CSF opening pressure in children with optic nerve head edema

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ABSTRACT

Background: We previously reported that an abnormal CSF opening pressure (OP) in children was greater than 28 cm H_2O. Since elevated intracranial pressure can cause optic nerve head edema (ONHE), we would expect that most patients with ONHE would have an OP greater than 28 cm H_2O. This study describes the range of OP for children with ONHE and compared them to age-matched controls without ONHE.

Methods: Case subjects were children (1–18 years of age) enrolled in a prospective study of CSF OP that demonstrated ONHE at time of lumbar puncture and that the ONHE later resolved. Patients with ONHE secondary to infectious, inflammatory, or ischemic conditions were excluded. Control subjects from the same study, but without ONHE, were matched to cases.

Results: Of the 472 subjects enrolled in the study, 41 OP measurements were obtained from 33 patients with ONHE who did not have any exclusionary criteria and matched to 41 control subjects without ONHE. Case subjects had a significantly higher OP (mean, 41.4 cm H_20; range, 22–56) than control subjects (mean, 18.9 cm H_2O; range, 9–29; $p < 0.01$). Forty of 41 (97.6%) case subjects and 2 of 41 (4.8%) control subjects had OP measures >28 cm H_2O.

Conclusions: Children with ONHE not related to infectious, inflammatory, or ischemic causes typically have an OP >28 cm H_2O, significantly higher than age-matched controls without ONHE. This study provides further support to our previously published findings that suggests an abnormal OP in children is typically above 28 cm H_2O. *Neurology*® 2011;76:1658–1661

GLOSSARY

ICP = intracranial pressure; **IIH** = idiopathic intracranial hypertension; **LP** = lumbar puncture; **ONHE** = optic nerve head edema; **OP** = opening pressure.

Elevated intracranial pressure (ICP) can cause optic nerve head edema (ONHE), commonly referred to as papilledema. Elevated ICP is usually confirmed by manometric measurement of CSF opening pressure (OP) during lumbar puncture (LP). Previously, an OP greater than 20 cm H_20 in children was considered elevated.[1,2] However, some authors have reported that "normal" adults and children can have an OP as high as 28 cm H_2O.[3-6] In a prospective study of CSF OP in children, we reported that an abnormal CSF OP in children was greater than 28 cm H_2O.[6] Since elevated ICP can cause ONHE, we would expect that most patients with ONHE not due to infectious, inflammatory, or ischemic conditions would have an OP greater than 28 cm H_2O.

This study describes the range of OP for children with ONHE not due to infectious, inflammatory, or ischemic conditions and compared them with age-matched controls without ONHE.

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Study funding: Supported by the NIH (Loan Repayment Program and 1T32NS061779-01 to R.A., NIAID K01 AI73729 to S.S., NINDS NS-052380 to D.L., and NINDS NS053651 to J.H.), the Robert Wood Johnson Foundation (S.S.), the DANA Foundation (D.L.), and the June and Steve Wolfson Fund for Neurological Research (D.L.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure: Author disclosures are provided at the end of the article.

METHODS **Patients.** Subjects comprising this cohort were selected from a large prospective study performed at The Children's Hospital of Philadelphia (Philadelphia, PA), an urban tertiary care children's hospital. Inclusion and exclusion criteria have previously been described in detail.[6] Briefly, children 1–18 years of age undergoing LP in the lateral recumbent position as part of their clinical care were prospectively identified to participate. Those with documented ONHE on fundus examination with subsequent resolution were eligible for inclusion as case subjects in the present study. Patients with ONHE secondary to inflammatory (e.g., sarcoid), ischemic (e.g., vasculitis), or infections (i.e., Lyme disease) were excluded. Any subject (case or control) with abnormal CSF constituents (i.e., CSF white blood cells greater than 8 per mm^3 or protein >60 mg/dL), indwelling ventricular shunts, past or current diagnosis of a brain tumor, and abnormal MRI findings (i.e., demyelinating disease, optic neuritis, hydrocephalus, Chiari malformation, transependymal CSF flow) were excluded. Patients with a diagnosis of Guillain-Barré syndrome or a radiographic diagnosis of sinovenous thrombosis were included as cases since the etiology of their ONHE was presumably directly related to elevated ICP. Subjects without ONHE were chosen from the previously published study as control subjects.[6] Control subjects were matched 1:1 to case subjects based on age (within 6 months), category of sedation depth during LP (no sedation, mild sedation, moderate/severe sedation), and age-based body mass index category (underweight <5%, normal weight 5%–84%, overweight 85–95%, and obese >95%).[7]

Standard protocol approvals, registrations, and patient consents. Consent from the parent and verbal assent from the child (when applicable) was obtained prior to enrollment. Institutional review board approval was obtained prior to study initiation.

Measured outcome. The measured outcome was CSF OP, measured in cm H_2O. If the CSF pressure exceeded the maximum measurement at the top of the manometer (i.e., 55 cm H_2O), the OP was recorded as 56 cm H_2O.

Study definitions and protocol. Diagnosis of ONHE was made by a pediatric neuro-ophthalmologist or ophthalmologist (n = 35) or pediatric neurologist (n = 6). The patient's history, presence or absence of ONHE on fundus examination, resolution of ONHE, laboratory results, and discharge diagnosis were obtained through review of medical records with a minimum follow-up of 6 months after the date of the LP. The medical history of patients found to have ONHE was specifically reviewed to identify any known risk factors for developing idiopathic intracranial hypertension (IIH). Risk factors for IIH, defined according to 2 expert reviews,[8,9] included anemia, obesity, receipt of tetracycline-based medications, withdrawal from chronic corticosteroid therapy within the past 2 months, growth hormone injections, topical or systemic retinoids, and vitamin A supplements.

Statistical analysis. Continuous variables were described using means, median, and range. Categorical variables were described using frequencies and percentages. Paired *t* test was used to compare the OP distribution between case and control subjects. Data were analyzed using commercially available software (STATA, version 11; StataCorp, College Station, TX). A 2-tailed *p* value <0.05 was considered statistically significant.

RESULTS ONHE was identified in 60 (12.7%) of the 472 enrolled subjects. Twenty-seven subjects with ONHE were excluded for the following conditions: Lyme disease (n = 8), demyelinating/white matter disease (n = 4), drusen/anomalous optic nerves (n = 3), vasculitis/inflammatory (n = 5), sarcoid (n = 1), polyarteritis nodosum (n = 1), acute lymphoblastic leukemia (n = 1), suspected viral meningitis (n = 1), pituitary hypophysitis (n = 1), and optic nerve structural anomalies (n = 2).

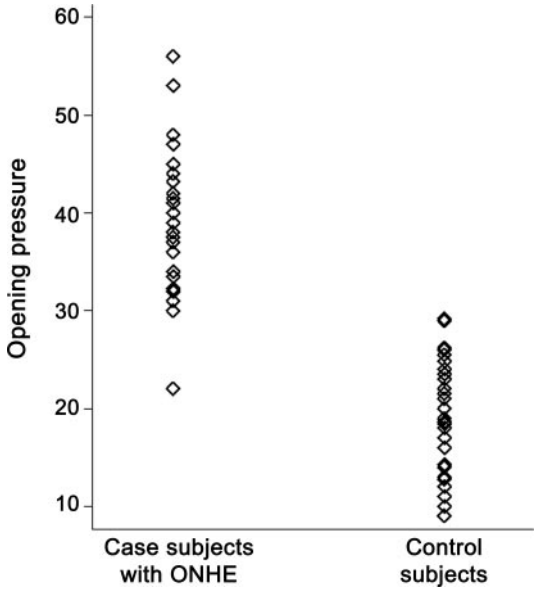
Forty-one OP measurements were obtained from the 33 patients with ONHE who did not have any exclusionary criteria. The table lists the demographic and clinical characteristics of case subjects with ONHE and control subjects without ONHE. The difference in mean OP between case and controls subjects was 22.5 cm H_2O ($p < 0.01$). Forty of 41 (97.6%) LPs performed on ONHE case subjects had OP measurements >28 cm H_2O as compared to 2 of 41 (4.8%) control subjects with OP measures >28 cm ($\chi^2 = 70.48$, $p < 0.01$; figure). ONHE was attributed to withdrawal of chronic steroids in 2 subjects and ingestion of minocycline in 5 subjects. Three case subjects were taking acetazolamide at the time of their LP and had OP measurements of 34, 44, and 53 cm H_2O. Elimination of these 3 subjects from the analysis did not alter the large difference in mean OP between case and control subjects ($p < 0.01$). Large differences in mean OP between groups remained ($p < 0.01$) when stratified by age (i.e., prepubertal <8 years old, peripubertal 9–12 years old, and postpuberty 13–18 years old).

Table Demographic and clinical characteristics of case subjects with ONHE and control subjects without ONHE

Characteristics	Case subjects with ONHE (n = 41)	Control subjects (n = 41)	*p* Value[a]
Age, y			
Mean/median	13.0/14.1	13.0/14.1	0.99
Range	(3.9–17.7)	(4.2–17.7)	
Female, n (%)	26 (63)	28 (68)	0.64
Body mass index[b]			
Mean/median	23.0/21.9	22.4/21.0	0.12
Range	(9.6–44.0)	(13.2–44.0)	
Opening pressure (cm H_2O)			
Mean/median	41.4/40.0	18.9/18.6	<0.01
Range	(22–56)	(9–29)	
Diagnosis, n (%)			
IIH	36 (88)	—	—
GBS/Miller-Fisher	3 (7)	—	—
Sinovenous thrombosis	2 (5)	—	—

Abbreviations: GBS = Guillain-Barré syndrome; IIH = idiopathic intracranial hypertension; ONHE = optic nerve head edema.
[a] Between-group differences using paired t test for age and opening pressure, Wilcoxon rank sum for body mass index, and the χ^2 test for categorical variables.
[b] Body mass index available on 40/41 case subjects.

Figure Comparison of CSF opening pressure measures (cm H_2O) between case subjects with optic nerve head edema (ONHE) and control subjects without ONHE



DISCUSSION This study demonstrates that an overwhelming majority of children found to have ONHE not due to infectious, inflammatory, or ischemic conditions and which later resolved have an OP greater than 28 cm H_2O. All but one case subject with ONHE had an OP 10 cm H_2O above the previously defined upper limit of normal (i.e., 20 cm H_20).[1,2] However, nearly 40% (16 of 41) of control subjects without ONHE had an OP greater than 20 cm H_2O. Although possible, it is doubtful this many control subjects had a clinically significant elevation in their ICP. These findings provide further support to our previously published findings that suggests an abnormal OP in children is typically above 28 cm H_2O and likely indicative of elevated ICP.[6]

Our observations are relevant for several reasons. Foremost, the diagnostic criteria for IIH have required an OP greater than 25 cm H_2O.[9] This study provides prospective data that support these criteria, but also suggest that the OP criteria in children may need to be increased to greater than 28 cm H_2O. Moving the criteria to greater than 28 cm H_2O may provide diagnostic clarity to children found to have an OP below this level who present with headache but without papilledema or to asymptomatic children discovered to have an OP that would previously have been considered abnormal. A recent study reported children with IIH had an OP above 28 cm H_2O, while all but one subject diagnosed with pseudopapilledema had an OP below 30 cm H_2O.[10] Increasing the OP criteria is further supported by the findings from our large prospective study that concluded that an abnormal OP in children was greater than 28 cm H_2O.[6]

The only subject in our study diagnosed with intracranial hypertension who had an OP below 28 cm H_2O had undergone renal transplantation and developed ONHE following withdrawal of long-term oral corticosteroids. Her LP demonstrating an OP of 22 cm H_2O was performed after restarting her oral corticosteroids. She still had papilledema, but most symptoms of IIH had improved following resumption of corticosteroid therapy.

This study may be limited by the fact that control subjects without ONHE may not have experienced elevated ICP long enough to produce ONHE. Additionally, control subjects did not undergo follow-up LPs to determine if their OP continued to rise. Clinician's knowledge of the presence or absence of ONHE at the time of LP may have influenced their final determination of the OP. The validity of our study results is strengthened by the prospective design that avoids biases inherent in retrospective case series. Additionally, most case subjects received an evaluation by the same experienced pediatric neuro-ophthalmologist, minimizing the consequences of interobserver variability in diagnosis of ONHE. The inclusion criteria that required that case subjects demonstrate subsequent resolution of ONHE decreased the chances of including subjects with elevated optic nerves not related to increased intracranial pressure (i.e., optic nerve drusen or anomalous optic nerves).

A measurement or indication of elevated ICP is required to further define ONHE as papilledema. Throughout the current study, we chose to use the term ONHE rather than papilledema since it would be inappropriate to have our primary outcome measure (i.e., OP) define our subject classification (i.e., case).

Our prospective study examining the relationship between OP and ONHE found that most children with ONHE not related to infectious, inflammatory, or ischemic causes typically have an OP greater than 28 cm H_2O. This study provides further support to our previously published findings that suggests an abnormal OP in children is typically above 28 cm H_2O and indicative of elevated ICP.

AUTHOR CONTRIBUTIONS

Dr. Avery: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data. Dr. Licht: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data. Dr. Shah: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data. Dr Huh: drafting/revising the manuscript for content, study concept or design. Dr. Seiden: drafting/revising the manuscript for content, study concept or design. Dr. Boswinkel: drafting/revising the manuscript for content, study concept or

design. Dr. Ruppe: drafting/revising the manuscript for content. Dr. Mistry: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data. Dr. Liu: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data.

ACKNOWLEDGMENT

The investigators thank all physicians at Children's Hospital of Philadelphia who helped enroll subjects and complete the study forms; the faculty and research staff in the Division of Neurology, Department of Anesthesiology and Critical Care, and Department of Emergency Medicine at Children's Hospital of Philadelphia for support; and the patients and their families who participated in this study.

DISCLOSURE

Dr. Avery receives research support from the NIH/NEI. Dr. Licht receives research support from the NIH/NINDS and the Dana Foundation and serves as an expert witness in medico-legal cases. Dr. Shah serves on the editorial boards of *Archives of Pediatrics and Adolescent Medicine* and *Infection Control and Hospital Epidemiology*, Assistant Editor for *Journal of Hospital Medicine*, and Associate Editor for *Pharmacoepidemiology and Drug Safety*, and receives publishing royalties for *Pediatric Practice Infectious Diseases* (McGraw-Hill, 2009), *Pediatric Complaints and Diagnostic Dilemmas* (Lippincott Williams & Wilkins, 2004), *Blueprints Pediatric Infectious Diseases* (Lippincott Williams & Wilkins, 2005), *Blueprints Infectious Diseases* (Lippincott Williams & Wilkins, 2006), *The Philadelphia Guide: Inpatient Pediatrics* (Lippincott Williams & Wilkins, 2005), *Pediatric Infectious Diseases* (Mosby Elsevier Inc., 2008), and *Patient Encounters: The Inpatient Pediatrics Workup* (Lippincott Williams & Wilkins, 2010). Dr. Huh serves on the editorial board of the *Journal of Anesthesia & Clinical Research* and receives research support from the NIH/NINDS. Dr. Seiden, Dr. Boswinkel, Dr. Ruppe, and Dr. Mistry report no disclosures. Dr. Liu serves as a consultant and on a scientific advisory board for Ipsen; serves on speakers' bureaus for and has received speaker honoraria from Endo Pharmaceuticals, Merck Serono, GlaxoSmithKline, Lundbeck Inc., and Pfizer Inc; serves on the editorial board of the *Journal of Neuro-Ophthalmology*; receives publishing royalties for *Neuro-Ophthalmology: Diagnosis and Management, 2nd edition* (Elsevier, 2010); and receives research support from the Children's Hospital of Philadelphia Women's Committee.

Received December 8, 2010. Accepted in final form January 28, 2011.

REFERENCES

1. Fishman RA. Examination of cerebrospinal fluid: techniques and complications. In: Fishman RA, ed. Cerebrospinal Fluid in Diseases of the Nervous System, 2nd ed. Philadelphia: WB Saunders; 1992:157–182.
2. Nechyba C. Blood chemistries and body fluids. In: Gunn VL, Nechyba C, eds. The Harriet Lane Handbook: A Manual for Pediatric House Officers, 16th ed. Philadelphia: Mosby; 2002:549–559.
3. Corbett JJ, Mehta MP. Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. Neurology 1983;33:1386–1388.
4. Ellis R. Lumbar cerebrospinal fluid opening pressure measured in a flexed lateral decubitus position in children. Pediatrics 1994;93:622–623.
5. Whiteley W, Al-Shahi R, Warlow CP, Zeidler M, Lueck CJ. CSF opening pressure: reference interval and the effect of body mass index. Neurology 2006;67:1690–1691.
6. Avery RA, Shah SS, Licht DJ, et al. Reference range for cerebrospinal fluid opening pressure in children. N Engl J Med 2010;363:891–893.
7. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. JAMA 2010;303:242–249.
8. Rangwala LM, Liu GT. Pediatric idiopathic intracranial hypertension. Surv Ophthalmol 2007;52:597–617.
9. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002;59:1492–1495.
10. Mishra A, Mordekar SR, Rennie IG, Baxter PS. False diagnosis of papilloedema and idiopathic intracranial hypertension. Eur J Paediatr Neurol 2007;11:39–42.