

Presumed Pseudotumor Cerebri Syndrome After Withdrawal of Inhaled Glucocorticoids

Young Joon Kwon,^a Julian L. Allen, MD,^{b,c} Grant T. Liu, MD,^{c,d} Shana E. McCormack, MD^{c,e}

Pseudotumor cerebri syndrome (PTCS) is characterized by increased intracranial pressure with normal brain parenchyma and cerebrospinal fluid constituents. PTCS after withdrawal of systemic corticosteroids also has been described in children. In contrast, to our knowledge, PTCS after withdrawal of inhaled glucocorticoids has not previously been described. Here we report the case of an 8-year and 6-month-old girl who developed signs and symptoms consistent with PTCS after withdrawal of inhaled glucocorticoids. The patient had excellent adherence to inhaled glucocorticoid therapy for ~1 year before presentation, after which the therapy was stopped for concern related to poor growth. The withdrawal of inhaled glucocorticoids was associated with the development of severe headaches and diplopia, and further clinical examination led to the patient's diagnosis of likely PTCS. Although its occurrence is likely rare, clinicians caring for the many children receiving inhaled glucocorticoid therapy should be aware of the potential for PTCS after abrupt withdrawal of such treatment, and consider ophthalmology evaluation if patients report suggestive symptoms, such as headaches or vision changes in this context.

Pseudotumor cerebri syndrome (PTCS) is characterized by increased intracranial pressure with normal brain parenchyma and cerebrospinal fluid constituents.¹ At presentation, visual acuity loss is reported in 6% to 20% of pediatric cases, although visual field loss occurs in up to 91% of cases.² Although the unifying mechanism(s) underlying PTCS are incompletely understood, past clinical observations have suggested abnormal glucocorticoid metabolism may contribute to the pathophysiology of PTCS.³ For example, PTCS has been described in patients with Addison disease,⁴ after surgical resection of the pituitary tumors for Cushing disease,⁵ and in adults after withdrawing of chronic systemic glucocorticoid therapy.⁶

PTCS after withdrawal of systemic corticosteroids also has been described in children.^{7,8} In contrast, to our knowledge, PTCS after withdrawal of inhaled glucocorticoids has not previously been described. Recently it has been shown that in some vulnerable patients, inhaled glucocorticoids also can be associated with impaired linear growth, although the magnitude of the effect is less than that of systemic glucocorticoids.⁹ Indeed, the combination of PTCS and decreased linear growth has been described before as a consequence of oral glucocorticoid therapy in children, but again, to date, not with inhaled glucocorticoid therapy.^{10,11} Specifically, 1 seminal case report described 3 children treated with oral glucocorticoid who developed Cushingoid features and

abstract



Divisions of ^aHuman Genetics, ^bPulmonary Medicine, ^cOphthalmology, Neuro-ophthalmology Service, and ^dEndocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and ^ePerelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Mr Kwon contributed to the presentation and analysis of clinical data and drafted the initial manuscript; Drs Allen, Liu, and McCormack critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-2091

Accepted for publication Mar 9, 2016

Address correspondence to Shana E. McCormack, MD, Perelman School of Medicine at the University of Pennsylvania, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, 11NW, Ste 30, 34th and Civic Center Blvd, Philadelphia, PA 19104. E-mail: mccormacks1@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr McCormack is supported by a K12 award (DK094723-01, Children's Hospital of Philadelphia, Endocrinology and Diabetes). Support also provided by NIH-DK102659 (SEM). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Kwon YJ, Allen JL, Liu GT, et al. Presumed Pseudotumor Cerebri Syndrome After Withdrawal of Inhaled Glucocorticoids. *Pediatrics*. 2016;137(6):e20152091

subsequently experienced growth failure; PTCS was precipitated when glucocorticoids were withdrawn.⁸

We now report a case of a patient who developed decreased linear growth related to inhaled glucocorticoids for the treatment of asthma, and then developed signs and symptoms consistent with PTCS when inhaled glucocorticoids were withdrawn.

CASE REPORT

An 8-year and 6-month-old girl with mild persistent asthma was referred for neuro-ophthalmic consultation at the Children's Hospital of Philadelphia with a chief complaint of severe headaches and diplopia. The patient stated that her headaches lasted ~1.5 hours and were located posteriorly. She denied associated photophobia, phonophobia, or nausea. She stated that she occasionally felt "unsteady." On sitting up, she would develop pulsatile tinnitus that would last ~5 minutes. She also had transient visual obscurations. Typically, diplopia would precede the headache; both resolved at the same time. There was no significant personal or family history of headaches noted. She complained of binocular double vision, but she could not characterize it as fully vertical or horizontal. Visual acuity (Snellen-Linear) on presentation without correction was 20/20-3 OD and 20/20-2 OS. She saw 8/8 color plates OD and 8/8 OS. That patient also had full visual fields to confrontation techniques, and had equally reactive pupils without an afferent pupillary defect. The eye movements and ocular alignment were normal; no sixth nerve palsies were noted. Eyelids were normal. Anterior segment examination was normal. Fundus examination revealed elevated optic nerves bilaterally without hemorrhages or cotton wool spots. Optic nerve ultrasound confirmed true papilledema. Brain MRI showed optic disc bulging

and prominence of the optic nerve sheaths, features consistent with elevated intracranial pressure, but no mass lesion, pituitary or sellar abnormalities, and mild cerebellar ectopia. Brain magnetic resonance venography showed no evidence for deep venous sinus thrombosis or flow-limiting venous stenosis. This patient had a long history of atopy and eczema, and had several likely mosquito bites. She had no antecedent fevers or other exposures. For completeness, serum (immunoglobulin M/immunoglobulin G) testing for Lyme disease was negative ~4 weeks after initial diagnosis. Due to the cerebellar ectopia, lumbar puncture was not performed. As a result, criteria for definitive primary PTCS¹ were not fulfilled. Despite this, her clinical presentation was felt to be most suggestive of PTCS,¹ so she was started on acetazolamide (250 mg, twice daily) to which she responded well.

Approximately 1 month after the neuro-ophthalmology consultation, endocrinology consultation occurred for poor growth and possible iatrogenic adrenal insufficiency. Medical history was reviewed. Briefly, the patient was born full-term and had been previously well except for asthma.

Detailed review of the patient's glucocorticoid exposure history indicated that she had been started on fluticasone propionate (110 µg inhaled twice daily) ~13 months before the onset of headaches and 2 months later the dose was increased to 3 times daily for increased wheezing. During this time, she had also received intranasal glucocorticoids, as well as montelukast, cetirizine, and omeprazole. She demonstrated excellent adherence and did not require significant amounts of rescue bronchodilators.

A taper of inhaled glucocorticoids was attempted, but the patient

developed pneumonia (which was treated with azithromycin) ~3 months before presentation. Her last doses of oral glucocorticoids were around this time, during which she received <5 days in total of oral prednisolone. After this, both fluticasone (110 µg inhaled 3 times daily) and intranasal steroid (ie, all glucocorticoids) were tapered to off over ~1 month. She presented ~1 month thereafter.

With respect to linear growth, during 6 months before glucocorticoid taper, there had been ~0-cm increase in height, which was associated with a height z score's decrease from -1.24 to -1.67 (Fig 1). Laboratory studies did not disclose any other organic cause for linear growth deceleration (not shown). First-morning cortisol was first performed after ~4 months off inhaled glucocorticoids, and was 8.7 µg/dL; dehydroepiandrosterone-sulfate was low at 0.3 µg/dL (26.1-141.9 µg/dL). The family was educated about the risk of iatrogenic adrenal insufficiency with oral or increasing inhaled doses of glucocorticoids and elected to defer provocative testing pending her clinical course. The patient was started on low-dose ciclesonide (80 µg, twice daily; with additional as needed for flares) for return of her asthma symptoms.

Approximately 3 months after the headaches and papilledema, the patient returned to the Division of Endocrinology. She had not required oral glucocorticoids. Her headaches and disc swelling had improved. During the ~5 to 6 months on inhaled ciclesonide only, her growth velocity increased to an annualized linear growth velocity of 7 cm per year (Fig 1). Acetazolamide was discontinued, and optic disc edema resolved.

DISCUSSION

Here we report a case in which signs and symptoms consistent with PTCS occurred related to the withdrawal

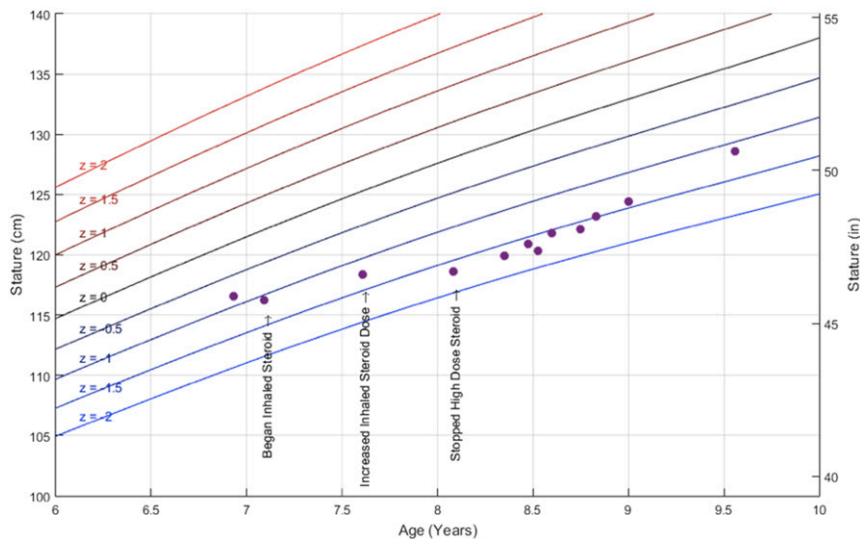


FIGURE 1 Growth chart (Centers for Disease Control and Prevention 2000, girls 2–20 years). The patient's height, plotted against age, over the course of the case described.

of inhaled glucocorticoids. We believe that the constellation of headache, papilledema, visual changes, pulsatile tinnitus, consistent MRI findings, and resolution of symptoms with acetazolamide together are most consistent with PTCS with withdrawal of inhaled glucocorticoids as an apparent trigger. Further in support of this association, 9 months of excellent adherence to inhaled and intranasal glucocorticoid therapy for asthma was also associated with a decrease in linear growth. The withdrawal of glucocorticoids restored the patient's growth velocity, but also appears to have precipitated headaches and papilledema. A lumbar puncture was not performed because of the mild cerebellar ectopia, so a formal diagnosis of PTCS¹ could not be made but was presumed. The otherwise normal MRI along with presence of papilledema, which resolved, in a child without evidence of infection, suggested highly that PTCS is the correct diagnosis. Headaches and papilledema improved with acetazolamide, as well as resumption of an alternative formulation of inhaled glucocorticoid therapy for asthma. Growth velocity has continued to be normal for age.

Previous case reports have illustrated that withdrawal of chronic steroid medications and surgical resection of corticotropin-secreting pituitary tumors for Cushing disease can lead to a development of PTCS.^{5,7,12} Causality is suggested here, because a short course of high-dose glucocorticoids is a treatment option in the acute management of vision-threatening PTCS.¹³ This observation has led to the conjecture that individuals with the highest initial glucocorticoid exposure would be the ones most likely to experience symptoms after withdrawal. However, there was no difference in the preoperative, absolute 24-hour urine-free cortisol, adjusted for body surface area, between pediatric patients who did and did not develop PTCS.⁵ This result suggests that it may be chronicity and adaptation to previous glucocorticoid exposure, rather than absolute reductions in cortisol levels per se, that predispose to the development of PTCS.³

It has been hypothesized that cortisol may act at the mineralocorticoid response element to influence cerebrospinal fluid production via downstream effects on epithelial sodium channel and Na⁺/K⁺ ATPase

activity in the choroid plexus.³ In addition, a potential role for tissue-specific "local" cortisol availability has been postulated. Specifically, 11- β -hydroxysteroid dehydrogenase type 1 (HSD1) and type 2 (HSD2) regulate the local tissue availability of cortisol. HSD1 catalyzes the conversion of cortisone to cortisol, whereas HSD2 catalyzes the reverse reaction. The complex and tissue-specific effects on the balance between HSD1 and HSD2 activity after chronic glucocorticoid therapy may explain why abrupt discontinuation can precipitate relative cortisol insufficiency, although more mechanistic investigation in this area is clearly needed.¹⁴

Ciclesonide has promise as a relatively pulmonary-specific inhaled glucocorticoid.¹⁵ However, by virtue of its relative specificity, while switching from less-specific inhaled steroids to ciclesonide may promote improved growth velocity and adrenal function in the long-term, it is possible that it could provoke steroid withdrawal syndromes such as adrenal insufficiency and the presumed PTCS described here in the short-term if the less-selective inhaled steroids are withdrawn too rapidly.

CONCLUSIONS

We describe a child who experienced growth impairment related to inhaled glucocorticoid therapy, and signs and symptoms consistent with PTCS after inhaled glucocorticoid therapy was withdrawn. To our knowledge, this is the first such reported observation of the latter. Although its occurrence is likely rare, clinicians caring for the many children receiving inhaled glucocorticoid therapy should be aware of the potential for PTCS after withdrawal of treatment, and consider ophthalmology evaluation if patients report suggestive symptoms

such as headaches or vision changes in this context.

ABBREVIATIONS

HSD1: hydroxysteroid dehydrogenase type 1
HSD2: hydroxysteroid dehydrogenase type 2
PTCS: pseudotumor cerebri syndrome

REFERENCES

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81(13):1159–1165
2. Rangwala LM, Liu GT. Pediatric idiopathic intracranial hypertension. *Surv Ophthalmol*. 2007;52(6):597–617
3. Sheldon CA, Kwon YJ, Liu GT, McCormack SE. An integrated mechanism of pediatric pseudotumor cerebri syndrome: evidence of bioenergetic and hormonal regulation of cerebrospinal fluid dynamics. *Pediatr Res*. 2015;77(2):282–289
4. Condulis N, Germain G, Charest N, Levy S, Carpenter TO. Pseudotumor cerebri: a presenting manifestation of Addison's disease. *Clin Pediatr (Phila)*. 1997;36(12):711–713
5. Kiehna EN, Keil M, Lodish M, Stratakis C, Oldfield EH. Pseudotumor cerebri after surgical remission of Cushing's disease. *J Clin Endocrinol Metab*. 2010;95(4):1528–1532
6. Liu GT, Kay MD, Bienfang DC, Schatz NJ. Pseudotumor cerebri associated with corticosteroid withdrawal in inflammatory bowel disease. *Am J Ophthalmol*. 1994;117(3):352–357
7. Parfitt VJ, Dearlove JC, Savage D, Griffith HB, Hartog M. Benign intracranial hypertension after pituitary surgery for Cushing's disease. *Postgrad Med J*. 1994;70(820):115–117
8. Dees SC, McKay HW Jr. Occurrence of pseudotumor cerebri (benign intracranial hypertension) during treatment of children with asthma by adrenal steroids; report of three cases. *Pediatrics*. 1959;23(6):1143–1151
9. Kelly HW, Sternberg AL, Lescher R, et al; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367(10):904–912
10. Blodgett FM, Burgin L, Iezzoni D, Gribetz D, Talbot NB. Effects of prolonged cortisone therapy on the statural growth, skeletal maturation and metabolic status of children. *N Engl J Med*. 1956;254(14):636–641
11. Avioli LV. Glucocorticoid effects on statural growth. *Br J Rheumatol*. 1993;32(suppl 2):27–30
12. Zada G, Tirosh A, Kaiser UB, Laws ER, Woodmansee WW. Cushing's disease and idiopathic intracranial hypertension: case report and review of underlying pathophysiological mechanisms. *J Clin Endocrinol Metab*. 2010;95(11):4850–4854
13. Liu GT, Glaser JS, Schatz NJ. High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri. *Am J Ophthalmol*. 1994;118(1):88–96
14. Morris DJ, Latif SA, Hardy MP, Brem AS. Endogenous inhibitors (GALFs) of 11beta-hydroxysteroid dehydrogenase isoforms 1 and 2: derivatives of adrenally produced corticosterone and cortisol. *J Steroid Biochem Mol Biol*. 2007;104(3-5):161–168
15. Schaffner TJ, Skoner DP. Ciclesonide: a safe and effective inhaled corticosteroid for the treatment of asthma. *J Asthma Allergy*. 2009;2:25–32

Presumed Pseudotumor Cerebri Syndrome After Withdrawal of Inhaled Glucocorticoids

Young Joon Kwon, Julian L. Allen, Grant T. Liu and Shana E. McCormack
Pediatrics 2016;137;

DOI: 10.1542/peds.2015-2091 originally published online May 17, 2016;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/137/6/e20152091>

References

This article cites 15 articles, 2 of which you can access for free at:
<http://pediatrics.aappublications.org/content/137/6/e20152091.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Ophthalmology
http://classic.pediatrics.aappublications.org/cgi/collection/ophthalmology_sub
Allergy/Immunology
http://classic.pediatrics.aappublications.org/cgi/collection/allergy:immunology_sub
Asthma
http://classic.pediatrics.aappublications.org/cgi/collection/asthma_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<https://shop.aap.org/licensing-permissions/>

Reprints

Information about ordering reprints can be found online:
<http://classic.pediatrics.aappublications.org/content/reprints>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Presumed Pseudotumor Cerebri Syndrome After Withdrawal of Inhaled Glucocorticoids

Young Joon Kwon, Julian L. Allen, Grant T. Liu and Shana E. McCormack
Pediatrics 2016;137;

DOI: 10.1542/peds.2015-2091 originally published online May 17, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/137/6/e20152091>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

