Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children

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Neurology published online August 21, 2013
DOI 10.1212/WNL.0b013e3182a55f17

Published Ahead of Print on August 21, 2013 as 10.1212/WNL.0b013e3182a55f17

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ABSTRACT

The pseudotumor cerebri syndrome (PTCS) may be primary (idiopathic intracranial hypertension) or arise from an identifiable secondary cause. Characterization of typical neuroimaging abnormalities, clarification of normal opening pressure in children, and features distinguishing the syndrome of intracranial hypertension without papilledema from intracranial hypertension with papilledema have furthered our understanding of this disorder. We propose updated diagnostic criteria for PTCS to incorporate advances and insights into the disorder realized over the past 10 years. *Neurology*® 2013;81:1–7

GLOSSARY

BMI = body mass index; **ICP** = intracranial pressure; **IIH** = idiopathic intracranial hypertension; **LP** = lumbar puncture; **MRV** = magnetic resonance venography; **PTC** = pseudotumor cerebri; **PTCS** = pseudotumor cerebri syndrome.

The syndrome of intracranial hypertension with normal brain parenchyma but without ventriculomegaly, mass lesion, or underlying infection or malignancy has been generally referred to as idiopathic intracranial hypertension (IIH). Problems with the term IIH, overuse and misuse of the diagnosis "IIH without papilledema,"[1–3] greater awareness of the associated radiologic abnormalities, and a better understanding of this condition in children and what constitutes a normal CSF opening pressure in this age group[4] make it necessary to offer a revision to the nomenclature and diagnostic criteria for all age groups.[5,6]

Although IIH is an appropriate name for this combination of findings in a subset of patients who have primary intracranial hypertension of unclear etiology, there remains a substantial segment of individuals with the syndrome precipitated by an identifiable secondary cause that is not well-served by the name IIH and may require etiology-specific treatment. "Idiopathic intracranial hypertension from a secondary cause" is an oxymoron. Additionally, many clinicians in practice have not adopted the term IIH and continue to call the syndrome pseudotumor cerebri (PTC). "Benign intracranial hypertension" should be banished from our vocabulary because of the condition's potential for vision loss and the reduction in quality of life.[7]

Thus, we concur with our international colleagues[8] that the condition is best described using the umbrella term PTC syndrome (PTCS). We propose that patients can be subdivided into those with primary vs secondary PTC. IIH is a subset within the primary PTC category, while the secondary PTC group would include causes such as venous sinus thrombosis, medications, and medical conditions (table 1).

The typical adolescent or adult patient with IIH is obese and female.[9,10] Less commonly, obese males[11] and prepubertal thin girls and boys can have IIH.[6,9] One aim of the ongoing Idiopathic Intracranial Hypertension Treatment Trial is to search for the etiology of IIH by studying genetic factors and vitamin A (retinoids).[12] It is hoped that within the near future, our understanding of the pathogenesis of this condition will advance to the point where it is no longer "idiopathic."

The literature regarding PTCS both for adults and children has exploded since the diagnostic criteria were revised in 2002.[5,6,13–15] For instance, the neuroimaging features are now defined well enough to provide reasonable certainty about the diagnosis in a patient with a typical presentation with papilledema prior to performing the lumbar puncture (LP).[16,17] A large study

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table 1 Pseudotumor cerebri syndrome

Primary pseudotumor cerebri
Idiopathic intracranial hypertension
Includes patients with obesity, recent weight gain, polycystic ovarian syndrome, and thin children
Secondary pseudotumor cerebri
Cerebral venous abnormalities
Cerebral venous sinus thrombosis
Bilateral jugular vein thrombosis or surgical ligation
Middle ear or mastoid infection
Increased right heart pressure
Superior vena cava syndrome
Arteriovenous fistulas
Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage
Hypercoagulable states
Medications and exposures
Antibiotics
Tetracycline, minocycline, doxycycline, nalidixic acid, sulfa drugs
Vitamin A and retinoids
Hypervitaminosis A, isotretinoin, all-trans retinoic acid for promyelocytic leukemia, excessive liver ingestion
Hormones
Human growth hormone, thyroxine (in children), leuprorelin acetate, levonorgestrel (Norplant system), anabolic steroids
Withdrawal from chronic corticosteroids
Lithium
Chlordecone
Medical conditions
Endocrine disorders
Addison disease
Hypoparathyroidism
Hypercapnia
Sleep apnea
Pickwickian syndrome
Anemia
Renal failure
Turner syndrome
Down syndrome

defined the normal values for LP opening pressure in children,[4] leading to the possible clinical dilemma of diagnosing a patient who has papilledema and is otherwise typical but whose measured LP opening pressure is not abnormally elevated. The converse situation also arises in patients who have chronic daily headaches with an elevated LP opening pressure but no papilledema or other signs of intracranial hypertension. This condition has been popularized as "IIH without papilledema."[18,19] These patients often have lower CSF opening pressures than those with papilledema,[20] and may simply have chronic daily headache with coincident elevated intracranial pressure (ICP).[21] They do not require vigilant ophthalmic monitoring, as they tend not to develop papilledema later, and any vision loss they might develop is typically nonphysiologic.[20] It is not at all certain that they have the same disorder as those patients with papilledema who may have rapid and severe visual deterioration at the time of presentation.[22] It is important to recognize that patients with a secondary cause and papilledema may be otherwise indistinguishable from those with IIH. In addition to addressing the secondary cause, these patients frequently require treatments used for IIH in order to prevent blindness.[23,24]

With these points in mind, we propose updated criteria for the diagnosis of PTCS in adults and children. Our objective is to provide accurate parameters for reliably diagnosing patients, in order to identify them promptly at presentation, obtain the necessary diagnostic testing, and institute treatment to avoid/minimize visual loss. As there is much heterogeneity of signs and symptoms among patients with PTCS, we also comment on variations that occur.

Aside from CSF opening pressure parameters, these criteria apply to patients of all ages; however, PTCS in children younger than 3 years and adults older than 60 is rare. Therefore, alternative causes of intracranial hypertension must be strongly considered in these extreme age groups.

DIAGNOSTIC CRITERIA FOR PTCS **Required for diagnosis.** Diagnostic criteria for PTCS are detailed in table 2. A patient is considered to have definite PTCS if criteria A–E are fulfilled. The diagnosis is considered probable if criteria A–D are met with bilateral papilledema present, and the measured CSF pressure is lower than specified for a definite diagnosis.

Papilledema. Papilledema is the hallmark of PTCS and is almost always present in the acute presentation of PTCS. Papilledema, or optic disc swelling due to elevated ICP, is characterized by disc elevation, blurring of the disc margin, a peripapillary halo, obscuration by the nerve fiber layer of blood vessels crossing the disc margin, venous distension, and overlying or peripapillary hemorrhages, exudates, or cotton-wool spots. It may be asymmetric,[25] or, uncommonly, unilateral.[26] Ophthalmologic or neuro-ophthalmologic consultation should be

Table 2 Diagnostic criteria for pseudotumor cerebri syndrome

1. Required for diagnosis of pseudotumor cerebri syndrome[a]
A. Papilledema
B. Normal neurologic examination except for cranial nerve abnormalities
C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
D. Normal CSF composition
E. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture
2. Diagnosis of pseudotumor cerebri syndrome without papilledema
In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy
In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, and in addition at least 3 of the following neuroimaging criteria are satisfied:
i. Empty sella
ii. Flattening of the posterior aspect of the globe
iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
iv. Transverse venous sinus stenosis

[a] A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

initiated if there is a question of subtle papilledema or pseudopapilledema. Orbital ultrasound and fluorescein angiography may be utilized to confirm the presence of papilledema and exclude causes of pseudopapilledema, such as optic nerve head drusen. Alternative etiologies of optic disc swelling such as optic neuritis, anterior ischemic optic neuropathy, and neuroretinitis should be excluded; these diagnoses are made clinically and cannot be distinguished from PTCS on the basis of the CSF opening pressure. Documentation of papilledema and the optic discs when papilledema has resolved with fundus photography is recommended, as these patients may present with recurrent symptoms years later.

Occasionally, patients may come to medical attention early in the course of the illness for symptoms suggesting PTCS prior to the development of papilledema. The presenting symptom in this case is usually a new or worsening headache, which merits further investigation in and of itself. Patients may be diagnosed with PTCS when papilledema is detected without other symptoms.[27–29] Papilledema may be less than expected or even absent if there is preexisting optic atrophy or previously resolved optic disc swelling.

Normal neurologic examination other than cranial nerve abnormalities. The patient's mental status must be normal (i.e., the individual must be awake and alert). Encephalopathy suggests an alternate diagnosis. Cranial neuropathies may occur due to VIth or VIIth nerve dysfunction, for instance, but there can be no other unexplained focal neurologic abnormalities.

Neuroimaging. There should be normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography (MRV) for all others. If MRI is unavailable or contraindicated, contrast-enhanced CT with or without venography may be used.

MRI is the study of choice for diagnosis, as the technique provides more details of intracranial structures without radiation associated with CT, and radiographic changes of meningeal infiltration and isodense tumors are best visualized with MRI. Signs of elevated ICP such as perioptic subarachnoid space distension and an empty sella are frequently found on MRI[30] (see below) and often cannot be discerned using CT. Small ventricular size is normal for young adults.[31] Occasionally, meningeal enhancement occurs if the patient had a LP prior to the MRI.

MRV may show venous narrowing supportive of a diagnosis of PTCS in any patient but should be performed to detect cerebral venous sinus thrombosis in atypical patients, such as non-obese individuals, prepubertal children, men, and patients with progressive visual loss despite therapy. Venous imaging should be considered for patients at high risk for cerebral venous sinus thrombosis, such as women taking oral contraceptives. Occasionally in patients with suspected venous thrombosis, CT venography, digital subtraction angiography, or a second venous imaging study is necessary when the first MRV is equivocal or even normal. Venous sinus occlusion and arteriovenous fistulas may produce PTCS.

The literature regarding neuroimaging findings in PTCS continues to evolve. Recent studies have suggested affected patients are more likely to have narrowing of Meckel's cave and the cavernous sinuses on MRI[32] and widening of the foramen ovale on CT.[33] These radiologic findings, however, need to be confirmed with further studies prior to incorporation into diagnostic guidelines.

Normal CSF composition. Following neuroimaging and exclusion of any contraindication to LP, a spinal fluid examination should be performed in all suspected cases of PTCS to rule out alternative etiologies, and the opening pressure should be measured (see below). CSF composition should be normal without pleocytosis, elevated protein, hypoglycorrhachia, abnormal cytology, or other evidence of infection or malignancy.

Elevated LP opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]).[4,34,35] A lumbar puncture demonstrating an elevated CSF pressure is required for the diagnosis of definite PTCS. Lumbar CSF pressure is most accurately measured with the patient in the lateral decubitus position, but fluoroscopically guided LPs are often performed in the prone position.[36] It is critical that the base of the manometer be level with the right atrium or an adequate height correction applied.[36] If possible, sedation should be avoided as the hypercapnia that occurs with sedation may artifactually raise the CSF pressure measurement.[4] CSF pressure may be increased with Valsalva maneuver (e.g., breath-holding or crying), and if the pressure is measured with the patient in the sitting position.[37] If the knees are flexed, the CSF pressure may also be artificially elevated, but one study in children found no clinically meaningful difference in pressure if legs are flexed or extended.[38]

The LP opening pressure measurement indicates the CSF pressure at that given moment and may therefore be misleading for diagnostic purposes. If the patient has typical symptoms of PTCS with papilledema, a low opening pressure measurement should not negate the diagnosis of PTCS. The low value may have been taken at the nadir of a pressure wave, for instance. In one study of children with papilledema, almost all patients had an elevated opening pressure.[39] However, elevated pressure measurement in the absence of other supporting symptoms and signs (e.g., papilledema) is not diagnostic as individuals with no medical abnormalities may have an elevated CSF opening pressure for no clear reason.[4] A repeat LP or continuous CSF pressure monitoring via lumbar drain or ICP monitor—with demonstration of B and plateau waves indicative of elevated ICP—may uncommonly be needed to confirm the diagnosis.[40,41]

The response to LP is not diagnostic. Many patients will experience temporary improvement of their headache following an LP, a phenomenon that is too subjective. Conversely, in patients with PTCS, headache relief may not occur and post-LP headache is possible. While many practitioners remove a large volume of CSF (more than 20 mL), and measure the closing pressure, the benefit of these practices is uncertain.

Diagnosis of PTCS without papilledema. In the absence of papilledema, a diagnosis of PTCS can be made if criteria B–E from table 2 are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy. The abducens palsy may be complete or incomplete, producing an esotropia. The most common symptom is horizontal diplopia that is worse at distance than at near.

In the absence of papilledema or sixth nerve palsy, a diagnosis of PTCS can be suggested but not made if criteria B–E from table 2 are satisfied, and in addition 3 of the following neuroimaging abnormalities are present. There is sufficient retrospective[30,33,42,43] and now prospective[16,17] evidence that as a group, these neuroimaging abnormalities are highly suggestive of PTCS.

1. Empty sella[44]
2. Flattening of the posterior aspect of the globe
3. Distension of the perioptic subarachnoid space with or without a tortuous optic nerve
4. Transverse venous sinus stenosis[45]

Transverse venous sinus stenosis is present in most patients with PTCS and generally represents a sign of increased ICP.[46–48] The imaging resolution on a conventional MRV may show irregularities that represent an artifact of the imaging technique rather than true venous sinus disease. Most individuals have a dominant right transverse sinus, so asymmetry of the transverse sinuses does not necessarily indicate pathology. However, bilateral venous sinus stenosis is rare in healthy individuals.[49] High-resolution (auto-triggered elliptic-centric-ordered [ATECO]) MRI or CT venography are superior techniques for this purpose.

Tonsillar ectopia (Chiari I–like malformation) is present more frequently in patients with PTCS than in controls[50] but is certainly not specific to PTCS; tonsillar descent may also be a sign of low CSF pressure. This finding is therefore not included as a neuroimaging criterion. The occasional patient with a significant tonsillar descent and an otherwise typical presentation of PTCS may be at high risk for herniation with LP[51,52] and therefore can be diagnosed with PTCS presumptively.

DISCUSSION In these revised criteria, documentation of an elevated CSF opening pressure is required for the diagnosis of definite PTCS, but the diagnosis of probable PTCS may still be made in an otherwise typical patient if bilateral papilledema is present and the measured opening pressure is not elevated. If papilledema is not present, then the combination of an elevated CSF pressure and a sixth nerve palsy can be used to make the diagnosis of PTCS. Without papilledema or a sixth nerve palsy, a combination of an elevated CSF

pressure and the presence of 3 of 4 radiologic criteria can only suggest the diagnosis. Notably, LP is always required in the workup of a patient considered to have PTCS.

Uncommon manifestations. A facial (VII) nerve palsy, hemifacial spasm, or radicular pain may infrequently accompany PTCS. CSF rhinorrhea or otorrhea are uncommon features of PTCS, but confirmation of a CSF leak in the presence of other supportive criteria highly suggests the diagnosis of PTCS. Oculomotor (III) nerve palsy, trochlear (IV) nerve palsy, and generalized ophthalmoparesis can rarely be manifestations of PTCS,[53] but they raise the possibility of an alternate diagnosis.

Relapse. Patients with previously diagnosed and treated PTCS may relapse years later. A precipitating factor is often identified such as weight gain or exposure to a substance associated with the PTCS.[54] Relapse is usually associated with recurrent papilledema but certain circumstances may preclude the development of papilledema, such as fibrosis of the nerve fiber layer or optic atrophy. In such cases, recurrent symptoms and signs, including LP opening pressure measurements, are helpful to confirm recurrence.

Symptoms suggestive of but less specific to PTCS. Headache, transient visual obscurations, pulse-synchronous tinnitus, binocular diplopia, and neck, shoulder, or back pain are symptoms suggestive of PTCS. However, they are too nonspecific to be considered diagnostic criteria.

Making the diagnosis of PTCS can be complicated. The following examples help illustrate the points of previous confusion.

Illustrative cases. ***Case 1.*** A 33-year-old woman has a 3-month history of global, aching headaches associated with mild nausea, photophobia, and phonophobia. She also reports episodes of transient visual loss in both eyes lasting seconds and pulsatile tinnitus. She takes naproxen 3 days weekly for her headaches but is on no other medications. Examination reveals a body mass index (BMI) of 33 kg/m^2, normal visual acuity, enlarged blind spots on perimetry, full ocular motility, and bilateral Frisén grade 3 optic disc edema. Her MRI shows distention of the perioptic subarachnoid space and a partially empty sella and is otherwise normal. LP reveals an opening pressure of 198 mm CSF with normal CSF contents.

Comment. The patient has typical physical characteristics, symptoms, and examination findings of primary PTCS, or IIH. Her diagnosis is considered probable as her measured LP opening pressure is lower than required for a definite diagnosis of PTCS.

Case 2. A 16-year-old girl has a 9-month history of constant, global aching headaches associated with mild nausea, photophobia, and phonophobia. There are no episodes of transient visual loss or pulsatile tinnitus. She takes naproxen 3 days weekly for her headaches but is on no other medications. Examination reveals a BMI of 33 kg/m^2, normal visual acuity, diffuse constriction of the visual fields on kinetic perimetry without physiologic expansion using a larger test target, full ocular motility, and normal optic discs bilaterally. Her MRI is normal. Lumbar puncture reveals an opening pressure of 270 mm CSF with normal CSF contents.

Comment. PTCS is a suspected cause of chronic daily headache in an obese female patient. However, this patient has no papilledema or other symptoms or signs of PTCS and the visual field constriction is not organic ("functional" visual field loss). The elevated LP opening pressure is neither specific nor diagnostic in this setting. She does not have PTCS.

Case 3. A 27-year-old woman was diagnosed with IIH at age 22 when she developed blurred vision, diplopia, and headaches. Her examination revealed visual acuities of 20/30 in both eyes, marked blind spot enlargement on perimetry, mild bilateral abduction deficits, and bilateral Frisén grade 4 papilledema. Imaging and LP confirmed the diagnosis. She was treated with acetazolamide and weight loss. Her symptoms and examination abnormalities resolved and the acetazolamide was discontinued after a year. Three months ago, she developed similar headaches, transient obscurations of vision, and blurred vision. Examination showed visual acuities of 20/25 in both eyes with blind spot enlargement on perimetry. Ocular motility was full and there was no active disc edema but the disc margins were mildly elevated and gliotic. Imaging showed a partially empty sella and distention of the perioptic subarachnoid space. LP opening pressure was 300 mm CSF. She reports a 15-pound weight gain over the past year.

Comment. Papilledema may not be present in recurrent PTCS because of gliotic changes in the nerve fiber layer or subtle optic atrophy. Based on her symptoms and other findings, this patient has recurrent PTCS.

AUTHOR CONTRIBUTIONS

Drs. Friedman, Liu, and Digre contributed to the concept of the paper and the drafting and revision of the manuscript for important intellectual content.

STUDY FUNDING

Supported by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology & Visual Sciences, University of Utah.

DISCLOSURE

D. Friedman has served as a site investigator for Quark Pharmaceuticals and MAP Pharmaceuticals and has received honoraria as a speaker for Allergan and for advisory work to MAP Pharmaceuticals and Merck. She received research support from Merck and the National Eye Institute and is on the Editorial Board of *Neurology Reviews*. G. Liu has consulted for Ipsen and received book royalties from Elsevier. K. Digre receives grant support from the National Eye Institute. Go to Neurology.org for full disclosures.

Received January 3, 2013. Accepted in final form May 24, 2013.

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