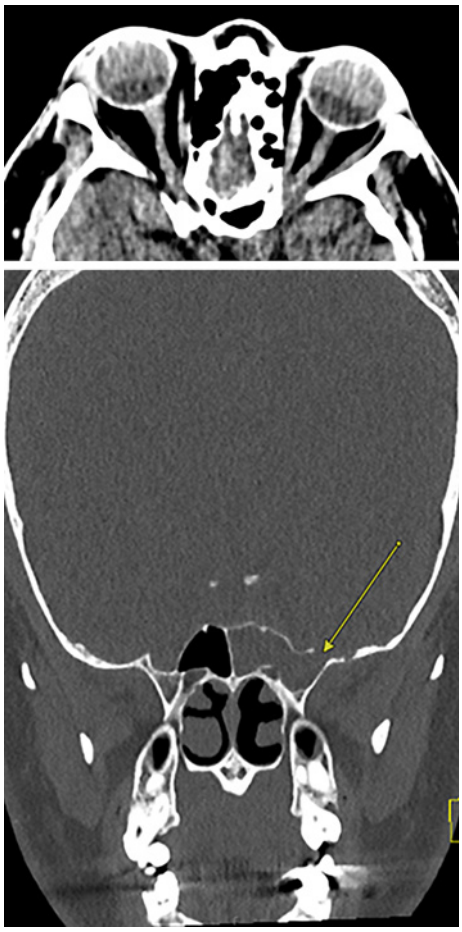

Fig. 1. Pre-Op CT head – slight tortuosity of the optic nerves bilaterally and abnormal arachnoid granulations (AGs) along the left middle cranial fossa floor.

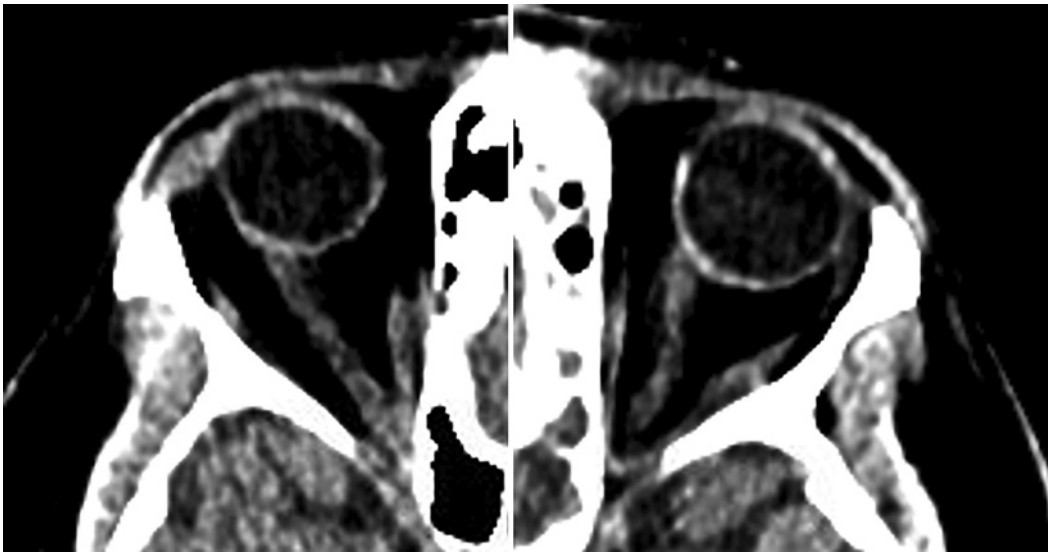

Fig. 2. Nine months post-Op CT head – bilateral optic nerve prominence and tortuosity, increased conspicuity from prior imaging, and increased arachnoid granulations (AGs) in the right middle cranial fossa floor.

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Table 1. Pertinent characteristics of cases of transgender patients diagnosed with IIH

Author, citation, year	BMI	Gender identity	Length of testosterone therapy prior to onset	Imaging findings	Treatment	Outcomes
Buchanan and Bedolla [6], 2017	–	FTM	On testosterone but unclear length of therapy	Magnetic resonance imaging (MRI) brain was normal	LP and acetazolamide	Resolution of symptoms
Hornby et al. [7], 2017	27.9	FTM	5 months	Partially empty sella on MRI, normal magnetic resonance venogram (MRV)	Lumbo-peritoneal shunt	Resolution of symptoms
Kogachi et al. [8], 2019	–	FTM	50 weeks	MRV with mild narrowing of the left transverse sinus and partially occluded right transverse sinus	Endovascular stenting of left transverse	Resolution of symptoms
Mowl et al. [9], 2009	27.05	FTM	On testosterone but unclear length of therapy	MRI with small Chiari I malformation	Reduce testosterone by 50 percent and start acetazolamide	Was able to titrate testosterone back to therapeutic goals
Park et al. [10], 2014	Normal	FTM	On testosterone but unclear length of therapy	MRV with no evidence of CVST	Acetazolamide	Resolution of symptoms
Sheets et al. [11], 2007	29.8	FTM	On testosterone but unclear length of therapy; discontinued 18 months prior to onset	CT angiogram with attention to venous phase was normal	Acetazolamide followed by optic nerve fenestration of the right eye	No improvement with acetazolamide but resolution of symptoms with surgery
Weinlander et al. [12], 2019	30.13	FTM	On testosterone but unclear length of therapy; discontinued 1 year prior to onset	MRI and MRV were normal	Resumed testosterone therapy	Resolution of symptoms

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Table 1 (continued)

Author, citation, year	BMI	Gender identity	Length of testosterone therapy prior to onset	Imaging findings	Treatment	Outcomes
Nguyen et al. [13], 2021	29.1	FTM	14 months	Partially empty sella, flattening of the posterior globes, enlarged optic nerve sheaths, distal tapering of the transverse sinuses	Acetazolamide	Resolution of symptoms
Nguyen et al. [13], 2021	35.0	FTM	2 years	MRI was normal	Acetazolamide without improvement; topiramate with improvement	Resolution of symptoms
Nguyen et al. [13], 2021	31.9	FTM	2 years	No MRI was done	Topiramate	Resolution of symptoms
Nguyen et al. [13], 2021	36.1	FTM	15 months	MRI with partially empty sella, enlarged optic nerve sheaths, distal tapering of the transverse sinuses	Lost to follow-up	Unknown
Nguyen et al. [13], 2021	44.0	FTM	15 months	MRI with partially empty sella	Acetazolamide increased to 500 twice daily, nortriptyline	Resolution of symptoms
Nayman et al. [14], 2021	25.8	FTM	4 years	CT head and CT angiography were normal	Acetazolamide and reduction in testosterone dose	Resolution of symptoms
Lin et al. [15], 2020	–	FTM	6 years	CT head with defect in the middle fossa lateral to the right foramen rotundum in a hyperpneumatized sphenoid sinus with extensive mottling of the skull base bilaterally including ovoid bony defects from arachnoid pits and aberrant granulations	Endonasal surgery by ENT and neurosurgery for CSF leak, lumbar drain, acetazolamide	CSF leak requiring repair

pallor and edema, consistent with a Frisen grade 3 papilledema. Nasal secretion was positive for beta-2 transferrin. His computed tomography (CT) head demonstrated a 5-mm defect in the medial left middle cranial fossa bordering the lateral recess of the left sphenoid sinus, a large quantity of material consistent with CSF and associated encephalocele in the left

sphenoid sinus, bilateral optic nerve prominence and tortuosity, and abnormal arachnoid granulations (AGs) along the left middle cranial fossa floor (Fig. 1).

After an interdisciplinary discussion, otolaryngology and neurosurgery scheduled him for an endoscopic endonasal repair of the left lateral sphenoid recess leak and resection of the encephalocele with intraoperative lumbar puncture of fluorescein dye for visualization. An opening pressure of 5 cm of water was observed during intraoperative lumbar puncture in the right lateral decubitus position. The 5-mm defect was noted just lateral to the foramen rotundum in the sphenoid bone with associated encephalocele. The encephalocele was separated from the underlying brain and surrounding mucosa, which was disconnected at the margins of the bony defect and corrected. The procedure was tolerated well without complication, and follow-up head CT was only notable for postoperative changes.

On subsequent 3-month follow-up visit, our patient reported resolution in his acute headaches and rhinorrhea but complained of reemergence of his chronic, intermittent left temporo-occipital and retro-orbital headache. Serum-free and total testosterone levels at 3-month follow-up visit were elevated to 296.0 ng/dL (ref. range 8.4–48.1 ng/dL) and 75.49 ng/dL (ref. range 0.77–9.30 ng/dL), and sex hormone binding globulin was low at 16.7 nmol/L (ref. range 24.6–122 nmol/L). After starting acetazolamide, our patient noted improvement of headache on follow-up. However, after discontinuing acetazolamide 7 months later, patient noted worsening symptoms and a repeat CT head demonstrated bilateral optic nerve prominence and tortuosity, increased conspicuity from prior imaging, and increased AGs in the right middle cranial fossa floor (Fig. 2).

Conclusion

The pathophysiology of IIH is not fully understood, and less is known about its development in FTM transgender patients. Given its nearly exclusive development in karyotypical females and close association with obesity and polycystic ovarian syndrome, a hormonally mediated mechanism of development in IIH has been suggested in the literature [3]. Independent of polycystic ovarian syndrome or BMI, hyperandrogenism in karyotypical females is associated with an earlier age of onset of IIH [4]. The association was made clear by O'Reilly et al. [5], who noted that karyotypical females with IIH have a particular pattern of androgen excess that targets the androgen-activating enzymes in the choroid plexus to stimulate production of CSF and lead to increased intracranial pressure.

FTM transgender patients can serve as an important study population, as an association between exogenous testosterone use in karyotypical females and development of IIH may support a hormonally mediated mechanism of development of this disease. Upon review of the literature, we found 14 cases that describe the development of IIH in FTM transgender patients [6–15]. Notably, each of these patients was on exogenous testosterone therapy prior to symptom onset, but differed in the overall length of testosterone therapy, ranging from 5 months to 6 years (Table 1). There have been comparatively few case reports that describe the development of IIH in male-to-female transgender patients on hormone replacement therapy [12, 13]. This disparity may indicate that karyotypical females are at an increased risk of developing IIH, despite gender identity, but that the mechanism is not mediated solely by estrogen or progesterone.

In the present case, serum-free and total testosterone levels were elevated above normal limits at 3-month follow-up, which strengthens the case that the development of IIH in our patient may have been causally related to androgen excess. In addition, it adds to a growing body of evidence indicating that circulating androgens play an important role in the

development of IIH in FTM patients on hormone replacement therapy, although the relationship has not been established in randomized controlled trials. Further studies are required to identify a causal relationship between testosterone excess and development of IIH in FTM transgender patients. Furthermore, the only other case report of a CSF leak in an FTM transgender patient with IIH was described in 2019 by Lin et al. [15]. The description of the case presented by Lin et al. [15] bears a number of similarities to our case, including a lengthy exogenous testosterone course, aberrant AG on imaging, and beta-2 transferrin-positive nasal secretions. That only 2 case reports of a CSF leak in an FTM transgender patient have been documented in the literature underscores the necessity for continued surveillance in this population and increased study about healthcare access and disparity in transgender patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540259).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Isaac Smith acquired and analyzed the data and designed the conception of this work. Raissa Aoun reviewed this work and edited the intellectual content. Rebecca Lalchan provided final approval of this work.

Data Availability Statement

All data generated or analyzed during this study are included in this article (and its supplementary material files). Further inquiries can be directed to the corresponding author.

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