

Association of Adrenal Insufficiency With Pediatric Pseudotumor Cerebri Syndrome

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[+ Supplemental content](#)

IMPORTANCE Pediatric pseudotumor cerebri syndrome pathophysiology is complex and not well delineated. Therefore, it is important to identify potential contributors or targets underlying the primary pathogenesis for its development.

OBJECTIVE To report cases highlighting the association of pediatric pseudotumor cerebri syndrome with adrenal insufficiency.

DESIGN, SETTING, AND PARTICIPANTS This noncontrolled, observational case series included pediatric patients diagnosed with pseudotumor cerebri syndrome and adrenal insufficiency at an urban academic children's hospital in Houston, Texas, from June 2015 to October 2019.

MAIN OUTCOMES AND MEASURES Monitoring optic nerve edema by clinical examination, fundus photography, and optical coherence tomography images of the optic nerve.

RESULTS Data were collected from 5 pediatric patients (age range, 5-10 years) diagnosed with pseudotumor cerebri syndrome and adrenal insufficiency. One was a girl; all were White and prepubertal. Three patients had unrecognized glucocorticoid exposure. All patients had bilateral optic nerve edema that was initially treated with acetazolamide or topiramate, but cortisol functional testing by either 8 AM cortisol or cosyntropin stimulation tests revealed a diagnosis of central adrenal insufficiency. Treatment with physiological doses of hydrocortisone resulted in resolution of optic nerve edema and clinical symptoms of pseudotumor cerebri syndrome, as well as a shorter time receiving medical therapy.

CONCLUSIONS AND RELEVANCE In this case series, adrenal insufficiency was associated with both primary and secondary prepubertal pediatric pseudotumor cerebri syndrome. As a potential target specific to causative mechanism, physiologic hydrocortisone therapy resolved the condition. To date, there remains a global unawareness among clinicians about the suppressive outcome that glucocorticoids may have on the developing hypothalamic-pituitary-adrenal axis, resulting in adrenal insufficiency and so-called episodic pseudotumor cerebri syndrome in young children. Ophthalmologists and pediatric subspecialists should implement cortisol testing via either 8 AM cortisol or cosyntropin stimulation tests at initial evaluation of all children with pseudotumor cerebri syndrome and risk factors for adrenal insufficiency, no predisposing causes, or nonresponse to conventional treatment. Further management and treatment should be in combination with ophthalmology and endocrine services.

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Pseudotumor cerebri syndrome (PTCS) is characterized by elevated intracranial pressure (ICP), relatively normal neuroimaging results, and normal cerebrospinal fluid panel results.¹ The classic ocular finding of PTCS is papilledema. Two distinct criteria for the diagnosis of PTCS exist: the modified Dandy criteria, which uses a threshold lumbar puncture opening pressure (OP) greater than 25 cm H₂O, and the revised PTCS criteria, which uses an OP greater than 28 cm H₂O (>25 cm H₂O in children who are sedated or nonobese).^{1,2}

The presence of PTCS in adults and children who are postpubertal is linked to female sex and obesity; in younger children who are prepubertal, these factors are not as relevant,³⁻⁶ suggesting puberty is a central factor in distinguishing the pathophysiology of pediatric PTCS.⁷ A neuroendocrine model of PTCS with association with the hypothalamic-pituitary-adrenal axis (HPAA) has been proposed.^{8,9} However, no cause-and-effect association with adrenal insufficiency (AI) has been established. We describe pediatric PTCS cases with papilledema and cortisol testing consistent with central AI.

Methods

The study is compliant with all existing regulations; written informed consent was obtained from patients' parents, as well as ethical approval from the Baylor College of Medicine institutional review board. All patients were referred to Texas Children's Hospital in Houston with optic nerve edema between June 2015 and October 2019, diagnosed with PTCS using existing criteria,¹ and followed up with ocular examinations and optical coherence tomography imaging (eMethods in the Supplement).¹⁰ Because of concerns of glucocorticoid (GC) withdrawal and/or the inability to resolve chronic PTCS in an otherwise healthy child, cortisol testing was longitudinally obtained (eMethods in the Supplement). Adrenal insufficiency was defined as an 8 AM cortisol test result of less than 6 µg/dL (to convert to nanomoles per liter, multiply by 27.588) or a peak cortisol level less than 17 µg/dL after a 1-µg cosyntropin stimulation (low-dose Synacthen test [LDST]); normal functioning was defined as an 8 AM cortisol level greater than 13 µg/dL or a peak cortisol level greater than 20 µg/dL.¹¹ Each case was initially treated with acetazolamide or topiramate; physiologic hydrocortisone therapy (6-9 mg/m²/d) was initiated with AI diagnosis.¹²

Cases are presented individually. Mean values were calculated without software. No statistical software was used for data analysis.

Results

Five pediatric cases, including 1 girl, presented with low-grade papilledema without visual acuity loss. All 5 were White and did not have obesity. Diagnosis of definite PTCS with papilledema was consistent with the revised PTCS criteria, with exception of the patient with case 1, who was considered to

Key Points

Questions Is there an association between adrenal insufficiency and pediatric pseudotumor cerebri syndrome?

Findings In this case series, 5 children who were prepubertal, were nonobese, and had pseudotumor cerebri syndrome and optic nerve edema were found to have abnormal cortisol function consistent with adrenal insufficiency. Initiation of physiologic hydrocortisone to treat adrenal insufficiency resulted in the resolution of clinical pseudotumor cerebri syndrome symptoms and optic nerve edema and a shorter duration of conventional medical therapy.

Meaning Pseudotumor cerebri syndrome is associated with hypocortisolism in the prepubertal pediatric population; identifying risk factors for adrenal insufficiency (exogenous glucocorticoid use), obtaining cortisol testing in the initial workup, and treatment based on causative mechanism may lead to improved outcomes.

have probable PTCS (Table). The following are case details (eMethods and eTable in the Supplement).

Case 1

An 8-year-old boy with a history of asthma, allergic rhinitis, eczema, and recent headaches presented with bilateral optic nerve edema. A PTCS workup demonstrated a partial empty sella and an OP of 24 cm H₂O. Four months prior, he had discontinued intranasal GC and reduced his use of a beclomethasone inhaler. Administration of acetazolamide improved but did not resolve his papilledema (Figure). One year later, he had a normal LDST result. Inhaled beclomethasone was discontinued 2 years after the diagnosis, worsening his papilledema despite acetazolamide use. An 8 AM cortisol test result was consistent with AI, and hydrocortisone was initiated. In 8 weeks, his papilledema resolved, and his acetazolamide was titrated to discontinuation.

Case 2

A 5-year-old boy with a history of eczema presented with bilateral optic nerve edema coinciding with the completion of 3 months of triamcinolone cream use. A PTCS evaluation included normal neuroimaging results, with a partially empty sella and an elevated OP. His LDST result was abnormal with no other pituitary deficiencies, and treatment was deferred. He received topiramate (because of an acetazolamide intolerance), and his papilledema resolved in 2 months. Topiramate was tapered off after 15 months, with papilledema recurring 3 months later. After an 8 AM cortisol test diagnosing AI, hydrocortisone was started. Within 8 weeks, the patient's papilledema resolved, and topiramate was discontinued with no recurrence (eFigure 1 in the Supplement).

Case 3

A 4-year-old boy with esotropia and headaches presented with bilateral optic nerve edema and had an assessment with findings consistent with PTCS. Acetazolamide was started, but symptoms worsened despite increasing dosages, with repeated lumbar puncture OPs greater than 45 cm H₂O. Meges-

Table. Clinical Features of Pediatric Pseudotumor Cerebri Syndrome Case Series

Characteristic	Case				
	1	2	3	4	5
Sex	Male	Male	Male	Female	Male
Ethnicity	Non-Hispanic White	Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White
Age at diagnosis, y	8	5	4	5	10
BMI at diagnosis, z score	1.16	-0.62	-1.37	-0.43	0.22
Pubertal (Tanner) stage	1	1	1	1	1
Risk factor	Beclomethasone dipropionate inhaler; mometasone nasal spray	Topical triamcinolone for eczematous lesions	Megestrol acetate	None	None
Presenting symptoms	Intermittent headaches	Headaches, nausea, and emesis	Cranial nerve VI palsy, headache, nausea, and emesis	None	Headache and vision changes
Pseudotumor cerebri syndrome diagnostic testing					
Opening pressure, cm H ₂ O	24	32	>45 ^a	34 ^a	28
Magnetic resonance imaging brain result	Normal with slight posterior bilateral ocular flattening; partial empty sella	Normal with partial empty sella	Normal with bilateral flattening of posterior globes; inversion of optic nerve heads	Normal	Normal
Modified Frisen grade, OD/OS	+2/+2	+2/+2	+1/+1	+2/+2	+1-2/+1-2
Pharmacologic treatment					
Maximum acetazolamide dose, mg/kg/d	14	13.4	88.2	20.3	24.2
Maximum topiramate dose, mg/kg/d	NA	30	NA	NA	NA
Cortisol output on diagnostic cortisol testing					
8 AM, µg/dL	5.8	4.1	<0.2	3.4	4.3
Peak 1-µg cosyntropin stimulation, µg/dL	NA	NA	1.9	16.1	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

SI conversion factors: To convert cortisol to nmol/L, multiply by 27.588.

^a While sedated; modified Frisen score, 0 to 5.

trol had notably been discontinued 3 weeks prior. An 8 AM cortisol test result and an LDST result confirmed AI. After hydrocortisone therapy, PTCS symptoms resolved, and acetazolamide was discontinued within 4 months. Eventually, hydrocortisone was discontinued without recurrence.

Case 4

A 5-year-old girl was referred for optic nerve swelling. Her evaluation confirmed PTCS, and despite acetazolamide use, her mild papilledema continued. After 16 months, an 8 AM cortisol test and LDST results confirmed AI. Following initiation of hydrocortisone, her papilledema resolved (eFigure 2 in the Supplement).

Case 5

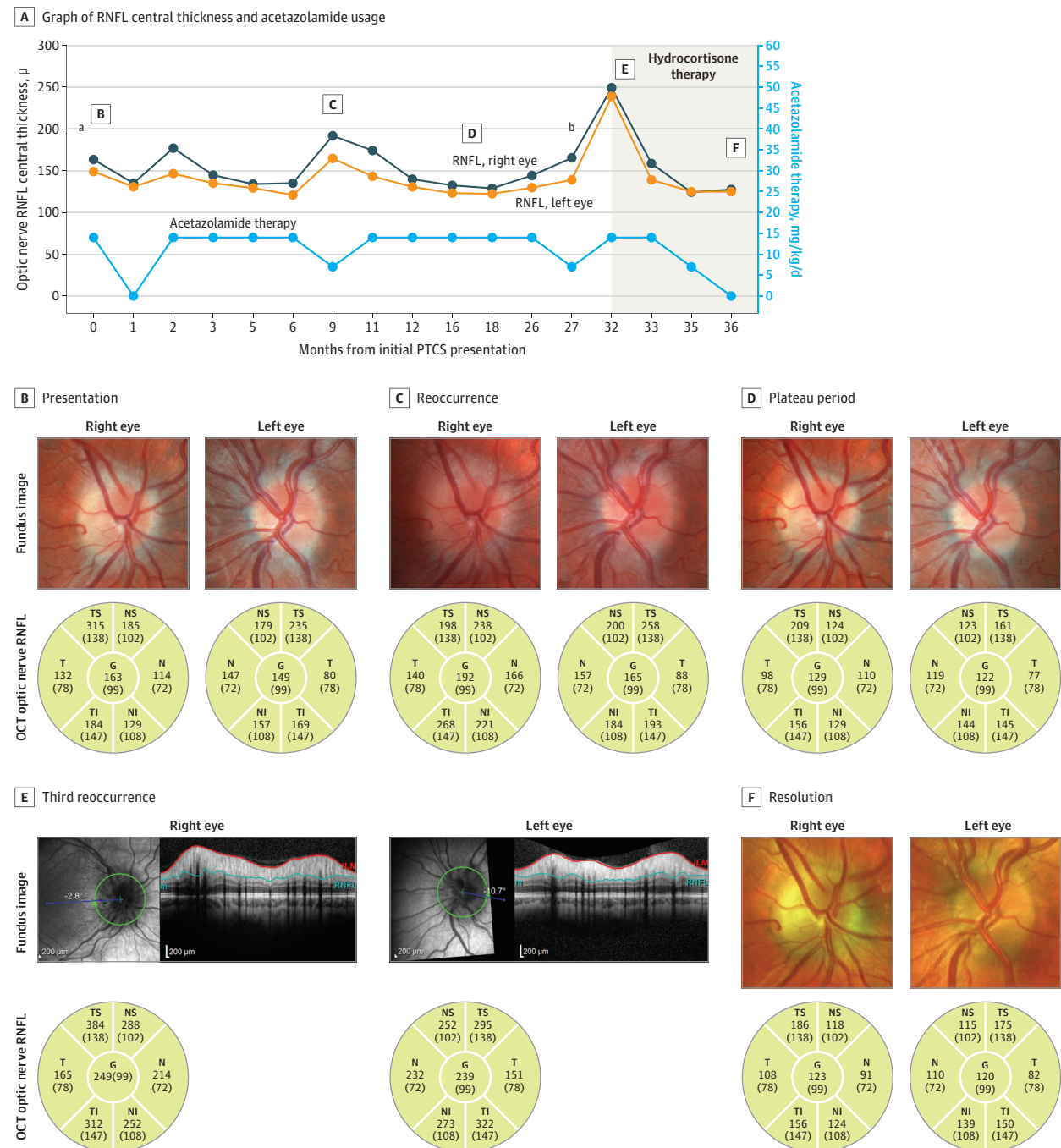
A 10-year-old boy with short stature presented with bilateral optic nerve edema and had workup results consistent with PTCS. Despite a 2-year course of fluctuating acetazolamide dosages, mild papilledema persisted. Endocrine evaluation showed low 8 AM cortisol and thyroid function test results, consistent with AI and central hypothyroidism. Following hormonal therapy, acetazolamide was discontinued in 4 months with papilledema resolution and no recurrence.

Discussion

To our knowledge, this is the first case series reporting physiologic and anatomic findings associated with AI and PTCS, demonstrating that cortisol physiology is either a primary contributor or modulator of PTCS. This study provides clinical evidence supporting a neuroendocrine hypothesis underlying the pathogenesis of pediatric PTCS: inherent defects of the HPA axis result in low basal cortisol production with reduced cerebrospinal fluid reabsorption and elevated ICP.^{8,9}

This case series matches the prepubertal pediatric PTCS subgroup in terms of age, a lower preponderance of girls, subclinical presentation, and a low-grade papilledema.³⁻⁶ All cases were consistent with the modified Dandy criteria except case 1; under the revised PTCS criteria, both case 1 and case 5 would be considered probable because of subthreshold OPs.^{1,2} Case 1 highlights the cyclical nature of GC withdrawal, papilledema, and then subsequent recovery. This case describes a distinctive clinical entity of episodic PTCS, in which incidental GC exposure and withdrawal cause mild AI with transient PTCS, depending on an individual's HPA axis capacity to recover. The postrecovery period lasts until a subsequent GC

Figure. Case 1 of Episodic Pseudotumor Cerebri Syndrome, With a Beclomethasone Inhaler



A, Summary of optic nerve edema and thickness by serial fundus and optical coherence tomography (OCT) from presentation and subsequent follow-up examinations. The patient's inhaler use was decreased prior to presentation (*). At month 18, he had a low-dose Synacthen (peak cortisol) test (22.4 µg/dL [to convert to nanomoles per liter, multiply by 27.588]) and endocrine workup with negative results; at month 27, a reduction in steroid inhaler use (†); at month 32, an 8 AM cortisol test result of 5.8 µg/dL that confirmed adrenal insufficiency, for

which hydrocortisone therapy was initiated. B-F, Specific points (corresponding to the letters in A) showing fundus and OCT images, with respective global mean thickness of the optic nerve peripapillary retinal nerve fiber layer (RNFL) in micrometers. Heidelberg-Spectralis OCT normative values for peripapillary RNFL global mean thickness for patients 4 to 18 years old are 104 ± 8.5 µm. G indicates global (360°); N, nasal; NI nasal inferior; NS, nasal superior; T, temporal; TI, temporal inferior; TS, temporal superior.

exposure or withdrawal, appearing as episodic bouts of PTCS. Depending on the timing of one's ocular examination, true optic nerve edema with a normal OP may be identified, deviat-

ing from conventional PTCS criteria, leading to a misdiagnosis of pseudopapilledema or optic nerve drusen. This intermittent insult may occur in patients with allergy or atopy

with seasonal patterns of GC use, sickness, or age-sensitive HPA characteristics, explaining pediatric PTCS with subclinical symptoms.¹³ A clear public safety issue is the unrecognized use of inhaled, topical, and systemic GC in young children. In the US, long-term inhaled GC use occurs in about 2.5 million children with asthma; atopy affects 1 in 5 children, causing widespread GC use.¹⁴

Aside from GC exposure, cases 1 and 2 involved partial empty sellae without other endocrinopathies, raising a causality dilemma with AI and elevated ICP. While unlikely that elevated ICP directly induces pituitary compression with isolated AI, given that healthy populations have empty sellae without hypopituitarism, it may still contribute.¹⁵ Unfortunately, follow-up investigations were deferred.

Case 3 describes fulminant PTCS attributable to exogenous GC withdrawal and the most severe AI by testing. This patient's refractory ICP elevation despite maximal acetazolamide use would commonly lead to surgical intervention but resolved with physiologic hydrocortisone therapy.

Primary and secondary causative mechanisms of PTCS without GC exposure also appear to be linked to AI. All patients in this study had low basal 8 AM cortisol levels. Basal cortisol production variations could precipitate PTCS development, accounting for idiopathic causes (as in case 4) and other, secondary causative mechanisms (as in case 5). Moreover, if basal function is compromised with a normal capacity to stimulate cortisol (as in 2 of 5 cases in this study), PTCS may develop without symptoms of overt AI.

Diagnosis of AI is challenging; many factors affect cortisol testing results and patterns (eMethods in the [Supple-](#)

ment). We recommend AI evaluation with either an 8 AM cortisol test or a LDST on initial evaluation of all children with PTCS and AI risk factors, no predisposing causes, or nonresponse to conventional treatment. Further management and treatment should be in combination with ophthalmology and endocrine services.

Strengths

Strengths include establishing biological plausibility for the neuroendocrine hypothesis and reporting sentinel events of unrecognized exposure associations. This study may facilitate new evaluation or treatment outcomes for pediatric PTCS.

Limitations

Limitations are inherent to the case series design. Possible confounders include a high male preponderance, alternative mechanism to PTCS resolution, and other underlying medical or genetic conditions affecting hypocortisolism or PTCS development.

Conclusions

This study provides clinical evidence for a neuroendocrine hypothesis involving the HPA in patients with prepubertal pediatric PTCS and highlights the association of exogenous GC with development of AI in episodic PTCS. It offers new recommendations to identify AI in PTCS and a causative mechanism-targeted treatment for improved outcomes.

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