Intracranial Hypertension Associated with Danazol Withdrawal: A Case Report

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Abstract- Pseudotumor cerebri (PTC) is a seldom seen entity characterized by signs and symptoms associated with the intracranial hypertension (IH) without obvious causes. Some medical disorders and exogenous agents have been implicated in the development of PTC. Danazol is a popular gonadotropin inhibitor used for the treatment of endometriosis, breast disease and hereditary angioedema. While PTC has been occasionally reported in patients receiving danazol treatment, it is barely mentioned in those who discontinued danazol therapy abruptly. Here we report a case of IH developed soon after the withdrawal of danazol.

Key Words: Pseudotumor cerebri, Intracranial hypertension, Danazol, Cerebral vascular tone

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INTRODUCTION

Pseudotumor cerebri (PTC), is also called idiopathic intracranial hypertension (IH) for its etiology is mostly unknown. It affects women more frequently, especially those who are overweight and of childbearing age, with a female to male ratio up to 8:1[1]. Its clinical manifestations are associated with elevated intracranial pressure (ICP) such as headache, blurred vision, and papilledema. Other minor symptoms of PTC also include diplopia, neck stiffness, paresthesias, dizziness, facial palsy, ataxia, and radicular pain[1]. Although PTC is seldom fatal; however, a delay in the diagnosis may result in permanent vision loss.

Without obvious anatomical and cerebral spinal fluid (CSF) abnormalities, the causes of PTC are largely unknown. However, some medical disorders and exogenous agents are implicated in the development of PTC[1]. Danazol, often used in the treatment of endometriosis, cystic breast disease and some hematological diseases, has been reported to be one of the drugs that may cause PTC[2]. A review of the medical literature (1987 and following) identified only seven articles relating PTC with danazol treatment[2-8]. However PTC appearing after discontinuing danazol treatment had been documented only once[8]. Here, we present another case of PTC who developed this disease soon after danazol withdrawal.

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CASE REPORT

A 32-year-old woman without migraine or other chronic headache history until two weeks prior to the admission reported experiencing intermittent and severe throbbing headache in her bilateral occipito-temporal regions accompanied by nausea and vomiting. She described the headache intensity often increasing upon awakening, bending forward or abdomen straining. There was no photophobia, phonophobia, tinnitus, monocular or binocular visual loss, or dilopia. There was no fever, othostatic edema, neck stiffness, arthralgia, ataxia or any other focal neurologic symptoms. This patient did not take any regular medication and had no relevant medical history except that she had been prescribed danazol 600mg per day for endometriosis 6 months ago and most notably, she elected to discontinue the drug 20 days prior to admission.

On examination, her body temperature was normal, neck remained supple and blood pressure was 120/80 mm Hg. Body weight at the time of admission was 73 kg with a height of 155 cm and a high body mass index (BMI= 30.4 kg/m^2). There were no abnormal signs on physical examination. A neurological examination disclosed papilledema and decreased visual acuity, which hinted at the possibility of increased ICP. Confrontation visual field testing and an automated perimetry did not show visual field defect. The other neurological examinations were normal.

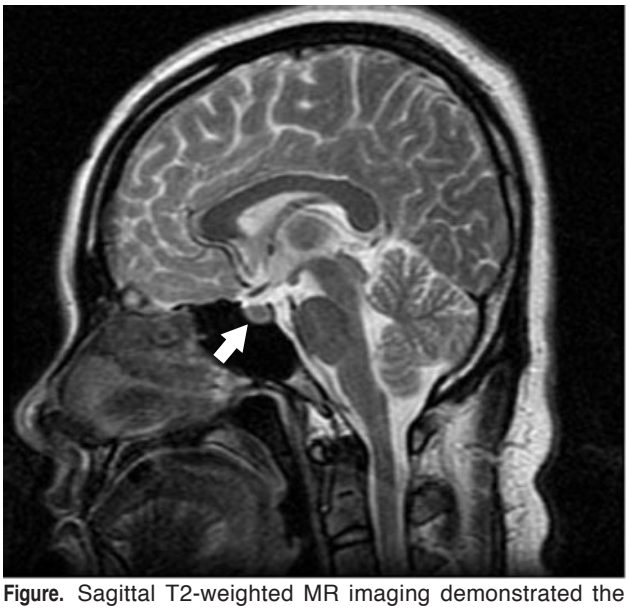

Figure. Sagittal T2-weighted MR imaging demonstrated the empty sella (white arrow) in this patient.

Systemic survey including complete blood count, ESR, and biochemical studies were normal. Serological and immunological studies for syphilis and a variety of autoantibodies were all negative. Contrast-enhanced brain magnetic resonance (MR) imaging and MR venography of the brain showed mild compression of the ventricular system and an empty sella. There were no mass lesions, no abnormal meningeal enhancement or cerebral venous thrombosis. A lumbar puncture study documented an elevated CSF pressure (270 mm H_2O), otherwise presented a normal CSF profile. There were no pleocytosis, normoglycorachia and a normal protein level in CSF examination. The CSF studies for VDRL, cryptococcal antigen, bacterial, fungal and tuberculosis cultures were all negative. The withdrawal of CSF produced immediate improvement in headache for several hours. Accordingly, we made a diagnosis of PTC in this patient. She was given a non-steroidal anti-inflammatory agent for symptomatic treatment and her headache subsided gradually within one month. She has not taken any further danazol and remained well over a 6-month follow-up.

DISCUSSION

In the presence of headache, papilledema, small ventricle and empty sella but without other anatomical abnormalities from MR imaging, and no systemic toxic signs; PTC was highly suggested in this patient. However, the spinal fluid examination is the most critical for diagnosing PTC. No patient should be diagnosed presumptively without a lumbar puncture. Clinically, the elevated ICP with normal CSF content in our patient fulfilled the diagnosis of PTC.

The etiology of PTC is unknown, but sometimes it is closely related to some medical conditions or exogenously administered agents. In the cases associated with some medical diseases, such as hypothyroidism, hypoparathyroidism, renal failure, adrenal insufficiency,

Cushing disease... etc., headache attributed to IH secondary to metabolic, toxic or hormonal causes has been included in the new diagnostic criteria published in the International Classification of Headache Disorders: 2nd edition (ICHD-II)[9]. Reviewing the patient's history, there is nothing special except the newly prescribed drug, danazol. In fact, several cases of danazol induced PTC had been reported[2-8] and in most of them PTC occurred 2-6 months after starting danazol treatment and disappeared within 1-3 months after discontinuing this drug. In a documented case, PTC recurred after re-administration of danazol[2].

Danazol, developed in the 1970' is a gonadotropin inhibitor and a weak androgenic agonist, which also has some immunomodulator effects[10]. It has been widely used in the treatment of endometriosis, menorrhagia, benign cystic breast disease and hereditary angioedema; sometimes it is also used in immune related disorders such as idiopathic infertility, idiopathic thrombocytopenic purpura and haemolytic anemia[4,10]. It suppresses the pituitary-ovarian axis, depresses the output of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH, one of the gonadotropins, stimulates testes and ovaries to produce testosterone and estradiol. Recently, testosterone and estrogen have been thought to have modulating effects on cerebral vasculature[11,12]. It has been found that estrogen can regulate cerebral blood flow (CBF) as it decreases cerebral vascular tone and increases CBF by enhancing the endothelial-derived nitric oxide and prostacyclin pathways[11,12]. The opposite has been shown in testosterone, which increases cerebral artery tone[11,12]. With its androgenic activity, danazol may result in fluid retention and weight gain[2,10]. Danazol also could bind to glucocorticoid receptors, and alter the body fluid homeostasis. Sometimes patients with PTC may also have symptoms of systemic fluid retention such as orthostatic edema or carpal tunnel syndrome[7,13]. Physical examination may reveal swelling of the fingers, eyelids or feet, and pedal edema. Furthermore, danazol has 60 different metabolites, some of them are hormonally active and having a tissue half-life of several days[2,10].

The pathophysiology of PTC includes: (A) an increased rate of CSF formation. (B) a sustained elevation of intracranial venous pressure. (C) a decreased rate of CSF absorption, and (D) an increase in brain volume and interstitial fluid pressure because of an increase in cerebral blood volume or interstitial fluid volume[1]. The cerebral vascular tone change probably plays a role in the pathogenesis of danazol related PTC[10-12]. From the literature review, some cases developed PTC and orthostatic edema or carpal tunnel syndrome simultaneously during danazol treatment, which suggests the interstitial fluid retention is also a causative factor for danazol induced PTC[7,13]. Cessation of danazol treatment usually leads to the resolution of PTC symptoms. Except for one previously documented case, PTC had not been associated with discontinuing danazol treatment and, in that case, the patient sought out further management three weeks later for progressive worsening of headache and visual obscurations[8]. The patient received acetazolamide therapy (1000 mg/day) and the symptoms of PTC subsided within two days and a complete resolution of the papilledema was found one month later[8]. Our patient is another example of PTC where headache appeared about one week after the drug withdrawal. Similarly, PTC presenting after steroid withdrawal has been identified before[14]. Whether the development of PTC after danazol withdrawal is due to the prolonged effects of its metabolites, the rebound phenomenon of cerebral vascular tone or the endocrine effect remains to be determined.

In most cases published, PTC was induced by danazol treatment, but in our case, PTC occurred in the drug withdrawal period. For the clinician, headache occurring in patients on danazol therapy or shortly after danazol withdrawal has to be carefully assessed to rule out the possibility of PTC.

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