Established Facts

• Intracranial hypertension (IH) is a poorly understood disease, with multiple known risk factors including female sex, obesity, and various endocrine medications such as recombinant growth hormone and levothyroxine, especially during the initial stages of treatment.
• IH can present with not only symptoms of headache and (transient) vision loss but also papilledema due to increased intracranial pressure.

Novel Insights

• Graves’ disease may be a rare cause of increased intracranial pressure, even in young children.
• Recurrent intracranial hypertension (IH) may also unexpectedly occur in patients in the chronic phase of Graves’ disease who have stable thyroid function tests on a fixed dose of thiamazole.
• Pediatric endocrinologists should be alert to the presence of new-onset headaches and blurred vision in any Graves’ disease patient, but IH may also present asymptptomatically and be diagnosed during routine ophthalmologic screening for Graves’ exophthalmopathy.
• A low index of suspicion should be kept for PIH in any young child with Graves’ disease, given the potential long-term vision disturbances associated with a delay in diagnosis.

Keywords
Graves’ disease · Pseudotumor cerebri · Idiopathic intracranial hypertension · Benign intracranial hypertension · Child

Abstract

Introduction: Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure without an evident cause. Obesity and the female sex have been recognized as risk factors for the development of this syndrome. Until now, Graves’ disease has only been described in the literature as the probable cause of IIH in 7 patients. This re-
Recurrent Intracranial Hypertension and Graves’ Disease

Case Presentation: A 21-month-old girl presented with progressive symptoms of poor weight gain and bilateral exophthalmos. She also experienced difficulty sleeping, diarrhea multiple times per day, irritability, and heat intolerance. Laboratory investigation showed elevated free T4, fully suppressed TSH, and elevated anti-TSH antibodies, consistent with a diagnosis of new-onset Graves’ disease. She was successfully treated with monotherapy thiamazole, titrated to the lowest possible dose of 1.25 mg once daily with normalization of thyroid function tests within 3 months of treatment initiation. After 18 months of treatment, her condition unexpectedly deteriorated as papilledema and slight esotropia were found at a routine checkup. An MRI and lumbar puncture showed increased intracranial pressure, but no underlying anatomical cause for the IH was found. Acetazolamide therapy was started, and papilledema in both eyes resolved within weeks. Unfortunately, papilledema has recurred several times over the following 2 years when attempts were made to decrease the acetazolamide dose. Discussion/Conclusion: This case report is the first to describe a very young patient who developed significant IH in the chronic stage of Graves’ disease. IH development seemed to be related to the progression of the Graves’ ophthalmopathy, rather than initiation of thiamazole therapy or fluctuations in serum fT4 levels.

Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri or benign intracranial hypertension (IH), is a neurological diagnosis “per exclusionem” characterized by increased intracranial pressure without evident etiology [1]. Symptoms can include (hordocular) headache and edema of the optic nerve, which can result in (transient) vision loss. In pediatric patients, however, IIH can manifest through a more varied set of symptoms, including nausea and vomiting and sometimes even without headache complaints or any symptoms at all [2]. The syndrome occurs predominantly in obese adolescent women (US incidence 0.9–1.07 per 100,000 in adults) and to a lesser extent in pediatric patients (0.63 per 100,000 in children) [3]. Predominantly IIH is reported in adolescents between 12 and 15 years, but in infants, it is quite uncommon [4, 5]. It is suggested to be influenced by various factors including increased levels of aldosterone, estrogen, and retinoic acid (all associated with obesity) [6, 7]. Other secondary causes of IH include medication (e.g., certain antibiotics, vitamin A, hormones, or withdrawal from corticosteroids), cerebral venous abnormalities, and various endocrine disorders (e.g., Addison’s disease and hyperparathyroidism) [8]. Until now, Graves’ disease has only been attributed to the development of intracranial IH in 7 patients [9–14] and was first described by Roos et al. [13] in 1985. This case report describes a young child with Graves’ disease who developed IH under chronic thiamazole treatment.

Case Report

A 21-month-old child without prior medical history presented at the outpatient clinic of the Department of Endocrinology with a poor weight-for-height score (SDS –2.2, Fig. 1a), increased height-for-age score (SDS +2.7, target height +1.1 SDS), and bilateral exophthalmos (Hertel 15/15 mm on 105 mm in July 2019, normal value would be below 14 [15]). In addition, her parents stated that she had difficulties sleeping, frequent diarrhea, irritability, frequent subfebrile temperature, and heat intolerance in the months preceding this visit. No family members had previously had any thyroid diseases, except for the paternal grandmother. Physical examination demonstrated no additional abnormalities apart from a benign cardiac (systolic) murmur. Further laboratory investigation showed an elevated free T4 of 83 pmol/L (ref 12–22 pmol/L), completely suppressed TSH <0.01 mU/L (ref 0.3–4.8 mU/L), and elevated anti-TSH receptor antibodies (EIA method) of 13 IU/L (ref <1.8 IU/L) and marginally elevated antithyroid peroxidase antibodies of 46 kU/L (ref <35 kU/L). These laboratory results in combination with the previously mentioned exophthalmos resulted in the diagnosis of Graves’ disease. Treatment with the thio-ureum derivative thiamazole was started at 5 mg once daily. In the months following the start of thiamazole, the exophthalmos, the various physical complaints, and laboratory results quickly normalized, and thiamazole was gradually reduced to a maintenance dose of 1.25 mg once daily with a stable thyroid function test (Fig. 1b). Thiamazole treatment did not lead to hives, rashes, or arthralgias at any point in time.

After 18 months of successful treatment, however, her condition deteriorated as exophthalmos, papilledema, and slight esotropia were found at a routine checkup visit. Figure 1c shows the optical coherence tomography scan of both eyes. An MRI of the brain showed a partially empty sella (Fig. 1d) as a secondary sign of increased intracranial pressure, and subsequent lumbar puncture confirmed an elevated intracranial pressure of 37 cm H2O. The combined results led to the diagnosis of IH, and acetazolamide therapy (30 mg/kg/day t.i.d.) was started. Since no other causes of IH, such as Chiari malformation [16] or cerebral venous sinus thrombosis [17], were found, a possible relation to Graves’ disease in this (now) three-year-old child on chronic thiamazole monotherapy could not be fully excluded. Papilledema in both eyes completely resolved within weeks, and acetazolamide therapy was stopped after 2 months. Unfortunately, papilledema recurred 2 months after acetazolamide therapy was stopped and has recurred several times over the past 2 years every time attempts have been made to taper the acetazolamide dose. Figure 1d displays the fT4 values and thiamazole dose in time.
Fig. 1. Graphical overview of the case report. a Weight (kg) versus height (cm) chart, showing poor weight gain. b Graphical display of the free T4 level (in blue, left axis scale), TSH level (in green, right axis scale), TSH receptor antibodies level (in yellow, right axis scale), thiamazole dose (in orange, right axis scale) over time, diagnosis of Graves’ disease (purple dot), and start of papilledema (red dot). c OCT showing bilateral papilledema. The upper two images show the OCT of both retinas and optical nerves with edema (indicated by the green circle). The middle two images represent the thickness of the 2 retinal layers: the retinal nerve filament layer (blue line) and internal limiting membrane (red line). The lower panels indicate the thickness of the retinal nerve filament layer at various locations of the retina. The bold black line represents the actual measured layer, which is supposed to be in the green zone. d Sagittal T1-weighted MRI image, showing partially empty sella suggestive of increased intracranial pressure. *Right axis scale represents dose in milligram for thiamazol, mU/L for TSH, and IU/L for TSH receptor antibodies. OCT, optical coherence tomography.
Discussion/Conclusion

This case report adds to the scarce evidence of Graves' disease being a possible cause of recurrent IH. In addition, this is the first report to describe this rare combination in such a young patient (3 years old). As demonstrated by the normalized thyroid function tests after thiamazole treatment and the 1.5-year period between diagnosis of Graves' disease and start of clinical signs of PIH, PIH does not necessarily seem to be caused by rapid fluctuations in serum thyroid hormone levels during initiation of therapy or as an idiosyncratic side effect of thio-ureum derivative therapy in general. Rather, it seems to be related to the progression of the Graves' ophthalmopathy, which is also known to occur in euthyroid patients [18]. Interestingly, a previous report by Strickler and Pilon [12] suggested a causal relation between the use of levothyroxine sodium tablets and the development of IIH. It has been suggested that an altered endocrine-metabolic homeostasis might influence the pressure regulation of CSF, similar to previous reports, linking levothyroxine and recombinant GH therapy to abnormal rates of CSF production and reabsorption, thereby causing IIH, but the underlying pathophysiology remains poorly understood unfortunately [19].

In conclusion, this case report suggests Graves' disease might be a rare cause of PIH in children and adults, even during the chronic phase of Graves' disease with stable thyroid function tests. Many patients with pediatric GD, especially those with associated exophthalmos, will already be evaluated periodically by an ophthalmologist, but this may not be the case for all GD patients, especially if the degree of exophthalmos is mild. We believe that our case report provides an additional argument to use a low threshold for periodical ophthalmological screening in all pediatric GD patients with any degree of exophthalmos and also in asymptomatic patients that are well-controlled and beyond the first year of treatment.

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Statement of Ethics

Ethical approval of the local review board was not required; however, the patient and her parents provided written informed consent to publish this case report (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare regarding this subject.

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Author Contributions

F.A.V. wrote the first draft of the manuscript and figures. F.A.V., C.B., C.M.P., C.D.P.-S., and I.C.N. wrote and agreed upon the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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