

Brain Imaging in Pediatric Pseudotumor Cerebri Syndrome

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Abstract

Pseudotumor cerebri syndrome (PTCS) is a clinical entity of unclear etiology characterized by raised intracranial pressure but normal cerebrospinal fluid contents and no associated anomalies evident in the brain parenchyma. Idiopathic intracranial hypertension, which is the primary (idiopathic) form of PTCS, generally affects adult obese females of childbearing age. Pediatric PTCS has been reported in association with various potential comorbidities, including chronic medical illness, infections, endocrine disorders, and ingestion and/or withdrawal of some drugs. Clinical signs and symptoms of PTCS in children are heterogeneous, but they classically include headache, papilledema, and visual disturbances (e.g., diplopia and/or vision loss). An important criterion for diagnosing PTCS involves imaging. The role of computed tomography is useful to rule out some secondary causes of elevated increased intracranial pressure (e.g., hydrocephalus, hemorrhage, mass effect); magnetic resonance imaging and magnetic resonance venography are helpful in many diagnostic challenges and in the detection of subtle intracranial anomalies (e.g., isodense tumors, meningeal infiltrations, pathologies of posterior fossa, sinus venous thrombosis). In addition, magnetic resonance imaging is able to identify some secondary signs supportive of a diagnosis of PTCS, such as flattened posterior globe/sclera, empty sella, partially empty sella/decreased pituitary height, patulous optic nerve sheath, intraocular protrusion of optic nerve head, and enhanced and increased tortuosity of the optic nerve, though these are not specific. We briefly discuss the application of imaging in the assessment of pediatric PTCS patients.

Keywords

- ▶ magnetic resonance imaging
- ▶ idiopathic intracranial hypertension
- ▶ pseudotumor cerebri
- ▶ venography
- ▶ transverse sinus stenosis

Introduction

Pseudotumor cerebri syndrome (PTCS) is an umbrella term used for the constellation of symptoms caused by increased intracranial pressure (ICP) without hydrocephalus, space-occupying lesion, or anomalies of brain parenchyma and with a normal cerebrospinal fluid (CSF) composition.¹ PTCS has a reported incidence of 0.9 per 100,000 in the general population, but it rises to 19 per 100,000 in obese women of childbearing age.² In adults, primary PTCS, also known as

idiopathic intracranial hypertension, tends to mainly affect overweight females of childbearing age who present with headache and papilledema.³

The term “primary” is reserved for those cases in which known secondary causes have been excluded. The term “secondary” is used for those cases in which an underlying potential cause is identified; current data suggest that prepubertal children affected with intracranial hypertension are more likely to be secondary rather than primary.⁴ In fact,

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systemic conditions, cerebral venous abnormalities, drugs, infections, and endocrine abnormalities, have been identified as possible secondary causes of PTCS in the pediatric literature,⁵⁻⁸ although the exact mechanism by which these conditions result in secondary intracranial hypertension is not entirely understood.

Clinically, the physical and neurologic examination should be normal with the exception of cranial nerve (e.g., abducens nerve) palsy (more frequent in children rather than in adults and typically a false localizing sign) and papilledema on funduscopic examination, which is present in almost all patients. The absence of papilledema or the presence of focal neurological deficits should put the diagnosis of PTCS in doubt. As weight gain and obesity are an important risk factor of PTCS in the pediatric age group,⁹ weight loss for overweight children may lead to a relief of clinical symptoms.¹⁰

Medical treatment (e.g., carbonic anhydrase inhibitors) is performed to reduce ICP and the severity of headache and visual disturbances in children with PTCS^{4,8,10}; CSF diversion procedures (e.g., lumbar puncture [LP]) or surgical procedures (e.g., lumboperitoneal shunt, optic nerve sheath fenestration) are reserved for those patients who do not respond to conservative treatments or who had complications following diuretic administration.¹¹ Although PTCS has been for long considered a benign condition, a small number of patients, especially if not promptly diagnosed and treated, can follow a more aggressive course, with permanent visual impairment occurring in one or both eyes in up to 8 to 10% of patients.¹²

Of note, the advent of magnetic resonance imaging (MRI) revolutionized the imaging paradigm in PTCS, from simply applying imaging to exclude concomitant intracranial processes (e.g., intracranial mass) to depicting signs thought to indicate and/or diagnose this syndrome itself (► **Table 1**).¹³ We briefly discuss on the increasingly emergent role of MRI in the assessment of pediatric PTCS patients.

Initial Radiologic Assessment in a Child with Increased Intracranial Pressure

The diagnosis of PTCS in children should be regarded always as a diagnosis of exclusion, as central nervous system tumors

and/or space-occupying lesions have to be first ruled out in all children who present with a constellation of symptoms, including headache, nausea, vomiting, and papilledema⁴; in this context, both computed tomography (CT) and MRI of the brain are extremely useful in the initial assessment of pediatric patients with increased ICP.^{4,8} As younger children with PTCS may develop torticollis, gait imbalance, and/or other clinical signs of posterior fossa lesion, MRI is useful also to exclude posterior fossa pathologies or postinflammatory torticollis.¹⁴

A normal CT scan of the brain is never adequate in diagnosing PTCS or excluding its differentials. MRI of the brain (with and without gadolinium) and MR venography (MRV) are therefore the studies of choice to rule out known secondary causes.^{1,4,13} For instance, some infiltrating neoplastic processes (e.g., gliomatosis cerebri) may mimic PTCS, making crucial and careful MRI assessment in all cases of suspected PTCS. Leptomeningeal spread of lymphoma, leukemia, and germ cell tumors may also lead to signs and symptoms of intracranial hypertension in children, with only subtle anomalies on brain MRI.^{15,16} The diagnosis may be evident by meningeal enhancement on MRI.^{1,4} Furthermore, MRV is performed to exclude cerebral venous sinus thrombosis which can also mimic PTCS in clinical presentation. According to the recent diagnostic criteria, MRV should be performed in the initial radiologic assessment to exclude the presence of cerebral venous sinus thrombosis in those patients who do not fit the “typical” picture of primary PTCS (e.g., prepubertal children, not overweight patients, men).¹

To diagnose PTCS, neuroimaging should demonstrate normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement.^{1,4,8} However, several abnormal MRI findings have been reported (i.e., empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, transverse venous sinus stenosis).^{13,17} In this regard, brain imaging has acquired an important role in support to the diagnosis of PTCS, especially in those patients who have an incomplete presentation of the syndrome (i.e., without papilledema) but suggestive neuroimaging findings on MRI.^{1,4,8,13,17}

Table 1 Key radiologic features of pseudotumor cerebri syndrome

Radiological features
Empty sella
Partially empty sella
Intraocular protrusion of optic nerve head
Decreased pituitary height
Flattened posterior sclera
Enlarged perioptic subarachnoid space
Increased tortuosity of optic nerve
Transverse venous sinus stenosis
Enhancement of optic nerve

Imaging Findings in Pseudotumor Cerebri Syndrome

According to the recent diagnostic criteria of PTCS in adults and children,¹ a definitive diagnosis requires (1) papilledema, (2) a normal (excepting for cranial nerve abnormalities) neurologic examination, (3) a normal CSF composition, (4) an elevated LP opening pressure (≥ 28 cm H₂O in children or ≥ 25 cm H₂O in adults or in unsexed/nonobese children); and (5) the exclusion of secondary causes of raised ICP by brain imaging. According to diagnostic criteria,¹ in the absence of papilledema or cranial nerve abnormalities (most commonly sixth nerve palsy), a diagnosis of PTCS can be suggested but not made if criteria 2 through 4 are satisfied and, additionally, if the patient meets at least three of the following (typical) PTCS-related imaging anomalies: (1)

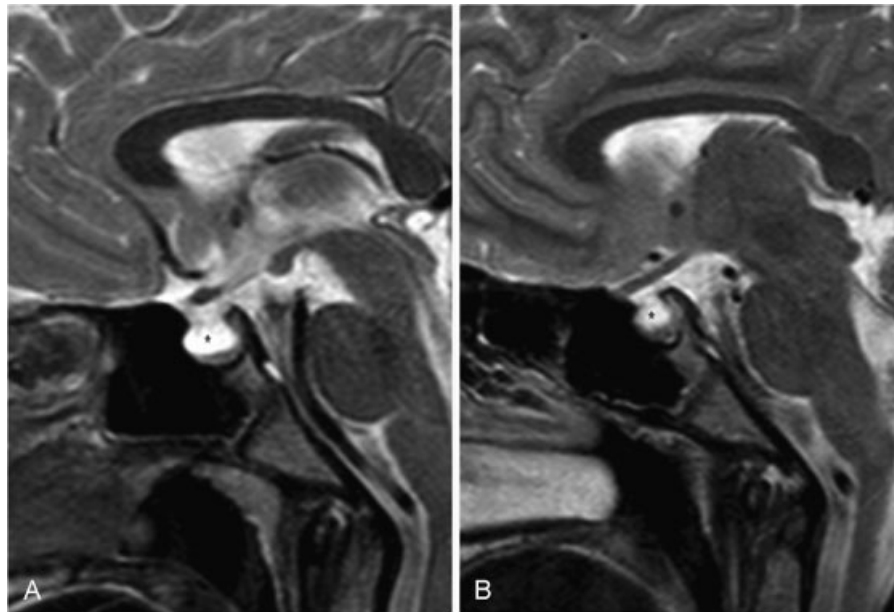


Fig. 1 (A, B) Sagittal fast-spin echo T2-weighted images show (asterisks) a partial empty sella.

empty sella, (2) flattening of the posterior aspect of the globe, (3) distension of the perioptic subarachnoid spaces (either associated or without a tortuous optic nerve), (4) transverse venous sinus stenosis. In fact, previous retrospective and/or prospective studies showed a significant incidence of specific radiologic findings in the context of PTCS.¹³

The presence of empty sella in PTCS patients represents the consequence of long-standing effects of increased ICP. Importantly, the term *empty sella* should be used to refer to the most severe cases, in which no pituitary gland can be identified on brain imaging. The incidence of concomitant increased ICP and empty sella is usually related to the severity and duration of PTCS and increase in the chronic PTCS group.¹⁸ While empty sella is a later manifestation of (severely) increased ICP, a moderate concavity of the pituitary gland without empty sella would suggest shorter duration and/or milder increase of CSF pressure.¹⁸ A preexisting

diaphragmatic defect has been proposed as an important factor in making some patients with PTCS prone to develop empty sella.¹⁹ Increased ICP transmitted to the intrasellar subarachnoid space through an anatomic variant and/or anomaly (e.g., congenital or acquired defect of the diaphragm) likely results in remodeling of the sella turcica (and the nearby bone structures) and in compression of the pituitary gland.^{18,19}

However, in the PTCS-related radiologic spectrum, there is a broad range of variations in pituitary height, and many cases of empty sella should be indeed regarded as partially empty sella or as compressed pituitary gland (→ **Figs. 1** and **2**). The wide range of sensitivities and specificities reported reflects this ambiguity.¹³ Transverse sinus narrowing is frequently seen in MRV in patients with PTCS. A study²⁰ identified stenotic transverse sinuses in 90% of patients with PTCS and the authors suggested, basing on the similar clinical

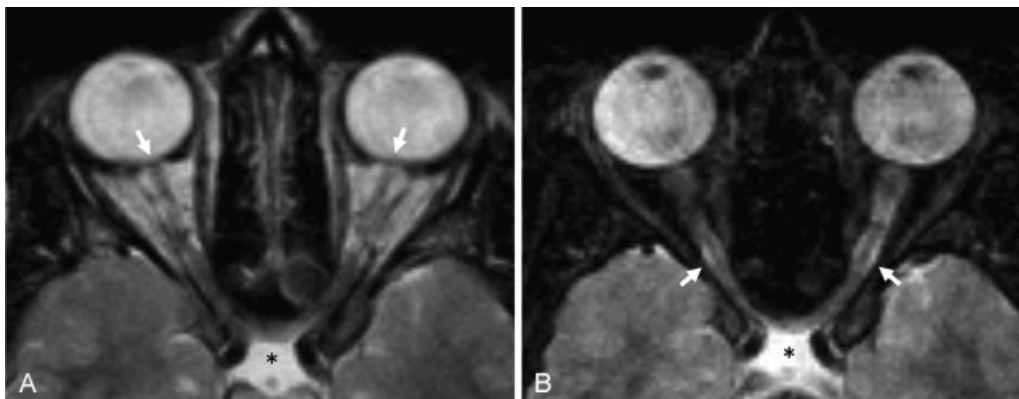


Fig. 2 Magnetic resonance imaging examination. (A, B) Axial T2-weighted fast-spin echo images of intraocular protrusion of optic nerve head (white arrows); enlarged perioptic subarachnoid space with cerebrospinal fluid hyperintensity surrounding the optic nerves (white arrows). The optic nerve sheath widening is thought to coincide with papilledema. Partial empty sella has been shown (black asterisk) in both images.

presentation of “primary” PTCS and transverse sinus thrombosis, that most cases of PTCS are due to venous outflow obstruction, which can take the form of either thrombosis or stenosis. Even if it is assumed that venous stenosis exists in PTCS, there is still controversy as to whether venous stenosis and elevated venous pressure are due to elevated ICP or constitute the proximal cause of PTCS.²¹

In this respect, several authors suggested that an unsuspected previous abnormality, such as an anatomic variant (congenital narrowing) of the transverse sinus, can be present in a large number of asymptomatic healthy patients,²¹ and evidences from cadaveric studies also suggested that the stenosis of the transverse sinus observed in PTCS might be due to the presence of a large septum within the venous sinus.²² Thus, increased CSF pressure related to PTCS could exacerbate the underlying venous sinus abnormality and create a flow-limiting stenosis and resultant pressure gradient; this could worsen the elevation of the ICP.²³ However, the compressible nature of the transverse sinus makes this structure vulnerable to tapering with increased ICP and this is now accepted by most authors as the effect (rather than the cause) of increased ICP.²⁴ Posterior globe flattening could be regarded as one of the most frequent radiologic feature of PTCS and can be visualized on both CT and MRI. This sign presumably reflects the transmission of elevated perioptic CSF pressure to the compressible posterior sclera.²⁵

Intraocular protrusion (► **Fig. 2**) likely occurring in a similar fashion to posterior globe flattening (i.e., due to elevated perioptic CSF pressure) and could be regarded as an infrequent radiologic feature associated with pediatric PTCS²⁶; this finding on MRI imaging may well correspond to the presence of visual disturbances, because of its absence in patients with PTCS without visual symptoms.²⁷ Widening of the optic nerve (► **Fig. 3**) and optic nerve tortuosity have also been reported in pediatric PTCS, and both signs are considered to be related to increase ICP.^{25,26}

Perspectives on Self-Expanding Vascular Stents in Sinus Venous Stenosis

An important developing therapeutic intervention for PTCS involves the use of self-expanding vascular stents in cases where there is evidence of sinus venous stenosis. This was first reported by Higgins et al²⁸ with promising results, and other groups have also published results in which stenting of the transverse sinus was undertaken in the setting of idiopathic stenosis of the sinus.²⁹ Overall, most patients showed improvement or complete resolution of the symptoms. In these studies, stenting significantly improved both the pre-stenotic transverse sinus pressures and pressure gradients. Furthermore, the results also showed improvement or resolution of papilledema in the majority of patients.

The results highlight that stenting in cases of isolated dural sinus stenosis may represent a successful alternative option to CSF diversion procedures. However, as outlined previously, the mechanism by which the stenosis occurs is unclear. It has been proposed that increased ICP itself was the major reason of venous sinus stenosis and it has been shown that regression of the stenosis after serial LPs, performed to decrease the ICP, can occur.²³ Additionally, in an emblematic case study on PTCS associated with narrowing of the transverse sinuses, the removal of 20 mL of CSF led to a dimensional increase in the transverse sinuses with clinical remission after 2 months of follow-up.³⁰

In conclusion, neuroimaging alone is not sufficient to diagnose PTCS, although some radiologic signs are highly suggestive of the syndrome. CT can identify secondary causes of intracranial hypertension, but MRI is the diagnostic gold standard in all patients suspected to have PTCS. In the MRI approach, it is important to first rule out subtle intracranial anomalies (e.g., infiltrating neoplastic processes). MRV allows detection of an underlying cerebral venous sinus thrombosis and has to be performed always in the atypical patients (e.g., not obese, not females). Sinus venous stenosis has been

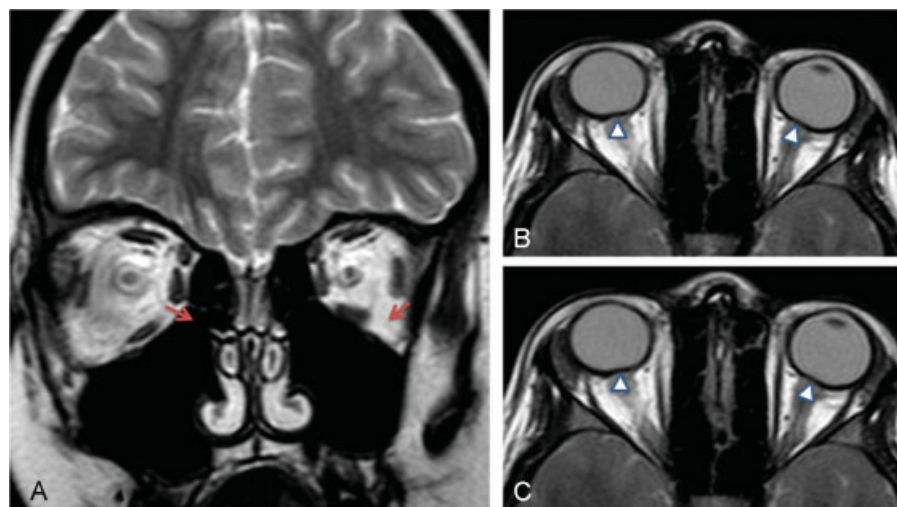


Fig. 3 (A) Coronal fast-spin echo T2-weighted image; (B, C) axial fast-spin echo T2-weighted images. Bilateral widening of the optic nerve sheath (red arrows). Bilateral optic papilla protrusion (arrowheads) with posterior globe flattening.

frequently identified in PTCS, although this finding should be regarded as a consequence (rather than a cause) of increased ICP. The use of self-expanding vascular stents has been adopted in some PTCS patients with sinus venous stenosis on brain imaging and some authors propose that it may represent a successful alternative option to CSF diversion procedures. The evidence for this is, however, not absolute.

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