

Severe headaches from intracranial hypertension (pseudotumor cerebri) abrogated by treatment with dextroamphetamine sulfate

J.H. Check^{1,2}, R. Cohen³

¹Cooper Medical School of Rowan University, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ

²Cooper Institute for Reproductive Hormonal Disorders, P.C., Marlton, NJ

³Philadelphia College of Osteopathic Medicine, Department of Obstetrics and Gynecology, Philadelphia, PA (USA)

Summary

Purpose: To determine if sympathomimetic amines may relieve migraine headache pain from pseudotumor cerebri (PTC) similar to its effect on helping other types of migraine headaches that were recalcitrant to other therapies. **Materials and Methods:** A woman with severe migraine headaches which did not respond to treatment with acetazolamide was treated with dextroamphetamine sulfate sustained release capsules 25 mg daily. **Results:** The patient demonstrated marked improvement within a month. The marked decrease in headache pain has persisted over a year. Her papilledema also completely disappeared. **Conclusions:** The sympathetic neural hyperalgesia edema syndrome can manifest as PTC. Besides headaches, other symptoms that the patient manifested were part of this syndrome including chronic fatigue, inability to lose weight despite dieting, and backache. All of these additional symptoms also improved with sympathomimetic amine therapy.

Key words: Intracranial hypertension; Pseudotumor cerebri; Migraine headaches; Sympathomimetic amines.

Introduction

The gynecologist is frequently presented with a woman complaining of headaches. Physicians have a greater role than being merely “triage officers” and merely referring the woman to the “appropriate” specialist such as to a neurologist for headache complaints.

The gynecologist could consider that the headaches could be related to the estrogen in a birth control pill and may consider choosing an oral contraceptive with less estrogen, or a progesterone only pill, or trying an alternative form of contraception. Sometimes headaches may be part of the pre-menstrual syndrome and may improve with progesterone supplementation in the luteal phase.

Another common cause of headaches in women is related to hypofunction of the sympathetic nervous system [1-3]. This condition known as the sympathetic neural hyperalgesia edema syndrome is more familiar to gynecologists than neurologists or specialists in internal medicine because it is the most common remediable cause of pelvic pain [4].

Both the headache and pelvic pain usually improve considerably if not completely following treatment with the sympathomimetic amine dextroamphetamine sulfate [1-8].

By the gynecologist being familiar with this sympathetic nervous system disorder, the physician could institute sympathomimetic amines therapy without subjecting the woman to non-essential painful, expensive, and sometimes risky

tests and still not come up with a solution. One may suggest, what if some serious pathological condition is missed by this approach, e.g. a brain tumor? The answer is that a serious pathologic state e.g. a brain tumor should not respond to dextroamphetamine sulfate.

The case below describes a woman whose headaches were related to the condition known as pseudotumor cerebri (PTC) (benign idiopathic intracranial hypertension - IIH). Though the testing allowed the diagnosis, unfortunately standard therapy failed to provide relief. However, sympathomimetic amine therapy completely corrected the problem. It not only corrected the headaches but the increase in cranial blood pressure and the papilledema also resolved.

Case Report

A 34-year-old woman with a history of a simple hysterectomy began experiencing sudden headaches which would have a sudden onset, were relatively severe in pain intensity, and would last several days at a time. The pain free interval in the beginning was about two weeks. After a year, the headaches were constant with no pain free intervals and were associated with chronic fatigue and inability to lose weight, despite dieting. The headaches were so severe at times, trips to the emergency room were needed for narcotics.

Though she was diagnosed with hypothyroidism, thyroid hormone replacement which allowed restoration of normal thyroid values did not help the headaches, backaches, chronic fatigue or weight problems.

She was referred to a neurologist and a neuro-ophthalmologist. Significant papilledema was found. Spinal tap found an elevated

Revised manuscript accepted for publication June 24, 2013

pressure but no other abnormalities. A magnetic resonance imaging study of the brain failed to detect a tumor. She was thus diagnosed with PTC (benign IIH).

The woman at this point judged her headaches intensity on the basis of 1 to 10 as 10. Following combined therapy of topiramate and acetazolamide, she stated she had some relief and now judged the intensity as a 7.

She initially consulted our practice merely to manage her hypothyroidism having moved to a new state. She was advised that the thyroid dosage was correct. However she was advised that there was a good likelihood that treatment with dextroamphetamine sulfate may improve the chronic fatigue, backache, and inability to lose weight [8-10]. Furthermore, she was advised that the treatment may help the headaches in view of previous experience even though it had never been tried on headaches from PTC [1-3].

When she returned after one month of taking dextroamphetamine sulfate extended release capsules, she had marked improvement in the chronic fatigue and the headaches. The headaches had improved and were rated as a 5 on severity. The dosage was increased to 25 mg and when she returned the next month, the headaches had completely disappeared. When she had another fundoscopic evaluation by her neuro-ophthalmologist, there was no longer any papilledema.

There have been no headaches now for over one year of treatment. Furthermore, she has lost 47 pounds. The headaches disappeared long before any significant weight was lost.

Discussion

IIH is a disorder characterized by increased intracranial pressure (ICP) of unknown cause, predominantly seen in women of childbearing age and associated with a history of recent weight gain [11]. The concept of raised ICP in the absence of a space occupying lesion was first introduced by Nonne [12] as "pseudotumor cerebri".

The term "benign intracranial hypertension" became popular and was often used interchangeably with PTC. The condition was considered "benign" in comparison with cases of tumor [13], but it has been argued that loss of visual function in up to 25% of cases and progression to blindness if untreated means that it should not be considered "benign" as far as visual function is concerned.

Recently publications have looked again at the question of weight gain in IIH, some suggesting pathogenic mechanisms which may explain how weight gain can lead to raised ICP. Others suggested the reverse-that raised ICP is the cause of weight gain. However there is no convincing evidence that weight loss results in lowering of the ICP according to Fraser and Plant [14].

Based on this case, since the headaches improved, before there was significant weight loss the response in this case suggests that sympathetic nervous system hypofunction can be the etiology for benign IIH and weight gain is merely a frequent associated issue with this syndrome called sympathetic neural hyperalgesia-edema syndrome related to the edema. It is not clear if the improvement in headaches is related to inhibition of absorption of toxins into brain tissues by correcting cellular permeability issues or by lowering ICP or both [15].

Acetazolamide (a carbonic anhydrase inhibitor) has been considered by the neurologist as the mainstay of medical therapy. Topiramate has also been used. Two drugs not tried on this woman are frusemide and bendroflumethiazide. Some think the advantage of topiramate over acetazolamide is that the former can cause weight loss and losing weight may also help this condition [16]. However, the subject of this case report did not lose weight until she was treated with dextroamphetamine sulfate.

There are surgical treatments also including lumbo-peritoneal shunt, ventriculo-peritoneal shunt, and optic nerve sheath fenestration [17]. Other surgical options considered have been bariatric surgery [18]. Also in some cases where venous sinus stenosis is diagnosed, endovascular stenting has had some success [17].

Because of potential blindness the word benign should probably be removed from the name of IIH. The potential seriousness of this condition and the probabilities of missing a brain tumor could be used to justify the need to refer to a neurologist. Even IIH seems at first glance too complicated for the gynecologist.

However again, to re-iterate it is unlikely that headaches from a brain tumor would respond to dextroamphetamine sulfate. It is not clear if rare causes of IIH e.g.: giant arachnoid granulation in the left dominant transverse sinus or other causes of IIH e.g.: dural venous sinus stenosis would even respond to sympathomimetic amine therapy [11].

On the other hand, when the woman returned to her neuro-ophthalmologist, she did not seem interested in the patient's story of marked improvement with dextroamphetamine sulfate. Instead she spend only five minutes, did a fundoscopic exam, told the patient her papilledema was gone, and to return in six months for a repeat fundoscopic examination. The physician just assumed that her prescribed therapy finally worked.

Similarly an unreported case of a woman with 20 years of severe migraine headaches that were refractory to standard therapy was told by her neurologist that he believed that she will eventually develop multiple sclerosis and that was the cause of her headaches. Twenty years later she never developed multiple sclerosis. She heard that dextroamphetamine sulfate therapy could help headaches and she was placed on it. Within two weeks, her headaches of 20 year duration, cleared completely. When she advised her neurologist of these events, he advised her to stop the drug immediately because there are no prospective evidenced based randomized controlled studies proving its efficacy. She actually listened to him, stopped the dextroamphetamine sulfate, and within a week her headaches returned. After two months of severe headaches she returned to our practice, was placed on the amphetamine, and was immediately relieved again of her headaches.

Thus until this condition related to sympathetic nervous system hypofunction becomes known by neurologists and internal medicine specialists, it is important for the primary

care physician of women, i.e., the gynecologists, to either initiate therapy with sympathomimetic amines first without consulting a neurologist or referring the women to a neurologist, but advise the woman before proceeding with any suggested tests or therapies, to return to the gynecologist to decide if the proposed therapy seems reasonable, or should sympathomimetic amines be tried first?

References

- [1] Check J.H., Check D., Cohen R.: "Sympathomimetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women". *Clin. Exp. Obst. Gyn.*, 2009, 36, 189.
- [2] Check J.H., Cohen R., Check D.: "Evidence that migraine headaches in women may be related to a common defect in the sympathetic nervous system as evidenced by marked improvement following treatment with sympathomimetic amines". *Clin. Exp. Obst. Gyn.*, 2011, 38, 180.
- [3] Check J.H., Cohen R.: "Marked improvement of headaches and vasomotor symptoms with sympathomimetic amines in a woman with the sympathetic hyperalgesia-edema syndrome". *Clin. Exp. Obst. Gyn.*, 2011, 38, 88.
- [4] Check J.H., Cohen R.: "Chronic pelvic pain – traditional and novel therapies: Part II medical therapy". *Clin. Exp. Obst. Gyn.*, 2011, 38, 113.
- [5] Check J.H., Wilson C.: "Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines – case report". *Clin. Exp. Obstet. Gynecol.*, 2007, 34, 55.
- [6] Check J.H., Katsoff B., Citerone T., Bonnes E.: "A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin: case reports". *Clin. Exp. Obst. Gyn.*, 2005, 32, 247.
- [7] Check J.H., Cohen G., Cohen R., DiPietro J., Steinberg B.: "Sympathomimetic amines effectively control pain for interstitial cystitis that had not responded to other therapies". *Clin. Exp. Obst. Gyn.*, 40, 227.
- [8] Check J.H., Wilson C., Cohen R.: "A sympathetic nervous system disorder of women that leads to pelvic pain and symptoms of interstitial cystitis may be the cause of severe backache and be very responsive to medical therapy rather than surgery despite the presence of herniated discs". *Clin. Exp. Obst. Gyn.*, 2011, 38, 175.
- [9] Check J.H., Cohen R.: "Sympathetic neural hyperalgesia edema syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue". *Clin. Exp. Obst. Gyn.*, 2011, 38, 412.
- [10] Check J.H., Shanis B.S., Shapse D., Adelson H.G.: "A randomized study comparing two diuretics, a converting enzyme inhibitor, and a sympathomimetic amine on weight loss in diet failure patients". *Endoc. Pract.*, 1995, 1, 323.
- [11] Wall M.: "Idiopathic intracranial hypertension". *Neurol. Clin.*, 2010, 28, 593.
- [12] Nonne M.: "Über Falle vom Symptomenkomplex "Tumor cerebri" mit Ausgang in Heilung (Pseudotumor cerebri). Über eine letal verlaufene Falle von "Pseudotumor cerebri" mit Sektionsbefund". *J. Neurol.*, 1904, 27, 169.
- [13] Pearce J.M.: "From pseudotumour cerebri to idiopathic intracranial hypertension". *Pract. Neurol.*, 2009, 9, 353.
- [14] Fraser C., Plant G.T.: "The syndrome of pseudotumour cerebri and idiopathic intracranial hypertension". *Curr. Opin. Neurol.*, 2011, 24, 12.
- [15] Check J.H., Cohen R., Katsoff B., Check D.: "Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with sympathomimetic amines". *Med. Hypoth.*, 2011, 77, 717.
- [16] Celebisoy N., Gokcay F., Sirin H., Akyurekli O.: "Treatment of idiopathic intracranial hypertension: topiramate vs. acetazolamide, an open-label study". *Acta Neurol. Scand.*, 2007, 116, 322.
- [17] Uretsky S.: "Surgical interventions for idiopathic intracranial hypertension". *Curr. Opin. Ophthalmol.*, 2009, 20, 451.
- [18] Fridley J., Foroozan R., Sherman V., Brandt M.L., Yoshor D.: "Bariatric surgery for the treatment of idiopathic intracranial hypertension". *J. Neurosurg.*, 2011, 114, 34.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com