Journal of
Medical Case Reports

CASE REPORT

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Antithrombin III deficiency and idiopathic intracranial hypertension: a case report

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Abstract

Background Idiopathic intracranial hypertension (IIH) is a condition where the pressure of the cerebrospinal fluid in the brain increases without a known cause. It typically affects adults but can also occur in adolescents and children, although it is less common. Numerous elements, including coagulopathy, have been documented in previous cases as potential etiological factors of IIH. Nonetheless, our objective was to present the insufficiency of a coagulation factor as an additional contributing factor to IIH, a notion that has not been previously reported.

Case presentation In this case, a 34-year-old West Asian female patient presented with a subacute generalized headache, bilateral blurred vision, and papilledema. The patient's brain magnetic resonance imaging showed flattening of the posterior globe and empty sella, but no other abnormalities were detected. The results of magnetic resonance venography and cerebrospinal fluid analysis were also normal, except for an opening cerebrospinal fluid pressure of 600 mm H_2O during the lumbar puncture. Rheumatologic and endocrine disorders were ruled out on the basis of clinical assessment and laboratory tests. The patient was started on acetazolamide (1 g/day, increased to 2 g/day) and furosemide (20 mg/twice a day) and was encouraged to lose weight. These treatments led to some improvement for about 1 year, but her symptoms then worsened without an obvious cause. Given the prolonged duration of the disease and the lack of expected response to treatment, the patient was reevaluated for endocrinopathy and collagen vascular disease, which were negative. An additional workup revealed an antithrombin III (AT III) deficiency, for which the patient was prescribed acetylsalicylic acid (80 mg/day) in addition to the previous medications. As a result, the patient's papilledema, macular thickness, and nerve fiber layer edema decreased, as observed by fundoscopy and optical coherence tomography. Clinical examination and imaging also showed improvement in the patient's symptoms.

Conclusion This case highlights the importance of considering coagulopathy in cases of IIH and suggests that antiplatelet therapy with acetylsalicylic acid may be beneficial for such patients.

Keywords Antithrombin III deficiency, Headache, Idiopathic intracranial hypertension, Pseudotumor cerebri, Papilledema

Background

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a condition that causes symptoms that are only caused by increased intracranial pressure (ICP) [1]. These include headache and papilledema, abducent nerve palsy, and tinnitus, which indicate high pressure within the skull. People with IIH have normal cerebrospinal fluid (CSF) composition, which rules out other potential causes of intracranial hypertension, such

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as infections or structural abnormalities. It should be noted that neuroimaging and other evaluations are unable to identify underlying causes of elevated ICP [2–4].

Cerebral venous outflow impairment and increased resistance to CSF outflow could be implicated in the pathogenesis of IIH [5, 6]. It is most common among young obese women. Although the predisposing factors for this disorder are unknown, vitamin A metabolism impairment, severe anemia, endocrinological diseases, such as hyperparathyroidism or glucocorticoid deficiency [5, 6], obesity, and excess androgen have been linked to IIH [7, 8]. Research has shown that coagulation disorders contribute to IIH, and some studies have reported coagulopathy as the possible mechanism in the pathogenesis of IIH. A few of the patients in these studies were diagnosed with cerebral venous sinus thrombosis (CVST), but most were not [9–11].

Some patients with IIH exhibit prothrombotic impairment, including anticardiolipin antibodies, antithrombin III (AT III) deficiency, thrombocytosis, polycythemia, and hyperfibrinogenemia [12]. Our study presents the case of an obese woman suffering from prolonged intracranial hypertension and AT III deficiency, which improved with antiplatelet treatment. We have included a brief literature review.

Case presentation

Initial examination

A 34-year-old obese West Asian female with a confirmed case of IIH, without remarkable medical and family histories and psychosocial issues, was referred to our clinic with recurrent headaches and blurred vision. She had been prescribed 3.5 g/day of acetazolamide, which was gradually decreased to 1 g/day over 1.5 years of treatment. She was obese, with a body mass index of 36 kg/m^2, and a history of irregular menstruation. Fundoscopic examination confirmed bilateral papilledema. Perimetry indicated peripheral field restriction and bilateral enlarged blind spots. Laboratory tests included a blood cell count, C-reactive protein, erythrocyte sedimentation rate, liver, thyroid, renal, parathyroid, and adrenal function tests, as well as serum cortisol level, all of which proved to be within normal range. Magnetic resonance imaging (MRI) of the brain revealed no parenchymal lesions or vascular or meningeal abnormalities associated with intracranial hypertension. MRI findings were compatible with imaging markers of IIH [empty sella (complete/total empty sella: > 50% of the sella filled with CSF; pituitary thickness ≤ 2 mm)]. In this case, the pituitary thickness was 1.6 mm [13] and there was perioptic nerve sheath distention (an enlargement surrounding the protective sheath of the optic nerve, often attributed to elevated ICP, potentially affecting visual acuity). This dilation, typically measuring approximately 3 mm posterior to the globe, exceeded 6 mm [14] (Fig. 1). A lumbar puncture revealed an opening pressure of 600 mm H_2O in the left lateral decubitus position.

The results of CSF microbiological smears and assays showed no evidence of *Brucella*, *Streptococcus*, or the most common infectious etiologies of chronic meningitis (*Cryptococcus*, *Mycobacterium tuberculosis*, histoplasmosis, blastomycosis, aspergillosis, and syphilis), and CSF results were: glucose, 65 mg/dl; protein, 25 mg/dl; white blood cells, two lymphocytes. The serological tests were negative for *Brucella* and *Borrelia*. Medical evaluation

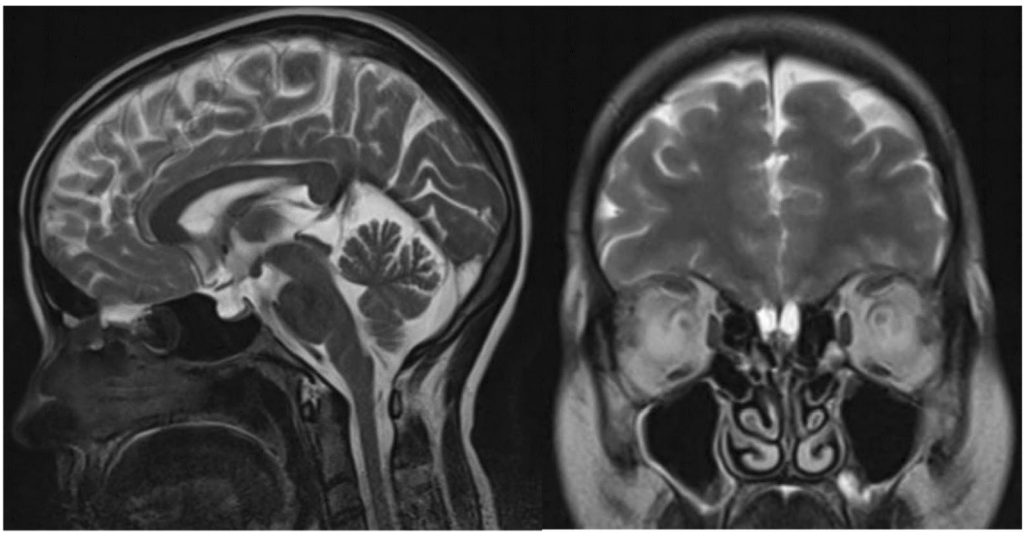

Fig. 1 Magnetic resonance imaging of the brain demonstrates empty sella (left) and increased bilateral optic nerve sheath diameter (right)

and laboratory examinations excluded the possibility of rheumatoid disorders.

The patient suffered from dizziness with the ingestion of more than 2 g/day of acetazolamide, thus, furosemide and topiramate were prescribed to control the ICP. We also assessed her blood pressure, pulse rate, and cardiac function to rule out other possible causes of dizziness, all of which were normal. A nutritionist consult was made for weight reduction.

Fortunately, there was no progression in visual impairment during the follow-up. The headaches improved to some extent. The papilledema became less severe but was still present. Perimetry showed a mild decrease in peripheral field restriction in both eyes.

Second examination after 2 months of treatment

The second lumbar puncture revealed an opening pressure of 280 mm H_2O. Mild ganglion cell-layer atrophy was observed through optical coherence tomography (OCT). The furosemide dosage was increased to 20 mg/three times daily. Additionally, the individual experienced a weight reduction of 15 kg through a specialized dietary regimen to manage body mass (initial weight: 105 kg, initial height: 170 cm). The therapy with acetazolamide, topiramate, and furosemide combined with weight reduction resulted in decreased edema, as evidenced in the OCT, and no visual field deficit, as revealed by perimetry. The patient's health demonstrated a marked improvement with the effective response to the therapy.

Third examination after 3 months of treatment

After 3 months, the papilledema and visual field defect recurred, although the patient experienced no episodes of headache or blurred vision. Disorders affecting the endocrine and rheumatologic systems were considered at this time, but no such disorders were diagnosed. The third lumbar puncture indicated an opening pressure of 300 mm H_2O. Magnetic resonance venography (MRV) was performed but showed no evidence of CVST. Because of the prolonged course of the disease and its failure to respond to treatment, coagulation tests were carried out.

The coagulation tests indicated that the patient showed AT III deficiency (AT III: 73%; normal range: 80–125%). The coagulation test was reevaluated, and the same result was obtained. Subsequently, a hematologist consultant recommended antiplatelet therapy because the patient did not have a history of cerebral venous thrombosis (CVST) or any other evident thrombosis in other parts of the body. A daily dose of 80 mg of acetylsalicylic acid (ASA) was added to the daily doses of 2 g of acetazolamide, 75 mg of topiramate, and 60 mg of furosemide. After 3 months of treatment, fundoscopy and OCT showed decreases in the papilledema of the nerve fiber layer and a decrease in ICP. The perimetry findings had also improved. At 1 year follow-up, and a gradual decrease in the prescribed medications, the IIH is under control and she is symptom-free.

Discussion

This report presents the case of a young, obese woman with prolonged and recurrent headaches, with visual impairment, who responded to the addition of antiplatelet medication to drugs regimen to lower the CSF pressure. IIH is well-documented as being associated with obesity and the female sex [15]. The criteria for diagnosis of IIH are as follows: papilledema, normal neurological examination except for cranial nerve abnormalities, no lesion identified in brain imaging (CT/MRI/MRV), normal CSF composition, and elevated lumbar puncture opening pressure ($\geq$ 250 mm CSF in adults and $\geq$ 280 mm CSF in children) [16, 17]. In atypical cases (women or men of normal weight), an additional workup is required to exclude secondary cases of intracranial hypertension (sIH) [17].

The untreated elevation of ICP is a severe condition that may cause permanent visual loss and even death in critical cases. Consequently, the identification and treatment of the underlying condition necessitates a comprehensive evaluation of potential differential diagnoses for IIH [18]. Several factors have been recognized as the underlying causes of IIH. The use of medications, such as antibiotics [19–22] (for example, tetracycline, levofloxacin, oral fluoroquinolones, nalidixic acid, and so on), lithium [23], methotrexate [24, 25], and cyclosporine [26, 27] as well as hypervitaminosis A [28–30] and corticosteroid withdrawal [31, 32] could be associated with IIH. Despite the lack of definitive understanding regarding the mechanism by which vitamin A induces intracranial hypertension, the majority of research suggests an alteration in CSF homeostasis [29, 30].

Organisms such as *Cryptococcus* [33], *Enterovirus* [34], neurobrucellosis [35], neuroborreliosis [36], and *Treponema pallidum* [37] can also induce IIH. Endocrine disorders (Addison's disease, hypoparathyroidism, hypothyroidism, hyperthyroidism) [17], rheumatological disorders (systemic lupus erythematosus and Behcet's disease) [38–40], severe anemia, systemic disorders (renal failure and obstructive sleep apnea syndrome), and syndromes (Down and Turner syndromes) [16–18] can be factors contributing to IIH. Cerebral venous abnormalities (CVST, arteriovenous fistulas, bilateral jugular vein thrombosis, and so on) should also be considered as differential diagnoses of IIH [16].

Normal neurological examination, except for papilledema, along with a high CSF opening pressure

with normal composition and normal imaging (MRI and MRV), meet the specific criteria for diagnosis of IIH. In the case study presented, no abnormalities were detected from laboratory tests, CSF microbiological smears and assays, or serological tests. Furthermore, the patient's medical evaluation and laboratory examinations excluded the possibility of rheumatoid and endocrinal disorders.

The primary goal of treating IIH is to lower ICP. Acetazolamide is the first line of treatment. If the clinical situation dictates, acetazolamide can be used for a prolonged period [41, 42]. Studies have shown that acetazolamide improves visual field function and papilledema in patients with IIH [10, 43–46]. Our patient was initially treated with acetazolamide and furosemide. This decreased the incidence of blurred vision and visual loss, but these conditions subsequently worsened. The patient was also advised to lose weight, as obesity plays a vital role in the development of intracranial hypertension [18].

Assessment of coagulopathies was undertaken after ruling out other diagnoses because of the prolonged course of the disease and lack of adequate response to acetazolamide and furosemide. There was no past or present evidence of venous thrombosis in the patient; however, AT III deficiency was confirmed. AT III deficiency usually increases the risk of recurrent thrombosis because of a failure to block the coagulation cascade [47]. As AT III has a strong affinity for heparin, it enhances the formation rate of the protease/inhibitor complex and also blocks XIIa, XIa, IXa, and Xa factors serine proteases in the coagulation cascade [48, 49].

One study [50] disclosed that D-dimer blood levels were significantly higher in patients with IIH, in the absence of occlusive sinus thrombosis, compared with healthy controls and that the administration of acetazolamide with an anticoagulant for a period of 6 months brought about notable improvements in the papilledema, visual field, and visual acuity. In that study, anticoagulant therapy effectively removed the microthrombi that impeded CSF drainage owing to an unrecognized nonocclusive venous cerebral thrombus. It is worth noting that we did not assess the serum D-dimer levels for our patient during the study, which necessitates consideration in future investigations.

Three studies on female and male patients with IIH, treated with acetazolamide, revealed that impaired coagulation factors [for example, elevated levels of lipoprotein A, factor VIII, plasminogen activator inhibitor activity (PAI-Fx), lupus anticoagulant, and prolonged activated partial thromboplastin time] were more prevalent among patients with IIH compared with healthy control groups [10, 44, 51, 52]. No significant differences were reported in AT III between patients with IIH and control groups. Additionally, only a few of the female patients and none of the male patients were diagnosed with CVST. It has been suggested that polycystic ovary syndrome (PCOS) is associated with obesity and that high levels of PAI-Fx and endogenous estrogen could contribute to the development of IIH. Coagulopathy, pregnancy, and PCOS could also contribute to the development of thrombotic intracranial CSF outflow obstruction. This could cause an increase in ICP and papilledema in patients with IIH.

Upon confirmation of AT III deficiency in our patient, we added ASA to her treatment regimen in accordance with a hematologic consult. This produced a gradual decrease in ICP and symptoms.

The treatment approach for IIH cases presenting with coagulopathies is determined by the individual's condition and the specific coagulation factors involved. It has been documented that acetazolamide therapy alone was effective in the treatment of patients with IIH exhibiting thrombophilia and hypofibrinolysis [44]. Moreover, literature reveals a limited number of investigations examining coagulopathy-related IIH, with a portion of these studies describing the use of antiplatelet agents in treatment. Moreover, this study is the first investigation to report AT III deficiency as a contributing factor for IIH. The lack of sufficient studies prevents a thorough comparison between our research and prior investigations. Further research employing larger sample sizes is necessary to facilitate meaningful comparisons.

Conclusion

We report this unique case because of the rarity of reported IIH being associated with suggested coagulopathy, without obvious CSVT. Our investigation emphasizes the need for a multidisciplinary approach in the management of IIH, including endocrine, rheumatological, and imaging evaluations. Furthermore, our case stresses the importance of closely monitoring for coagulopathic disorders during the initial phase of IIH, especially in patients with recurrent or prolonged episodes, to prevent serious complications. The addition of anticoagulation and antiplatelet treatments to treat this disease could be beneficial in severe or intractable cases.

Abbreviations

ASA	Acetylsalicylic acid
AT III	Antithrombin III
CSF	Cerebrospinal fluid
CVST	Cerebral venous sinus thrombosis
ICP	Intracranial pressure
IIH	Idiopathic intracranial hypertension
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
PCOS	Polycystic ovary syndrome
PAI-Fx	Plasminogen activator inhibitor activity
sIH	Secondary intracranial hypertension

Acknowledgements
The authors would like to thank the patient for participating in this study.

Author contributions
MT collected data and revised the manuscript; YM drafted the manuscript; EJ collected data.

Funding
This paper was not funded and the authors conducted this study with their own resources and expertise.

Availability of data and materials
The data are available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by Tehran University of Medical Sciences. The details of this study were explained to the patient, and the patient provided informed consent to participate in the project.

Consent for publication
Written informed consent was obtained from the patient for publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

Received: 30 October 2024 Accepted: 4 December 2024
Published online: 04 January 2025

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