CASE REPORT

Pseudotumor Cerebri Syndrome with Resolution After Discontinuing High Vitamin A Containing Dietary Supplement: Case Report and Review

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ABSTRACT

A 24-year-old non-obese, but slightly overweight, female presented with a two-week history of progressive severe headache associated with two days of blurry vision. Clinical exam was significant for bilateral papilledema and an enlarged blind spot on visual field testing. Contrast enhanced MRI head revealed no space occupying lesion. A lumbar puncture revealed an elevated opening pressure of 38 cm H₂O with normal cerebrospinal fluid composition leading to a diagnosis of pseudotumor cerebri syndrome (PTCS). The patient lacked the typical risk factors of high body mass index or obvious antecedent medications; however, on subsequent questioning, she was chronically ingesting a high vitamin A containing weight loss dietary supplement (Thrive W[®] – Table 1), which we believe had caused intracranial hypertension. Discontinuation of the diet pill and treatment with acetazolamide led to marked improvement of her PTCS. This case highlights the fact that non-traditional products or medications with high vitamin A may cause pseudotumor cerebri, which treating physicians should assess for while dealing with non-obese PTCS patients.

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Introduction

Pseudotumor cerebri syndrome (PTCS) is a syndrome of increased intracranial pressure without a space-occupying lesion and has an estimated incidence of 0.5–2 per 100,000 people per year, with most cases occurring in obese females of reproductive age.^{1–4} It is further classified into primary PTCS (or idiopathic intracranial hypertension [IIH]) and secondary PTCS, in which there is an identifiable underlying cause.^{2,5} Multiple secondary causes have been identified (Table 2), and include certain antibiotics such as minocycline, hormonal factors, excess vitamin A retinoids, various other drugs, and certain disorders, such as cerebral venous sinus thrombosis.^{2,4,6} It is important to inquire into these secondary causes in any patient with PTCS, but especially so in those without the typical IIH risk factors, including obesity and recent weight gain.^{2,7,8}

Current standard of care in PTCS includes acetazolamide combined with weight loss through dieting in obese patients,^{3,9–13} which has shown modest benefit in randomized controlled trials.^{14,15} When a secondary cause is identified, removal of the offending

agent usually leads to remission, with a temporary course of acetazolamide used concurrently in most reported cases.^{3,16,17} We report a case of PTCS in a non-obese female secondary to chronic use of a dietary supplement containing excess vitamin A with the goal of highlighting that treating physicians should look for usage of such non-traditional therapies as a precipitating cause in non-obese pseudotumor cerebri patients. The assessment and knowledge of recent weight loss is also important in patients with new PTCS symptoms.

Case report

A 24-year-old Caucasian female with a body mass index (BMI) of 25.1 presented to the ER with a two-week history of persistent headache, described as a dull, aching pain in the posterior neck and occipital area with progressive worsening over the previous two days. This was associated with nausea, vertigo, and pulsatile tinnitus in both ears. Two days prior to presentation, she woke up with blurry vision in her right eye that then progressed to the left. She also endorsed temporary

Table 1. Thrive W® contents*.

Vitamin A – 1500 IU per capsule (as vitamin A acetate)
Other vitamins/minerals: vitamin B1, B2, B3, B5, B6, B12 and D3, folic acid, chromium, selenium, vanadium
Other ingredients: probiotic bacteria, guarana caffeine, green tea caffeine, glucosamine, glutamine, green coffee bean, phenylethylamine, kelp, various extracts (white willow, irvingia, ginger, citrus aurantium, grape seed, white tea), branch chain amino acid blend, theobromine, aspartic acid, serine, CoQ 10, stearic acid, silica, gelatin

*Based on product supplement facts available on the Le-Vel Brands website (premier.le-vel.com/Experience)

Table 2. Pseudotumor cerebri syndrome (PTCS).

Primary pseudotumor cerebri (IIH)
Includes patients with obesity, recent weight gain, and polycystic ovarian syndrome
Secondary pseudotumor cerebri
Cerebral venous abnormalities
Cerebral venous sinus thrombosis, bilateral jugular vein thrombosis, middle ear or mastoid infection, increased right heart pressure, superior vena cava syndrome, arteriovenous fistulas, decreased CSF absorption from previous intracranial infection of subarachnoid hemorrhage, hypercoagulable states
Medications and exposures
Antibiotics (tetracycline, minocycline, doxycycline, nalidixic acid, sulfa drugs), vitamin A and retinoids, hormones (human growth hormone, thyroxine, tamoxifen, anabolic steroids), withdrawal from chronic corticosteroids, lithium, chlordecone
Medical conditions
Endocrine disorders (Addison disease, hypoparathyroidism, Cushing's disease), hypercapnia (sleep apnea, Pickwickian syndrome), anemia, renal failure, chromosomal conditions (Turner syndrome, Down syndrome), autoimmune disorders (systemic lupus erythematosus, Sjögren syndrome)

blackout of vision upon arising quickly. She denied photophobia, phonophobia, diplopia, paresthesia, focal weakness or prior history of similar headache. There was no recent weight gain. Over the counter medications such as ibuprofen and intravenous ketorolac in the emergency department did not provide relief.

On exam her visual acuity was 20/25 in both eyes with no afferent pupillary defect. Anterior segment

and intraocular pressures were unremarkable bilaterally. Dilated funduscopy exam revealed bilateral grade 5 papilledema with peripapillary retinal exudates (Figure 1A, 1B). Papilledema grading was based on the Frisén Papilledema Grading Scale, with grade 5 being the most severe and defined as dome-shaped protrusion of the optic nerve with a narrow and smoothly demarcated halo with major retinal vessels climbing steeply over the domed surface.¹⁸ Optical coherence tomography (OCT) demonstrated retinal nerve fiber layer edema with extension of subretinal fluid into the fovea (Figure 2A), and Humphrey visual fields (24–2 SITA Fast) revealed enlargement of the blind spot bilaterally (Figure 3A, 3B).

Contrast enhanced MRI of her head revealed low-lying cerebellar tonsils, small pituitary gland and flattening of the globes, and all features suggestive of intracranial hypertension. Contrast enhanced MR venogram revealed severe stenosis of the transverse sinuses bilaterally with no evidence of venous sinus thrombosis. A lumbar puncture revealed an opening pressure of 38 cm H₂O with normal cerebrospinal fluid (CSF) composition. She felt symptomatic relief after the spinal tap.

Based on her exam and imaging, she fully met criteria for diagnosis of PTCS.² However, her normal BMI led us to consider a secondary cause for PTCS or some other optic neuropathy masquerading as PTCS. Upon further questioning, she endorsed intentional weight loss of 45 pounds over the previous six months. In addition to dieting, she had been taking two capsules daily of the dietary supplement Thrive W® (Le-Vel Brands, Frisco, Texas, United States), which contains 1500 IU of vitamin A per capsule, for about a year and had stopped one month prior

Figure 1. Optic disc photos at presentation showing grade 5 papilledema bilaterally.

Figure 2. (A) Optical coherence tomography. Initial exam demonstrating retinal nerve fiber layer edema with subretinal fluid extending into the fovea, which is slightly worse on the right. (B) At one-month follow-up there was improvement in the retinal nerve fiber layer edema and resolution of the subretinal fluid collection.

to her presentation. Given that excess vitamin A ingestion is a well-documented cause of PTCS,^{6,19} a diagnosis of secondary PTCS was suspected.

She was started on acetazolamide 500 mg twice daily and asked to discontinue all high vitamin A containing products. When re-evaluated one month later in the ophthalmology clinic, she reported improvement of all her symptoms including headache, blurred vision, transient vision loss, and pulsatile tinnitus. She endorsed discontinuing the dietary supplements and all products with high concentrations of vitamin A. Her visual acuity was 20/20 in both eyes. Fundus exam revealed improving papilledema and improvement was also seen on OCT (Figure 2B) and visual fields (Figure 3C, 3D). At five month ophthalmology follow-up, vision was maintained at 20/20 in both eyes, there was complete resolution of papilledema and visual fields returned to normal.

Discussion

Patients with PTCS should always be questioned for secondary causes. This is particularly important in atypical patients without obesity or recent weight gain.^{2,7,8} In the modern era, where numerous nutritional supplement pills are being increasingly used,

secondary causes of PTCS can be easily overlooked without obtaining a careful history. Patients may not always be forthcoming due to stigma of weight loss or lack of awareness of nutritional supplements as problematic. One study of 407 consecutive PTCS patients found that only 4% had a normal BMI, and the syndrome was more frequently medication-induced in non-obese patients, with 28% exposed to an associated medication.⁸

One of the most well-established secondary causes of PTCS is hypervitaminosis A, and there is good evidence that this syndrome can be induced if enough vitamin A is ingested.^{6,19} Studies have found serum vitamin A levels, in the form of retinol, to be significantly higher in idiopathic PTCS patients,^{20,21} and others have found significantly higher retinol levels in the cerebrospinal fluid as well.²¹⁻²³ In 2007, Warner et al. found that the ratio of retinol to retinol binding protein (RBP) in the CSF was higher in patients with PTCS and was >1.0, suggesting the presence of unbound retinol, which they theorized may be toxic to arachnoid villi and lead to impaired CSF resorption.²¹ Increased RBP in the serum of individuals with PTCS has been reported in two studies, suggesting that the unbound toxic retinol in

Figure 3. SITA FAST 24–2 visual field testing. Initial exam demonstrating enlarged blind spot bilaterally with mean deviation of -7.21 db OD (A) and -7.29 db OS (B). At one-month follow-up there was improvement of enlarged blind spot bilaterally with mean deviation of -3.05 db OD (C) and -2.76 db OS (D).

the CSF may be due to insufficient RBP transfer into the CSF compartment.^{21,24}

The first case of adult pseudotumor cerebri associated with hypervitaminosis A was reported by Gerber et al. in 1954.^{25,26} Multiple cases of PTCS secondary to chronic excess vitamin A use have since been reported, included in a number of “vitamin junkies”.^{26–29} Hypervitaminosis A has been reported to cause PTCS in children and adults with daily vitamin A intake of 1500 to 150,000 IU/day, typically sustained for months to years before diagnosis.^{30–32} However, there is ongoing debate about the level at which toxicity can occur.^{29,32} Further, a wide inter-individual variability for the lowest intake required to elicit toxicity has been reported.^{29,32} For example, Benzimra et al. recently

reported a case of a 17 year-old girl who developed PTCS associated with a two-month usage of a multivitamin containing 8000 IU of vitamin A.²⁹

In our case, the patient had been taking a weight loss supplement, containing 1500 IU of vitamin A per capsule, twice daily for a year. We believe that chronic ingestion over many months led to cumulative toxicity. Her papilledema and symptoms started improving with discontinuation of the supplement and resolved by six months, similar to other cases linked to vitamin A.²⁷ Although the vitamin A level seems lower, we hypothesize that PTCS in this case could be a result of two factors. First, the level of vitamin A intake required for toxicity may be lower than previously reported, which could be especially true for cases of chronic daily use. Individual

tolerances to different amounts of vitamin A ingested on a chronic basis have not yet been adequately studied,³² and better understanding on the subject could provide insight into factors that result in chronic vitamin A toxicity. Therefore, in cases of chronic vitamin A intoxication, it may be prudent to characterize vitamin A consumption as a product of duration, rather than simply daily values, to determine likelihood of toxicity.

Another factor that may have contributed to her toxicity at this dose of vitamin A is her weight loss. Vitamin A is stored in the body as retinol, and although the majority is stored in the liver, adipose tissue also represents an important storage site and is the second largest retinol depot.³³ As it is a fat-soluble molecule,^{32,33} weight loss could have resulted in higher levels of circulating vitamin A, thus leading to toxicity at lower intake levels. However, further study is required to better understand how weight loss affects circulating retinol levels to determine the impact this may have on potential toxicity.

This case also highlights the association between high vitamin A containing dietary supplements and PTCS, and the risk that they pose on dieting individuals for developing this syndrome. Weight loss is usually recommended for obese patients with IIH, the benefits of which has been documented in multiple studies.^{3,9–13} Weight gain has also been associated with recurrence of IIH, providing further evidence for the necessity of dieting in these individuals.^{12,13,34} With the existence of vitamin A containing dietary supplements, patients should be advised to read nutritional labels and avoid consuming products with high levels of vitamin A, as this could lead to recurrence of the syndrome and treatment failure. Therefore, we should be more specific in our guidance regarding appropriate weight loss strategies when recommending this for PTCS patients. Further, for patients exhibiting new PTCS symptoms, recent weight loss should be assessed in addition to the more common risk factor of recent weight gain. This is especially true for intentional weight loss, as this case demonstrates that a common dietary supplement can potentially contain vitamin A levels high enough to provoke development of PTCS.

One shortcoming of this case is the lack of serum vitamin A levels at presentation, as elevated levels of vitamin A would have strengthened the causal link between excess vitamin A consumption and

development of PTCS in this patient. However, the dramatic improvement after discontinuing high vitamin A containing products, including complete resolution of papilledema and visual field deficits at 5 month follow-up, does provide some evidence to support this, though therapeutic lumbar puncture and treatment with acetazolamide also could have contributed. Evidence is also provided by the lack of typical risk factors seen in PTCS, such as obesity and weight gain, and the lack of other known secondary causes of PTCS in this case, with the only possible co-factor being that she was slightly overweight.

In conclusion non-obese pseudotumor cerebri patients should always be questioned about the use of non-traditional products or medications with high vitamin A or other contents that may cause pseudotumor cerebri. Even overweight pseudotumor cerebri patients who are counselled on weight loss for their disease should be educated to avoid high vitamin A containing weight loss products that can be detrimental. In pseudotumor cerebri recent weight loss should be assessed in addition to recent weight gain.

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Declaration of interest

The authors declare that there are no conflicts of interest. The authors alone are responsible for the writing and content of the article.

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References

- [1] Wall M. Idiopathic intracranial hypertension. *Neurol Clin* 2010;28(3):593–617. doi:10.1016/j.ncl.2010.03.003.
- [2] Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013;81:1159–1165. doi:10.1212/WNL.0b013e3182a55f17.
- [3] Friedman DI. The pseudotumor cerebri syndrome. *Neurol Clin* 2014;32:363–396. doi:10.1016/j.ncl.2014.01.001.
- [4] Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directives.

- Lancet Neurol* 2016;15:78–91. doi:[10.1016/S1474-4422\(15\)00298-7](https://doi.org/10.1016/S1474-4422(15)00298-7).
- [5] Wakerley BR, Tan MH, Ting EY. Idiopathic intracranial hypertension. *Cephalalgia* 2015;35(3):248–261. doi:[10.1177/0333102414534329](https://doi.org/10.1177/0333102414534329).
 - [6] Chen J, Wall M. Epidemiology and risk factors for idiopathic intracranial hypertension. *Int Ophthalmol Clin* 2014;54(1). doi:[10.1097/IIO.0b013e3182aabf11](https://doi.org/10.1097/IIO.0b013e3182aabf11).
 - [7] Mollan SP, Markey KA, Benzimra JD, Jacks A, Matthews TD, Burdon MA, Sinclair AJ. A practical approach to, diagnosis, assessment and management of idiopathic intracranial hypertension. *Pract Neurol* 2014;14:380–390. doi:[10.1136/practneurol-2014-000821](https://doi.org/10.1136/practneurol-2014-000821).
 - [8] Bruce BB, Kedar S, Van Stavern GP, Corbett JJ, Newman NJ, Biousse V. Atypical idiopathic intracranial hypertension. *Neurology* 2010;74:1827–1832. doi:[10.1212/WNL.0b013e3181e0f838](https://doi.org/10.1212/WNL.0b013e3181e0f838).
 - [9] Johnson LN, Krohel GB, Madsen RW, March GA Jr. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). *Ophthalmology* 1998;105:2313–2317. doi:[10.1016/S0161-6420\(98\)91234-9](https://doi.org/10.1016/S0161-6420(98)91234-9).
 - [10] Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M. Effects of weight loss on the course of idiopathic intracranial hypertension in women. *Neurology* 1998;50:1094–1098. doi:[10.1212/WNL.50.4.1094](https://doi.org/10.1212/WNL.50.4.1094).
 - [11] Sinclair AJ, Burdon MA, Nightingale PG, Ball AK, Good P, Matthews TD, Jacks A, Lawden M, Clarke CE, Stewart PM, Walker EA, Tomlinson JW, Rauz S. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. *Bmj* 2010;340:c2701. doi:[10.1136/bmj.c2701](https://doi.org/10.1136/bmj.c2701).
 - [12] Mollan SP, Ali F, Hassan-Smith G, Botfield H, Friedman DI, Sinclair AJ. Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management. *Neurol Neurosurg Psychiatry* 2016;87:982–992. doi:[10.1136/jnnp-2015-311302](https://doi.org/10.1136/jnnp-2015-311302).
 - [13] Subramaniam S, Fletcher WA. Obesity and weight loss in idiopathic intracranial hypertension: a narrative review. *J Neuro-Ophthalmol* 2016;0:1–9.
 - [14] Wall M, McDermott MP, Kiebertz KD, Corbett JJ, Feldon SE, Friedman DI, Keltner JL, Schron EB, Kupersmith MJ, NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *Jama* 2014;311(16):1641–1651. doi:[10.1001/jama.2014.3312](https://doi.org/10.1001/jama.2014.3312).
 - [15] Piper RJ, Kalyvas AV, Young AMH, Hughes MA, Jamjoom AAB, Fouyas IP. Interventions for idiopathic intracranial hypertension. *Cochrane Database Syst Rev* 2015;8:Art. No.: CD003434. doi:[10.1002/14651858.CD003434.pub3](https://doi.org/10.1002/14651858.CD003434.pub3).
 - [16] Sirdofsky M, Kattah J, Macedo P. Intracranial hypertension in a dieting patient. *J Neuro-Ophthalmol* 1994;14(1):9–11. doi:[10.1097/00041327-199403000-00004](https://doi.org/10.1097/00041327-199403000-00004).
 - [17] Friedman DI, Gordon LK, Egan RA, Jacobson DM, Pomeranz H, Harrison AR, Goldhammer Y. Doxycycline and intracranial hypertension. *Neurology* 2004;62:2297–2299. doi:[10.1212/WNL.62.12.2297](https://doi.org/10.1212/WNL.62.12.2297).
 - [18] Friedman DI. Papilledema and idiopathic intracranial hypertension. *Continuum (Minneapolis)* 2014;20(4):857–876.
 - [19] McGeeney BE, Friedman DI. Pseudotumor cerebri pathophysiology. *Headache* 2014;54:445–458. doi:[10.1111/head.12291](https://doi.org/10.1111/head.12291).
 - [20] Jacobson DM, Berg R, Wall M, Digre KB, Corbett JJ, Ellefson RD. Serum vitamin A concentration is elevated in idiopathic intracranial hypertension. *Neurology* 1999;53(5):1114–1118. doi:[10.1212/WNL.53.5.1114](https://doi.org/10.1212/WNL.53.5.1114).
 - [21] Warner JEA, Larson AJ, Bhosale P, Digre KB, Henley C, Alder SC, Katz BJ, Bernstein PS. Retinol-binding protein and retinol analysis in cerebrospinal fluid and serum of patients with and without idiopathic intracranial hypertension. *J Neuro-Ophthalmol* 2007;27:258–262. doi:[10.1097/WNO.0b013e31815b9af0](https://doi.org/10.1097/WNO.0b013e31815b9af0).
 - [22] Warner JEA, Bernstein PS, Yemelyanov A, Alder SC, Farnsworth ST, Digre KB. Vitamin A in the cerebrospinal fluid of patients with and without idiopathic intracranial hypertension. *Ann Neurol* 2002;52:647–650. doi:[10.1002/ana.10377](https://doi.org/10.1002/ana.10377).
 - [23] Tabassi A, Salmasi AH, Jalali M. Serum and CSF vitamin A concentrations in idiopathic intracranial hypertension. *Neurology* 2005;64:1893–1896. doi:[10.1212/01.WNL.0000163556.31080.98](https://doi.org/10.1212/01.WNL.0000163556.31080.98).
 - [24] Selhorst JB, Kulkantrakorn K, Corbett JJ, Leira EC, Chung SM. Retinol-binding protein in idiopathic intracranial hypertension (IIH). *J Neuro-Ophthalmol* 2000;20(4):250–252. doi:[10.1097/00041327-200020040-00009](https://doi.org/10.1097/00041327-200020040-00009).
 - [25] Gerber A, Raab AP, Sobei AE. Vitamin A poisoning in adults: with description of a case *Amer J Med*. 1954;16:729–745. doi:[10.1016/0002-9343\(54\)90281-8](https://doi.org/10.1016/0002-9343(54)90281-8).
 - [26] Feldman MH, Schlezinger NS. Benign intracranial hypertension associated with hypervitaminosis A. *Arch Neurol* 1970;22:1–7. doi:[10.1001/archneur.1970.00480190005001](https://doi.org/10.1001/archneur.1970.00480190005001).
 - [27] Morrice G Jr., Havener WH, Kapetansky F. Vitamin A intoxication as a cause of pseudotumor cerebri. *Jama* 1960;173:1802–1805. doi:[10.1001/jama.1960.03020340020005](https://doi.org/10.1001/jama.1960.03020340020005).
 - [28] Libien J, Blanner WS. Retinol and retinol-binding protein in cerebrospinal fluid: can vitamin A take the “idiopathic” out of idiopathic intracranial hypertension? *J Neuro-Ophthalmol* 2007;27(4):253–257. doi:[10.1097/WNO.0b013e31815c44bc](https://doi.org/10.1097/WNO.0b013e31815c44bc).
 - [29] Benzimra JD, Simon S, Sinclair AJ, Mollan SP. Sight-threatening pseudotumour cerebri associated with excess vitamin A supplementation. *Pract Neurol* 2015;15:72–73. doi:[10.1136/practneurol-2014-000934](https://doi.org/10.1136/practneurol-2014-000934).
 - [30] Marcus DF, Turgeon P, Aaberg TM, Wiznia RA, Wetzig PC, Bovino JA. Optic disk findings in hypervitaminosis A. *Ann Ophthalmol* 1985 Jul;17(7):397–402.

- [31] Olson JA. Upper limits of vitamin A in infant formulas, with some comments on vitamin K. *J Nutr* 1989 Dec;119(12 Suppl):1820–1824.
- [32] Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr* 2006;83:191–201.
- [33] Donahue SP. Recurrence of idiopathic intracranial hypertension after weight loss: the carrot craver. *Am J Ophthalmol* 2000;130:850–851. doi:[10.1016/S0002-9394\(00\)00607-3](https://doi.org/10.1016/S0002-9394(00)00607-3).
- [34] Ko MW, Chang SC, Ridha MA, Ney JJ, Ali TF, Friedman DI, Mejico LJ, Volpe NJ, Galetta SL, Balcer LJ, Liu GT. Weight gain and recurrence in idiopathic intracranial hypertension. *Neurology* 2011;76:1564–1567. doi:[10.1212/WNL.0b013e3182190f51](https://doi.org/10.1212/WNL.0b013e3182190f51).