

## CASE REPORT

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# Medroxyprogesterone-induced idiopathic intracranial hypertension in a non-obese woman with a negative fundoscopic examination

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## ABSTRACT

**Introduction:** Idiopathic intracranial hypertension (IIH) is an uncommon pathology of unknown etiology that is characterized by chronically elevated intracranial pressure, with manifestations that include headaches that start behind the orbits, tinnitus, and diplopia. The incidence of IIH in the general population is 0.9 per 100,000. The most preponderant risk factors are female sex, obesity and steroid withdrawal. For the diagnosis of IIH, a patient must fulfill the modified Dandy criteria. **Case Report:** A 29-year-old female patient using medroxyprogesterone acetate as a contraceptive method for the last two months with no past medical history visited the Emergency Department due to throbbing, holocranial headache 8/10 in intensity. One week before admission, she was treated with ibuprofen, without any improvement. Symptoms included nausea and diplopia. Management included ketorolac, dexamethasone and orphenadrine IV, but there was no improvement. She was admitted to the internal medicine ward due to an intractable headache. Head computed tomography scan showed an empty Sella turcica. Findings were confirmed with a magnetic resonance imaging/magnetic resonance venography. Lumbar

puncture showed elevated intracranial pressure. The headaches disappeared by the sixth week with the discontinuation of Medroxyprogesterone acetate. **Conclusion:** The most common risk factors for IIH are female sex and obesity with associated fundoscopic findings of papilledema; however, this case demonstrates that IIH cannot be ruled out only on the base of body mass index. Patients suffering from an unusual headache, unresponsive to therapy should be evaluated with an imaging study, even if the fundoscopic examination is negative. There are different findings on imaging studies associated with IIH, such as an empty sella turcica and posterior globe flattening.

**Keywords:** Drug-induced, Headache, Hormonal contraceptive, Idiopathic intracranial hypertension, Intracranial pressure, Medroxyprogesterone acetate

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## INTRODUCTION

Idiopathic intracranial hypertension (IIH), formerly known as pseudotumor cerebri, is an uncommon

pathology of unknown etiology that is characterized by an elevated intracranial pressure, manifested as headache (94%), intracranial noises (58%), back pain and diplopia (38%) [1] Chart 1). Vitamin deficiencies and excesses, as well as certain antibiotics, but female and obesity (20% over ideal body weight) are the most preponderant risk factors [2]. In a prospective study of patients diagnosed with IIH, investigators found that 92% were women, of which 94% of them were linked to obesity [1]. The incidence has been described as 0.9 per 100,000, but in childbearing obese women, it is estimated that it increases up to 19 per 100,000, with a preferential age ranging from 15 to 44 years [3, 4]. The most common symptoms associated with IIH are headache, transient visual problems, and pulsatile tinnitus, being the former a practically universal symptom, although the presentation of IIH in children with no headache is not uncommon [5]. A headache related to IIH has poor differentiation from other common types of headaches and are usually confound when addressed only by history because nausea and vomiting are not uncommon [6]. Although patients with suspected IIH would undoubtedly benefit from a fundoscopic evaluation, recent studies have proven that a bedside ocular sonogram is an acceptable option when a fundoscopic evaluation is not readily available [7]. Head Computed Tomography scan (CT) and a brain Magnetic Resonance Imaging (MRI) can be used for evaluating IIH as well, where an empty Sella turcica has been described in both imaging studies, which possess a sensitivity of 65.9% and a specificity of 100% [8]. There are other findings in MRI that have been set out as possible IIH markers, which include posterior globe flattening, vertical tortuosity of the optic nerve, optic nerve sheath distention and increased foramen ovale size, where there's a stipulated sensitivity fluctuating from 50–65% and a specificity of 100% [8].

## CASE REPORT

A 29-year-old Hispanic female patient, G1P1 with satisfied parity, using intramuscular (IM) medroxyprogesterone acetate as a contraceptive method for the last two months with an uneventful medical history, arrived at the Emergency Department due to an intermittent, throbbing, holocephalic headache described as being 8/10 in intensity, with no apparent worsening. One week before she was treated with ibuprofen, there was no improvement. Associated symptoms included nausea, mild non-radiating neck pain 4/10 and intermittent diplopia. Triage vital signs revealed a heart rate of 96 bpm, respiratory rate of 18 bpm, blood pressure of 134/81 mmHg, pulse oximetry at room air of 97%, a height of 63 inches, weighing 60 kg, and a body mass index (BMI) of 23.4 kg/m<sup>2</sup>. The patient was managed at the emergency department with ketorolac intravenous (IV), dexamethasone IV and orphenadrine IV, but there was no overall improvement, A head CT scan was ordered

and surprisingly revealed a partially empty sella turcica (Figure 1). The patient was admitted on August 2017 to the internal medicine ward with a diagnosis of an intractable headache. Complete blood count (CBC), comprehensive metabolic panel, sedimentation rate, C-reactive protein, and PT/PTT/INR were unremarkable.

Ophthalmology staff was consulted. The patient underwent a fundoscopy, with no abnormalities, and the visual field showed no deficit (no hemianopsia neither quadrantanopia).

Nonetheless, despite the lack of abnormal findings (including papilledema), it was decided to perform a lumbar puncture, but not before performing an MRI/MRV to rule out obstruction or stenosis of venous outflow like sagittal sinus thrombosis, which must be excluded before idiopathic intracranial hypertension can be diagnosed (Figure 2).

After a negative MRV official report, neurology staff performed the lumbar puncture, which showed an elevated opening pressure of 44 cm H<sub>2</sub>O (Figure 3), with negative cerebrospinal fluid (CSF) culture and unremarkable chemistry results; 22 ml of clear CSF collected. Although the fundoscopic examination was negative, the patient fulfilled the modified Dandy criteria and was diagnosed with IIH.

The patient was then posteriorly discharged with a prescription of topiramate 25 mg orally at bedtime in combination with acetazolamide 500 mg orally twice daily. Before her discharge home, a review of medications was performed, which was remarkable for medroxyprogesterone acetate 150 mg IM every three month for the last six months. Neurology staff recommended to stop the contraceptive medication and seek an alternative non-hormonal method. The patient was followed at the outpatient clinic two weeks later, where she complained of a mild intermittent headache 3/10; neurology staff decided to repeat the lumbar puncture, an opening pressure of 24 cm H<sub>2</sub>O was reported, and 10 ml of clear CSF collected. The patient was followed up in six weeks, where she reported complete resolutions of symptoms, despite having stopped the prescribed medications due to side effects (excessive thirst and somnolence). The patient was followed monthly for three months with no recurrence of initial symptoms.

## DISCUSSION

Our case demonstrates a patient with no remarkable past medical history (including no known history of prior headaches) and an adequate BMI who developed an intractable headache several weeks after starting medroxyprogesterone contraceptive injection hormone. The suspicion index for IIH was low given her adequate BMI (23.4 kg/m<sup>2</sup>). The first imaging study (head CT scan) was ordered to evaluate extra-axial fluid collection, midline shifting, amongst others, but instead, the official report described a partially empty sella turcica.

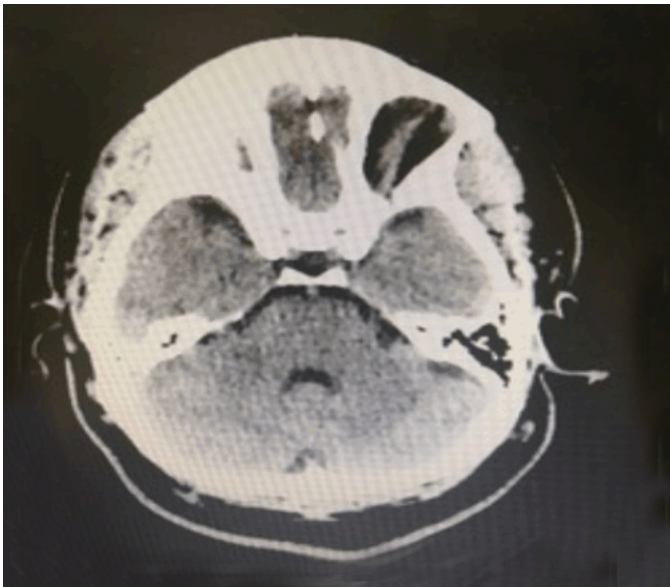


Figure 1: Head CT scan with empty Sella.

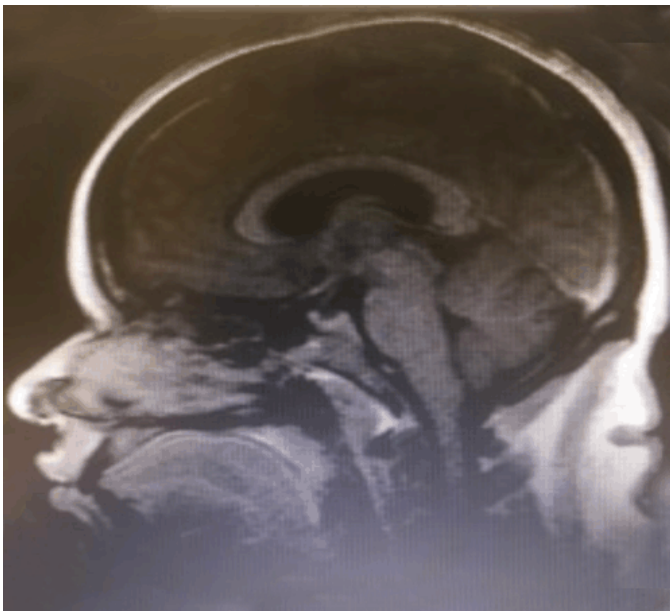


Figure 2: Brain MRI/MRV.

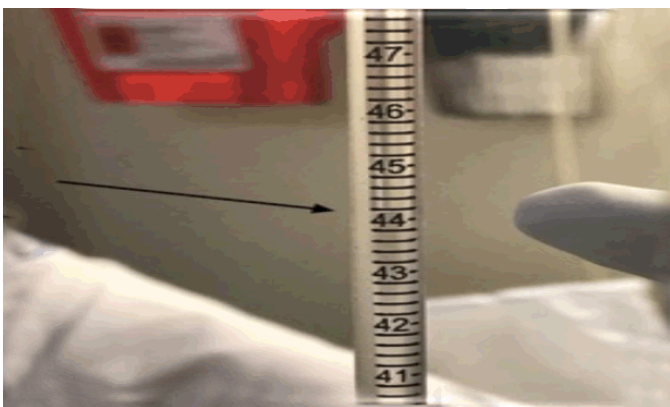


Figure 3: Elevated CSF opening pressure.

This finding came as a surprise to the medical staff, as this is usually observed in overweight female patients. Additionally, the fundoscopic examination performed by the ophthalmology staff came back negative.

Further evaluation with MRI/MRV was recommended, reporting findings compatible with IIH. Lumbar puncture showed marked elevated intracranial pressure, and there was a partial resolution of patient's headache after the removal of 22 ml of spinal fluid. Patients with IIH have shown improvement with acetazolamide; our patient was discharged with said medication in combination with topiramate. After the discontinuation of the contraceptive method, the patient greatly improved her symptoms, even after she stopped taking the prescribed medications.

Idiopathic intracranial hypertension is a term that was first described in the late 1800'. Since then, it has suffered several modifications, most of them regarding the diagnosis, but not directly related to the approach and risk factors [9]. The cause of IIH is unknown. It is a disorder that typically affects overweight women of childbearing age, between 18 and 45 years old and is characterized by an elevated intracranial pressure, manifested as severe nonspecific pulsatile headache associated with nausea and vomiting (94%), transient visual obscurations (68%), tinnitus (58%), photopsia (54%), retrobulbar pain (44%), diplopia (38%) and visual loss (30%) [1, 3, 4] (Chart 1). Generally, there is a normal neurological examination and abnormal findings are frequently detected on eye examination and fundoscopy [6].

Atypical IIH includes normal BMI, older patients more than 50 years old and male gender. Normal BMI patients and older patients tend to have better, if not, similar outcomes with less headache and mild papilledema. Thus, as expected from clinical experience, otherwise typical IIH occurs very rarely in these patients so careful evaluation for alternate causes of IIH should be undertaken when the diagnosis is considered in this group [10, 11].

Today the standard for the diagnosis of IIH is the Dandy modified criteria. In 1937, Dr. Walter Dandy had described clinical findings of intracranial hypertension without a space-occupying lesion; those descriptions yield the first Dandy criteria [12]. Later, in 1985, those

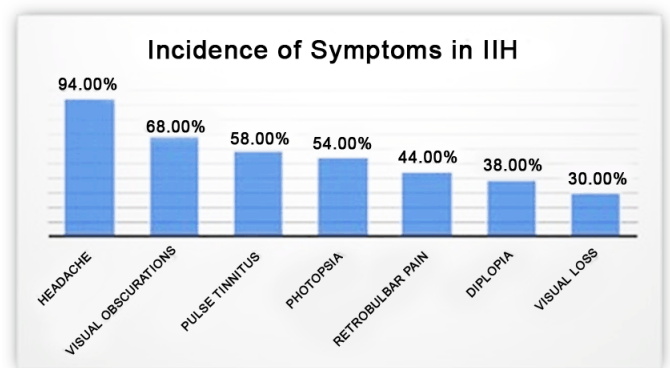


Chart 1: Percentage of symptoms in Idiopathic Intracranial Hypertension, modified from Wall et al. 2010a.

criteria were reevaluated and modified, today known as the modified Dandy criteria, and are currently the standard for IIH diagnosis (Table 1). Although, before diagnosing IIH structural causes of increased ICP need to be excluded with neuroimaging studies, and a lumbar puncture must be performed to evaluate the CSF for other etiologies of elevated ICP.

Two findings have been practically universal for the diagnosis of IIH: obesity and papilledema, which can decrease the suspicion index for IIH in their absence. The fundoscopic examination has been a cornerstone as an initial tool for patients with suspected IIH, but physicians must be aware that in the acute phase (less than one week of symptom onset) fundoscopic examination could be negative despite a mild to moderate elevated intracranial pressure [7, 13]. Further large clinical trials should be performed for the appropriate evaluation of the delayed onset of papilledema in the acute phase of IIH. A complete ophthalmologic evaluation is essential to determine the severity of visual loss and to monitor disease progression. Bedside ultrasonography has been used to measure the diameter of the optic nerve sheath when a fundoscopic examination is not readily available for patients with IIH [7, 14].

A patient with papilledema should have as soon as possible a head Ct or brain MRI (the preferred imaging study in IIH) which significantly increases the diagnosis of IIH if there is no intracranial occupying mass or a Dural sinus thrombosis [15]. MR venography is also useful particularly in patients at risk for Dural venous sinus thrombosis, those with hypercoagulable states, non-obese female, and male individuals. Extraluminal narrowing of the transverse sinuses may be one of the typical features of IIH [16].

The definitive diagnosis of IIH is detecting a high CSF opening pressure greater than 25 cmH<sub>2</sub>O, natural laboratory and imaging studies including CT scans and MRI. Any disorder that causes decreased flow through the arachnoid granulations or obstructs the venous

Table 1: Modified Dandy criteria for Idiopathic Intracranial Hypertension [7]

- Symptoms of increased intracranial pressure (ICP) like headaches, nausea, vomiting, transient visual obscurations, or papilledema
- No localizing findings in neurological examinations (except for false localizing signs such as abducens or facial palsies)
- Awake and alert
- Normal Head CT/ brain MRI findings without evidence of Dural sinus thrombosis
- ICP of > 250 mm H<sub>2</sub>O with normal cerebrospinal fluid cytological and chemical findings
- No other cause of increased ICP found

return from the granulations to the right heart is accepted as a cause of intracranial hypertension. Arteriovenous malformations and Dural fistulae with high flow may overload venous return and result in elevation of ICP. Steroid withdrawal, hypoparathyroidism, and Addison's disease are associated with IIH, but links to other endocrine abnormalities remain unproven. Pregnancy, irregular menses and oral contraceptive use have been shown merely associations. Case reports describing some drugs appear convincing: nalidixic acid, nitrofurantoin, or ketoprofen in Bartter's syndrome, vitamin A intoxication, isotretinoin, thyroid replacement therapy, lithium, and anabolic steroids [9].

The treatment of IIH involves lifestyle modifications, weight loss, nutritional counseling, medication, and exceptionally surgical treatment [11]. First line medication is acetazolamide which inhibits the carbonic enzyme anhydrase at the choroid plexus reducing the production of CSF controlling the ICP. Topiramate is a second line agent that has less potent carbonic anhydrase inhibition but has the advantage that one of its side effects is weight loss. Corticosteroids are indicated in patients with severe papilledema and compromise visual function as a short-term treatment.

Since many of the patients with IIH experience headaches very similar to migraine headaches, these headaches can often be controlled with medications usually prescribed to control a migraine such as amitriptyline, propranolol or other migraine prophylaxis agents. These drugs do not always work and have potentially dangerous side effects as a decrease in serum bicarbonate, dizziness, fatigue, anorexia, confusion, convulsions, drowsiness, dry mouth and somnolence among others.

When medical treatment fails, a surgical intervention like optic nerve sheath fenestration, a procedure where a small opening in the sheath around the optic nerve are performed to try to relieve the papilledema, and stent shunts remain the last resort.

About ten percent of the people with IIH experience progressive vision deterioration and may become blind. IIH still can recur months or even years after initial presentation, even after the symptom has resolved [9]. The purpose of the treatment of patients with IIH is to preserve optic nerve function which should be monitored during treatment assessing visual acuity, color vision, optic nerve head appearance, and perimetry [17].

Finally, there are no standard guidelines for the treatment of IIH [18]. In patients with early visual field loss, or inadequate response to standard medical therapy, a short course of high-dose oral corticosteroids temporarily is given before surgical intervention. If visual field loss is documented, or if the visual function continues to deteriorate or does not improve immediately with corticosteroid treatment medical management should be coupled with emergency surgical intervention because the visual loss can evolve rapidly and is permanent despite all efforts to contain its progression.

## CONCLUSION

Idiopathic intracranial hypertension cannot be ruled out based on body weight solely and should be part of the differential diagnosis in female patients experiencing intractable headache, where an imaging study must be requested even when there is a negative fundoscopic examination.

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## Author Contributions

Ivonne Hernández Castro – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published  
Mónica Zanconato Campitruz – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published  
Mariana Martínez Aguiar – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published  
Fermín López-Rivera – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor of Submission

The corresponding author is the guarantor of submission.

## Source of Support

None.

## Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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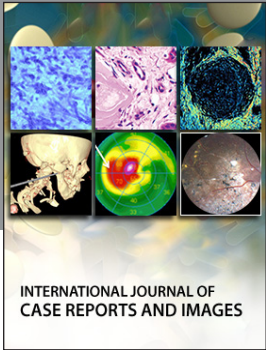
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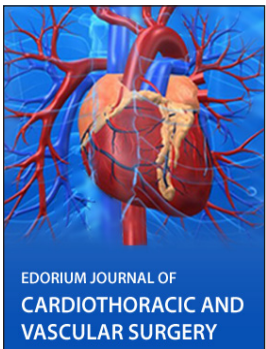
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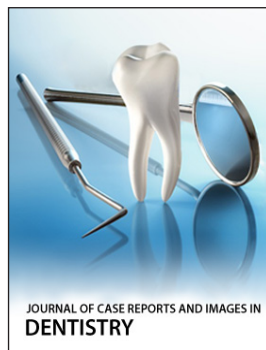
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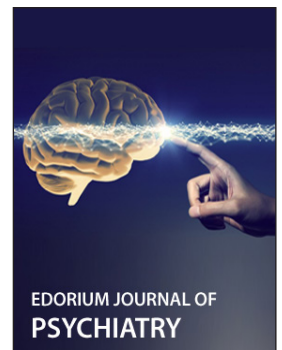
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