

2018

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## Recommended Citation

Kanner LA, Klein J, Gaffar M, Pomeranz H, Frank G. New-Onset Isolated Asymptomatic Papilledema in Two Patients Treated With Recombinant Growth Hormone. . 2018 Jan 01; 57(4):Article 4682 [ p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/4682>. Free full text article.

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Published in final edited form as:

*Clin Pediatr (Phila)*. 2018 April ; 57(4): 471–474. doi:10.1177/0009922817698808.

## New-Onset Isolated Asymptomatic Papilledema in Two Patients Treated With Recombinant Growth Hormone

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### Background

Growth hormone therapy is a well-recognized risk factor for the development of idiopathic intracranial hypertension (IIH). IIH, also known as pseudotumor cerebri (PTC), is a rare complication of growth hormone (GH) treatment. In the Kabi International Growth Hormone Study (KIGS) of 2007, the incidence of IIH as an adverse event during recombinant human growth hormone (rhGH) replacement for idiopathic growth hormone deficiency (GHD) was 13/100,000 treatment years.<sup>1</sup> IIH developed anywhere between 2 weeks to 8 years after initiating GH therapy at a dose of 0.18 to 0.33 mg/kg/wk.<sup>1,2</sup> IIH is characterized by elevated intracranial pressure, papilledema, and symptoms including headache, vision changes, nausea, and vomiting.

Herein we present 2 cases of new onset, asymptomatic papilledema in patients receiving GH therapy for GHD.

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#### Author Contributions

LAK was responsible for manuscript conception and design, data collection, analysis and interpretation and drafting of the manuscript. JK contributed to data collection and drafting of the manuscript. MG and HP contributed to study concept and critically revised the manuscript. FG contributed to manuscript conception, data analysis and interpretation and critically revised the manuscript. All authors were involved in these patients' care and approved the final manuscript.

#### Authors' Note

Institutional review board (IRB) approval not obtained as study met exempt status for IRB of North Shore–Long Island Jewish Health System but patient information has been de-identified per HIPAA standards.

#### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Case 1

The patient was an 11-year-old non-obese female with past medical history of attention deficit hyperactivity disorder who was being treated with Concerta 36 mg daily as well as intermittent Ritalin 10 mg daily. She was evaluated by her pediatrician for growth failure and resultant short stature. She was found to have GHD (peak GH on GH stimulation testing 5.32 ng/mL). Noncontrast magnetic resonance imaging (MRI) of the hypothalamic/pituitary region was normal. She was started on growth hormone 0.26 mg/kg/wk. Seven months into GH therapy, at a routine ophthalmology evaluation, she was found to have new-onset papilledema (Figure 1). This papilledema was not present on a previously documented ophthalmological examination 2 years prior. She had no symptoms of blurry vision, diplopia, headache, dizziness, nausea, or vomiting. She was referred to the emergency room for evaluation. Neurological exam showed no focal deficits and ophthalmologic exam again demonstrated bilateral papilledema. A lumbar puncture was performed and the opening pressure was 20.25 cm H<sub>2</sub>O and closing pressure of 17 cm H<sub>2</sub>O. Computed tomography of the head, MRI of the orbit, and MRI/MR angiography of the brain were normal. MR venography of the brain showed focal narrowing within the distal transverse sinus bilaterally, but no evidence of venous sinus thrombosis. Laboratory work, including comprehensive metabolic panel, thyroid function tests, complete blood count and cerebral spinal fluid studies, lyme titers, and mycoplasma titers, were normal. She was evaluated by a neuro-ophthalmologist who found superior temporal and inferior nasal arcuate visual field defects in the left eye and slight enlargement of the blind spot in the right eye (Figure 2). The patient's GH therapy was discontinued and she was started on acetazolamide 90 mg thrice a day. At her 4-month follow-up appointment, improvement of visual field loss was noted. The patient followed up with neuro-ophthalmology 9 months after GH therapy was discontinued at which point her visual field abnormalities had corrected. GH therapy was resumed and ophthalmology follow-up was planned.

## Case 2

The patient was a 5-year-old non-obese male with a past medical history significant for unilateral left amblyopia, which had been routinely followed by an ophthalmologist. He was evaluated by pediatric endocrinology due to growth failure and short stature with longitudinal growth at the <3rd percentile and was found to have GHD (peak GH on GH stimulation testing 6.69 ng/mL). Noncontrast MRI of the hypothalamic/pituitary region was normal. He was started on GH at 0.284 mg/kg/wk. Seven months into GH therapy, at a routine ophthalmology follow-up for his amblyopia, he was found to have new-onset papilledema. He had no symptoms of blurry vision, diplopia, dizziness, headache, nausea, or vomiting. GH therapy was discontinued. He discontinued rhGH and underwent continued ophthalmologic follow-up. At 1 month following his diagnosis, his examination, although improved, had not completely normalized. Evaluation by neuro-ophthalmology was planned.

## Discussion

IIH is a well-recognized side effect of recombinant GH. In 1985, rhGH was introduced as a viable and safe alternative to human pituitary GH. Initial cases of IIH associated with rhGH

treatment were reported in 1986 and were thought to be due to the progressive trend in higher and more frequent doses of GH during treatment. A 1993 letter to the *New England Journal of Medicine* by the Food and Drug Administration<sup>3,4</sup> discussed the link between rhGH and IIH with respect to 23 patients (22 children, 1 adult) who presented with headaches and papilledema during treatment with rhGH at doses between 0.21 and 0.56 mg/kg/wk. Of these 22 children, therapy was initiated for GH deficiency or short stature from chronic renal failure, Prader-Willi syndrome, Turner syndrome, or delayed puberty. Discontinuation of rhGH resulted in the resolution of papilledema in all but one patient. The risk of visual deterioration, especially with continued rhGH treatment, is significant and some patients experience a chronic disabling course for many years.<sup>5-7</sup>

One of the cardinal physical findings of IIH is papilledema, noted on examination by swelling of the optic disc, venous engorgement and loss of venous pulsation, as well as blurring of the optic margins. Papilledema in cases of IIH is typically bilateral in nature, though some cases may have asymmetric or unilateral findings. Papilledema is generally not associated with marked loss of visual acuity or visual fields unless it has been present for a considerable time.<sup>8,9</sup> Chronic optic nerve edema can cause optic nerve pallor, color vision deficiency, persistent visual field changes, and significant vision loss.

We report 2 patients presenting with asymptomatic bilateral papilledema discovered during routine ophthalmologic follow-up in children being treated with rhGH for idiopathic GH deficiency. While the first patient did not have an increased opening pressure, she had objective findings of papilledema and visual field abnormalities that resolved with discontinuation of the GH therapy. The second patient is undergoing continued evaluation currently for IIH. Treatment with rhGH had been started in both cases 7 months prior to discovery of papilledema. The doses of rhGH were between 0.26 and 0.284 mg/kg/wk. Neither patient had risk factors associated with IIH or papilledema.

These cases raise questions of both the incidence and the natural history of rhGH-related IIH. In children with rhGH-related IIH, the spectrum of presenting signs and symptoms may be variable, nonspecific, and broader than once thought. These cases demonstrate that ophthalmologic findings of papilledema may precede signs and symptoms of increased intracranial pressure. Visual loss is an important endpoint in the natural history of untreated IIH and papilledema; temporary discontinuation of rhGH treatment with close monitoring of resumption of normal vision is crucial in ongoing follow up for those diagnosed with the condition. Routine ophthalmic screening beginning early in rhGH treatment has been recommended for years,<sup>10</sup> though it is not yet the accepted standard. Early screening may reduce morbidity associated with growth hormone induced IIH due to early recognition.<sup>2</sup>

It is important to recognize that optic nerve hypoplasia and other congenital disc anomalies may be associated with GHD and can cause pseudopapilledema.<sup>11</sup> Thus, optic disc abnormality during GH therapy may reflect pseudopapilledema, a benign condition, and not IIH. Nonetheless, routine screening would likely find these abnormalities prior to rhGH therapy onset, thus excluding them from consideration of true rhGH-related papilledema and IIH. Both our cases had complete ophthalmologic evaluation demonstrating normal optic

nerves prior to starting GH therapy. The first was seen 2 years prior for a failed vision screening; the second was followed for amblyopia.

Asymptomatic IHH has been described by Francois et al<sup>12</sup> who described an 11-year-old male with GH deficiency and empty sella syndrome with presentation of IHH after 6 months of treatment initiation of GH therapy, with later resumption of GH therapy after resolution with no further papilledema. In addition, Besch et al<sup>13</sup> described 2 prepubertal females on rhGH for growth failure who developed IHH presenting only as visual changes without headaches, nausea, or vomiting at 3 and 18 months. Neither patient was obese nor had renal insufficiency, both known risk factors for IHH. The diagnosis of IHH was made based on ophthalmologic examination, elevated cerebrospinal fluid opening pressure, and normal central nervous system imaging.

Two factors are noteworthy about patients. In both instances, the papilledema was asymptomatic and found incidentally. Second, the time to resolution was long. While most patients reported in the literature have resolution of papilledema and symptoms within days to weeks of discontinuation of growth hormone therapy, our first patient required acetazolamide for resolution of papilledema and recovery of loss of visual field took several months. This suggests that the pathogenesis of asymptomatic papilledema during GH therapy may be different from the well-described IHH associated with GH therapy.

While IHH is a rare complication of rhGH treatment, it appears that papilledema may present prior to the traditional signs and symptoms of increased intracranial pressure (headaches, nausea/vomiting, visual changes). Routine ophthalmological screening of children with idiopathic GHD should therefore be considered both before and during treatment with rhGH.

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## Acknowledgments

We would like to thank the Division of Pediatric Endocrinology and Department of Ophthalmology at NorthWell Health.

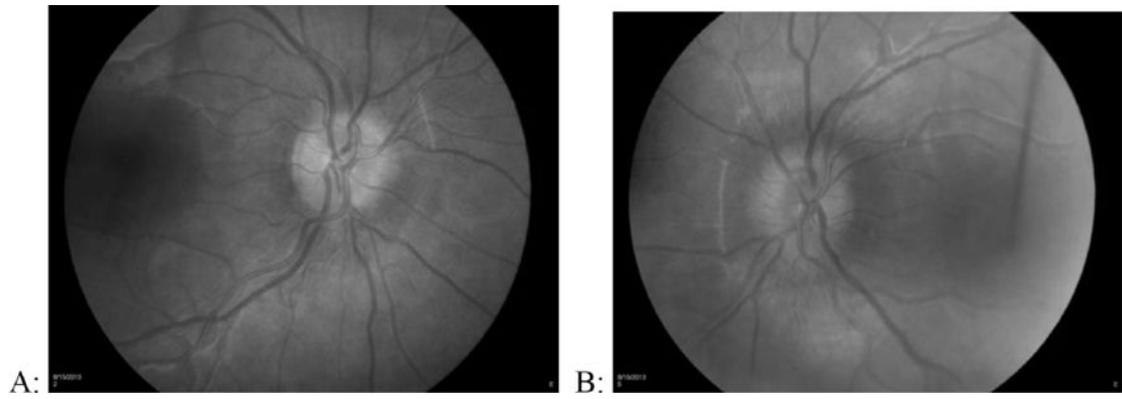
Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr Kanner is currently funded by National Institutes of Health Grant T32 DK077586.

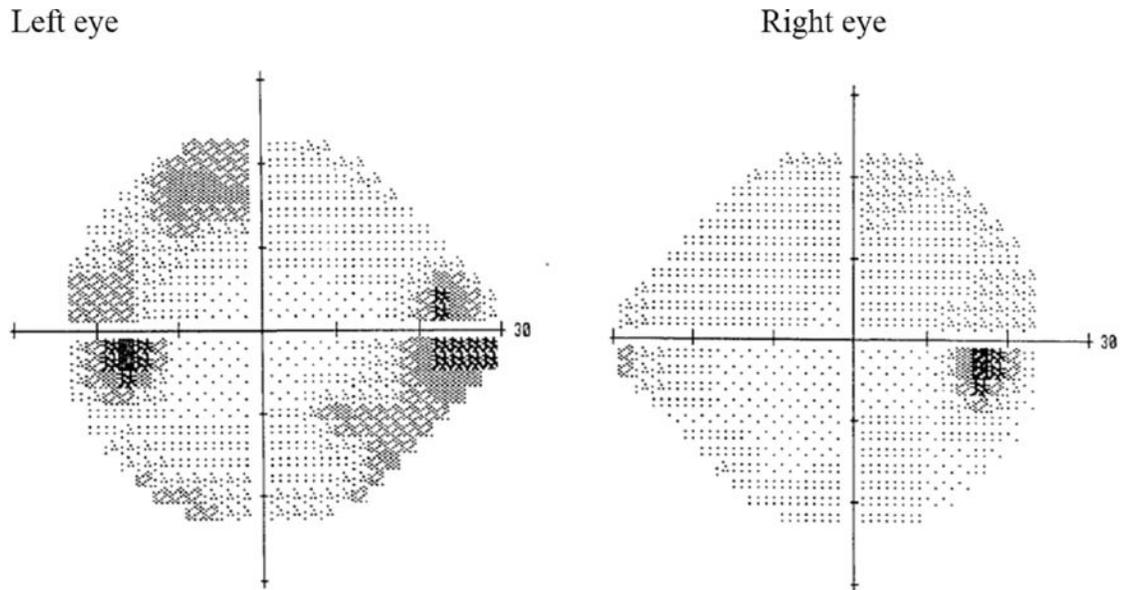
## References

1. Wilton, P. Adverse events reported in KIGS. In: Ranke, M., Reiter, E., editors. Growth Hormone Therapy in Pediatrics—20 Years of KIGS. Basel, Switzerland: Karger; 2007. p. 432-441.
2. Obinata K, Kamata A, Kinoshita K, et al. Prolonged intracranial hypertension after recombinant growth hormone therapy due to impaired CSF absorption. *Clin Pediatr Endocrinol*. 2010; 19:39-44. [PubMed: 23926377]
3. Malozowski S, Tanner LA, Wysowski DK, Fleming GA, Stadel BV. Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr*. 1995; 126:996-999. [PubMed: 7776116]
4. Wyatt D. Lessons from the national cooperative growth study. *Eur J Endocrinol*. 2004; 151(suppl 1):S55-S59. [PubMed: 15339245]
5. Koller EA, Stadel BV, Malozowski SN. Papilledema in 15 renally compromised patients treated with growth hormone. *Pediatr Nephrol*. 1997; 11:451-454. [PubMed: 9260244]

6. Rogers AH, Rogers GL, Bremer DL, McGregor ML. Pseudotumor cerebri in children receiving recombinant human growth hormone. *Ophthalmology*. 1999; 106:1186–1189. [PubMed: 10366091]
7. Vischi A, Guerriero S, Giampoli G, Lorusso V, Sborgia G. Delayed onset of pseudotumor cerebri syndrome 7 years after starting human recombinant growth hormone treatment. *Eur J ophthalmol*. 2006; 16:178–180. [PubMed: 16496267]
8. Bedell AJ. Papilledema without increased intracranial pressure. *Trans Am Ophthalmol Soc*. 1941; 39:242–261. [PubMed: 16693253]
9. Lordereau-Richard I, Roger M, Chaussain JL. Transient bilateral papilloedema in a 10-year-old boy treated with recombinant insulin-like growth factor I for growth hormone receptor deficiency. *Acta Paediatr Suppl*. 1994; 399:152. [PubMed: 7949605]
10. Crock PA, McKenzie JD, Nicoll AM, et al. Benign intracranial hypertension and recombinant growth hormone therapy in Australia and New Zealand. *Acta Paediatr*. 1998; 87:381–386. [PubMed: 9628291]
11. Collett-Solberg PF, Liu GT, Satin-Smith M, Katz LL, Moshang T Jr. Pseudopapilledema and congenital disc anomalies in growth hormone deficiency. *J Pediatr Endocrinol & Metab*. 1998; 11:261–265. [PubMed: 9642641]
12. Francois I, Casteels I, Silberstein J, Casaer P, de Zegher F. Empty sella, growth hormone deficiency and pseudotumour cerebri: effect of initiation, withdrawal and resumption of growth hormone therapy. *Eur J Pediatr*. 1997; 156:69–70. [PubMed: 9007496]
13. Besch D, Makowski C, Steinborn MM, Bonfig W, Sadowski B. Visual loss without headache in children with pseudotumor cerebri and growth hormone treatment. *Neuropediatrics*. 2013; 44:203–207. [PubMed: 23275258]
14. Skau M, Sander B, Milea D, Jensen R. Disease activity in idiopathic intracranial hypertension: a 3-month follow-up study. *J Neurol*. 2011; 258:277–283. [PubMed: 20853113]



**Figure 1.** Bilateral papilledema as noted on dilated retinal exam. (A) Right eye retinal examination showing significant papilledema. (B) Left eye retinal examination with notable diffuse papilledema.



**Figure 2.** Visual field losses documented for case 1 via Humphrey 24-2 visual field: Slight enlargement of the blind spot and a slight nasal arcuate visual field defect in the right eye. Denser superotemporal and infernasal arcuate defects in the left eye.