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Chiari I Malformation in Nephropathic Cystinosis

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Abstract

Objective—To determine the relative incidence of Chiari I malformations in children with cystinosis compared with those in the general population.

Study design—Magnetic resonance imaging (MRI) scans were performed on 53 patients with nephropathic cystinosis and 120 controls, age range 3–18 years.

Results—Ten of 53 (18.9%) cystinosis patients had Chiari I or tonsillar ectopia, and only 2 of 120 controls (1.6%) had a similar finding. At least 2 of the patients had symptoms or signs thought to be related to the malformation, and one had surgical decompression. Two had an associated cervical syrinx.

Conclusions—Children with cystinosis have a 12-fold higher prevalence of Chiari I malformations than the general pediatric population. Chiari I malformations should be high on the differential diagnosis when individuals with cystinosis develop neurologic signs and symptoms, and MRI scans should be performed on children with cystinosis who present with new-onset headache, ataxia, incontinence, or other unexplained neurologic symptoms.

Keywords

cystinosis; Chiari I; syrinx

Cystinosis is an autosomal recessive lysosomal storage disorder, in which affected individuals accumulate intracellular cystine [1]. Treatment with a cystine-depleting agent, cysteamine, can reduce cystine levels in lysosomes and maintain renal function for many years [4].

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Children with cystinosis may exhibit neurological signs and symptoms, including low muscle tone, gross and fine motor incoordination, and deficits in visual motor and visual spatial skills. [5-8]. In early adult life, dysarthria and swallowing difficulties may develop [9]. Anecdotally, a few children with cystinosis have been reported to have Chiari I malformations. Chiari I is generally considered to occur with a protrusion of the tonsils of greater than 3-5 mm into the spinal canal. When the protrusion is less than 5 mm it is sometimes referred to as tonsillar ectopia. Given the small size of the canal, there is the potential for the tonsils to come under pressure from surrounding bone. In this instance, neurological problems may develop.

Chiari I malformations may present with a variety of symptoms and signs including occipito-cervical headaches, ataxia, atypical esotropia, or nystagmus [10, 11, 12, 13, 14]. Speech and swallowing signs also may occur [10, 16, 17]. Brainstem dysfunction may be seen, and sinus bradycardia, hypertension, central sleep apnea, and drop attacks have been reported [10, 20, 21]. Downward herniation of the brainstem can occur in rare circumstances, including with a sudden change in intracranial pressure or a volume shift as might occur from a blow to the occiput or neck [22-26].

Diseases that have known associations with an increased occurrence of Chiari I malformations include rickets, growth-hormone deficiency, Pierre-Robin syndrome, Paget's disease, craniometaphyseal dysplasia, oxycephaly, and multisutural craniosynostosis, among others [10, 27-36]. These diseases all have mechanisms that can affect skull growth. Chiari I malformations in children and adults also have an association with smaller posterior fossa volumes [37-38]. These reports introduce a hypothesis that the mechanism of Chiari I malformation in individuals with the above conditions is related to skull plate formation and abnormal skull diameter [10].

Cystinosis has a known association with rickets [39-41] and rickets has a known association with abnormalities in skull dimensions (including flattening of the skull base) and vertebral abnormalities [42-43]. Therefore, patients with cystinosis may have an additional risk factor for developing a Chiari I malformation. The current study was designed to determine the likelihood of Chiari I malformations in children and adolescents with cystinosis as compared with children in the general pediatric population.

METHODS

Fifty-three individuals with cystinosis and 120 controls were included in the study. Age range was 3-18 years in both the cystinosis and control groups. Individuals with cystinosis were identified through advertisements placed with the National Cystinosis Foundation, the Cystinosis Research Network, and the Cystinosis Research Foundation. All participants had a diagnosis of infantile nephropathic cystinosis. Controls were recruited from the local community through advertisements in local parent magazines and newspapers, and through approved fliers placed in pediatricians' offices and at local youth centers. All subjects were healthy enough to participate in the study and none were sedated.

High-resolution 3-dimensional T1-weighted SPGR images were acquired on a 1.5 GE Signa scanner (General Electric, Milwaukee, WI, USA). MRI scans were read clinically by a neuro-radiologist blinded to diagnosis.

RESULTS

Of the 53 subjects with cystinosis who completed MRI scans, 10 (18.9%) had a Chiari I malformation or tonsillar ectopia, a milder form in which there is downward displacement of the cerebellar tonsils into the spinal canal but less than 5 mm of displacement (Figure). The Table provides information on sex, age at scan, and relevant other information on the cystinosis subjects with Chiari I or tonsillar ectopia. Of note, two individuals with cystinosis had additional anomalies involving the cervical cord, one syrinx and one syringohydromyelia. Two cystinosis subjects had neurological signs and symptoms that may have related to the Chiari I. The first, a 3-year-old male, had his symptoms resolve following decompressive surgery, strongly suggesting that the malformation was the cause of his symptoms. The second individual did not undergo surgery, and thus, possible causation cannot be confirmed at this time.

In contrast, of 120 controls who had MRI scans performed, only 2 (1.6%) had evidence of a Chiari I malformation or tonsillar ectopia. Neither was symptomatic at the time of the study.

DISCUSSION

We report a higher prevalence of Chiari I malformation/tonsillar ectopia in children and adolescents with nephropathic cystinosis compared with age-matched healthy controls. We found a 12-fold increase in likelihood of Chiari I malformation in the cystinosis population, as well as an almost 4% risk of associated syrinx in the cervical cord, a complication that could result in additional neurological compromise. This result is reminiscent of other diseases in which early deformations or abnormalities of bone growth occur, such as rickets and Paget's disease, and may reflect early problems with bone growth related to the renal Fanconi syndrome of cystinosis [42, 44]. Because the presence of a Chiari I malformation can be associated with at times significant neurological deficits, it is important to recognize the fact that this condition is present in almost one-fifth of patients. Even a relatively small degree of tonsillar ectopia (5 mm) can cause severe symptoms, as was seen in one of our patients described above. Thus, there should be a high index of suspicion for such a malformation if a child or adult with cystinosis develops new onset of neurological symptoms such as headache, ataxia, diplopia, or spasticity.

Two of the 10 individuals with cystinosis in our study who had Chiari I malformations had symptoms possibly referable to the malformation, and one had decompression, which relieved his symptoms. However, this does not imply that Chiari I is a benign condition. First, young children may be unable to articulate a complaint of headache; second, vomiting, incoordination, and similar complaints may be attributed to renal disease or medications used to treat cystinosis, rather than to a primary neurological problem. It is important to consider that symptoms of increased fussiness, headache, double vision, coordination, or behavior changes in children with cystinosis should prompt referral to a neurologist by the

primary care provider or nephrologist. Further, Chiari I malformations often do not become symptomatic until adolescence or adult life; thus, children with known Chiari I malformations should be monitored for neurological changes so that symptoms can be addressed promptly if they occur [10]. If symptoms occur, repeat imaging should be obtained and a neurosurgical consultation considered. There are no current guidelines for periodic imaging in asymptomatic children with Chiari I malformation.

Even small Chiari I malformations can be symptomatic, and decompressive surgery can provide symptomatic relief [45-46]. Of note, there have been reports of some children with Chiari I malformation having a delayed recovery time of symptoms or incomplete recovery of symptoms after decompressive surgery [45-46]. The reason for this incomplete recovery is currently unknown. Children with Chiari I malformation and syringomyelia who receive excision of the herniated cerebellar tonsils have been observed to experience shorter recovery times than similar children who do not have the tonsils excised [47]. It is therefore possible that patient-to-patient anatomic differences in pressure on the nerve roots may explain delayed recovery in some children.

Children with nephropathic cystinosis may have a higher than expected likelihood of developing idiopathic intracranial hypertension (pseudotumor cerebri) than the general population (48). To our knowledge, none of the individuals in our study who had a Chiari I malformation were diagnosed with IIH. We cannot, however, rule out the possibility of an association between IIH and Chiari malformations in this population. Certainly, an acute downward shift of the cerebellar tonsils could cause increased intracranial pressure and papilledema, but this would likely be an emergent situation and not a subacute problem such as typically found with IIH. In fact, caution should be utilized in considering a lumbar puncture in a person with a known Chiari I malformation.

Most of the children in this study were taking cysteamine. There was no indication of an association between cysteamine use and the presence or absence of a Chiari I.

Parents of children with cystinosis should be told to watch for sudden onset of neurological symptoms (headache, ataxia, change in level of consciousness, behavior change, vomiting) particularly if the child experiences a blow to the back of the head or after neck trauma such as from a roller coaster ride. If such changes occur acutely, families should be encouraged to take the child to the emergency room, because sudden intracranial pressure shifts can cause brainstem herniation and possibly death.

Chiari I malformations should be high on the differential diagnosis of neurological signs and symptoms in a child with known cystinosis, and MRI scans should be performed on children with cystinosis who present with new headache, ataxia, or nystagmus. If neurological examination of a child with known cystinosis reveals new findings, MRI of the brain should be obtained with thin-slice sagittal T1- and T2-weighted sequences through the posterior fossa. Because Chiari I malformations can be associated with syrinx, if a Chiari I malformation is found, additional imaging of the cervical spine is warranted in children with cystinosis with new neurological symptoms.

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REFERENCES

1. Kalatzis V, Antignac C. New aspects of the pathogenesis of cystinosis. *Pediatr Nephrol.* 2003; 18:207–15. [PubMed: 12644911]
2. Cherqui S, Sevin C, Hamard G, Kalatzis V, Sich M, Pequignot MO, et al. Intralysosomal Cystine accumulation in Mice Lacking Cystinosin, the protein defective in Cystinosis. *Mol Cell Biol.* 2002; 22:7622–32. [PubMed: 12370309]
3. Ueda M, O'Brien K, Rosing DR, Ling A, Kleta R, MacAreavey D, et al. Coronary artery and other vascular calcifications in cystinosis patients after kidney transplantation. *Clin J Am Soc Nephrol.* 2006; 1:555–62. [PubMed: 17699259]
4. Nesterova G, Gahl W. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol.* 2008; 23:863–78. [PubMed: 18008091]
5. Ballantyne AO, Spilkin AM, Trauner DA. Executive function in nephropathic cystinosis. *Cogn Behav Neurol.* 2013; 26:14–22. [PubMed: 23538568]
6. Viltz L, Trauner DA. Effect of age at treatment on cognitive performance in patients with cystinosis. *J Pediatr.* 2013; 163:489–92. [PubMed: 23462307]
7. Trauner DA, Williams J, Ballantyne AO, Spilkin AM, Crowhurst J, Hesselink J. Neurological impairment in nephropathic cystinosis: motor coordination deficits. *Pediatr Nephrol.* 2010; 25:2061–6. [PubMed: 20652328]
8. Trauner DA, Spilkin AM, Williams J, Babchuck L. Specific cognitive deficits in young children with cystinosis: evidence for an early effect of the cystinosin gene on neural function. *J Pediatr.* 2007; 151:192–6. [PubMed: 17643777]
9. Sonies BC, Ekman EF, Andersson HC, Adamson MD, Kaler SG, Markello TC, et al. Swallowing dysfunction in nephropathic cystinosis. *N Engl J Med.* 1990; 323:565–70. [PubMed: 2381441]
10. Tubbs RS, Lyster MJ, Loukas M, Shoja MM, Oakes WJ. The pediatric Chiari I malformation: a review. *Childs Nerv Syst.* 2007; 23:1239–1250. [PubMed: 17639419]
11. Levy WJ, Mason L, Hahn JF. Chiari malformation presenting in adults: a surgical experience in 127 cases. *Neurosurgery.* 1983; 12:377–390. [PubMed: 6856062]
12. Nohria V, Oakes WJ. Chiari I malformation: a review of 43 patients. *Pediatr Neurosurg.* 1990; 16:222–227. [PubMed: 2135191]
13. Paul KS, Lye RH, Strang FA, Dutton J. Arnold-Chiari malformation. Review of 71 cases. *J Neurosurg.* 1983; 58:183–187. [PubMed: 6848674]
14. Lewis AR, Kline LB, Sharpe JA. Acquired esotropia due to Arnold-Chiari malformation. *J Neuro-Ophthalmol.* 1996; 16:49–54.
15. Tubbs RS, McGirt MJ, Oakes WJ. Surgical experience in 130 pediatric patients with Chiari I malformations. *J Neurosurg.* 2003; 99:291–296. [PubMed: 12924703]
16. Tubbs RS, Webb D, Smyth MD, Oakes WJ. Magnetic resonance imaging evidence of posterior pharynx denervation in pediatric patients with Chiari I malformation and absent gag reflex. *J Neurosurg.* 2004; 101:21–24. [PubMed: 16206967]
17. Zager EL, Ojemann RG, Poletti CE. Acute presentation of syringomyelia. Report of three cases. *J Neurosurg.* 1990; 72:133–138. [PubMed: 2294173]
18. Greenlee JD, Donovan KA, Hasan DM, Menezes AH. Chiari I malformations in the very young child: the spectrum of presentations and experience in 31 children under the age 6 years. *Pediatrics.* 2002; 110:1212–1219. [PubMed: 12456921]
19. Nathadwarawala KM, Richards CA, Lawrie B, Thomas GO, Wiles CM. Recurrent aspiration due to Arnold-Chiari type I malformation. *BMJ.* 1992; 304:565–566. [PubMed: 1559068]

20. Selmi F, Davies KG, Weeks RD. Type I Chiari deformity presenting with profound sinus bradycardia: case report and literature review. *Br J Neurosurg.* 1995; 9:543–545. [PubMed: 7576283]
21. Tubbs RS, Wellons JC 3rd, Blount JP, Oakes WJ, Grabb PA. Cessation of chronic hypertension after posterior fossa decompression in a child with Chiari I malformation. Case report. *J Neurosurg.* 2004; 100:194–196. [PubMed: 14758949]
22. Zhang J, Shao Y, Qin Z, Liu N, Zou D, Huang P, et al. Sudden unexpected death due to Chiari type I malformation in a road accident case. *J Forensic Sci.* 2013; 58:540–3. [PubMed: 23278920]
23. Graham A, Davis JE, Gouvernayre AJ, Thomas JA. An unusual cause of neck pain: acquired Chiari malformation leading to brainstem herniation and death. *J Emerg Med.* 2012; 43:1000–3. [PubMed: 21215551]
24. Wolf DA, Veasey SP, Wilson SK, Adame J, Korndorffer WE. Death following minor head trauma in two adult individuals with the Chiari I deformity. *J Forensic Sci.* 1998; 43:1241–3. [PubMed: 9846405]
25. James DS. Significance of chronic tonsillar herniation in sudden death. *Forensic Sci Int.* 1995; 3:217–23. [PubMed: 8586346]
26. Murano T, Rella J. Incidental finding of Chiari I malformation with progression of symptoms after head trauma: case report. *J Emerg Med.* 2006; 30:295–8. [PubMed: 16677981]
27. Lee J, Hida K, Seki T, Kitamura J, Iwasaki Y. PierreRobin syndrome associated with Chiari type I malformation. *Childs Nerv Syst.* 2003; 19:380–383. [PubMed: 12748800]
28. Murphy RL, Tubbs RS, Grabb PA, Oakes WJ. Chiari I malformation and idiopathic growth hormone deficiency in siblings. *Childs Nerv Syst.* 2006; 22:632–634. [PubMed: 16418834]
29. Tubbs RS, Oakes WJ. Chiari I malformation, caudal regression syndrome and Pierre Robin Syndrome: a previously unreported combination. *Childs Nerv Syst.* 2006; 22:1507–1508. [PubMed: 17021725]
30. Tubbs RS, Oakes WJ. Pierre-Robin syndrome associated with Chiari I malformation. *Childs Nerv Syst.* 2004; 20:1–2. [PubMed: 14657997]
31. Tubbs RS, Rutledge SL, Kosentka A, Bartolucci AA, Oakes WJ. Chiari I malformation and neurofibromatosis type 1. *Pediatr Neurol.* 2004; 30:278–280. [PubMed: 15087107]
32. Tubbs RS, Smyth MD, Oakes WJ. Chiari I malformation and caudal regression syndrome: a previously unreported association. *Clin Dysmorph.* 2003; 12:147–148. [PubMed: 12868483]
33. Tubbs RS, Smyth MD, Oakes WJ. Chiari I malformation and cloacal exstrophy: report of a patient with both defects of blastogenesis. *Am J Med Genet A.* 2003; 119:231–23. [PubMed: 12749071]
34. Tubbs RS, Smyth MD, Wellons JC, Blount JP, Oakes WJ. Cutaneous manifestations and the Chiari I malformation. *Pediatr Neurol.* 2003; 29:250–252. [PubMed: 14629912]
35. Tubbs RS, Smyth MD, Wellons JC 3rd, Oakes WJ. Hemihypertrophy and the Chiari I malformation. *Pediatr Neurosurg.* 2003; 38:258–261. [PubMed: 12686770]
36. Tubbs RS, Wellons JC 3rd, Oakes WJ. Occipital encephalocele, lipomeningomyelocele, and Chiari I malformation: case report and review of the literature. *Childs Nerv Syst.* 2003; 19:50–53. [PubMed: 12541087]
37. Trigylidas T, Baronia B, Vassilyadi M, Ventureyra EC. Posterior fossa dimension and volume estimates in pediatric patients with Chiari I malformations. *Childs Nerv Syst.* 2008; 24:329–36. [PubMed: 17657497]
38. Furtado SV, Reddy K, Hegde AS. Posterior fossa morphometry in symptomatic pediatric and adult Chiari I malformation. *J Clin Neurosci.* 2009; 16:1449–54. [PubMed: 19736012]
39. Iancu TC, Lerner A, Shiloh HJ. Intestinal mucosa in nephropathic cystinosis. *J Pediatr Gastroenterol Nutr.* 1987; 6:359–64. [PubMed: 3430244]
40. Antoniazzi F, Mengarda F, Lauriola S, Serra A, Zamboni G, Tatò L. Growth and renal function. *Pediatr Med Chir.* 1997; 19:341–7. [PubMed: 9493225]
41. Betend B, Chatelain P, David L, François R. Treatment of rickets caused by infantile cystinosis using 1 alpha-hydroxyvitamin D. *Arch Fr Pediatr.* 1982; 39:615–8. [PubMed: 7159161]
42. Gjørup H, Kjaer I, Sonnesen L, Haubek D, Beck-Nielsen SS, Hintze H, et al. Craniofacial morphology in patients with hypophosphatemic rickets: a cephalometric study focusing on

- differences between bone of cartilaginous and intramembranous origin. *Am J Med Genet A*. 2011; 155A:2654–60. [PubMed: 21965080]
43. Gjørup H, Sonnesen L, Beck-Nielsen SS, Haubek D. Upper spine morphology in hypophosphatemic rickets and healthy controls: a radiographic study. *Eur J Orthod*. 2014; 36:217–25. [PubMed: 23882087]
44. Singer FR, Bone HG, Hosking DJ, Lyles KW, Hassan Murad M, Reid IR, et al. Paget's Disease of Bone: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2014; 99:4408–22. [PubMed: 25406796]
45. McGirt MJ, Attenello FJ, Atiba A, Garces-Ambrossi G, Datto G, Weingart JD, et al. Symptom recurrence after suboccipital decompression for pediatric Chiari I malformation: analysis of 256 consecutive cases. *Childs Nerv Syst*. 2008; 24:1333–9. [PubMed: 18516609]
46. Hekman KE, Aliaga L, Straus D, Luther A, Chen J, Sampat A, et al. Positive and negative predictors for good outcome after decompressive surgery for Chiari malformation type 1 as scored on the Chicago Chiari Outcome Scale. *Neurol Res*. 2012; 34:694–700. [PubMed: 22781921]
47. Changshun B, Fubing Y, Liang L, Bing W, Dingjun L, Yingjiang G, et al. Surgical treatment of Chiari I malformation complicated with syringomyelia. *Exp Ther Med*. 2013; 5:333–337. [PubMed: 23251294]
48. Dogulu CF, Tsilou E, Rubin B, Fitzgibbon EJ, Kaiser-Kupper MI, Rennert OM, et al. Idiopathic intracranial hypertension in cystinosis. *J Pediatr*. Nov.2004 145:673–8. [PubMed: 15520772]

Figure.
Sagittal section of brain MRI in child with nephropathic cystinosis and Chiari I malformation with ~5 mm protrusion of cerebellar tonsils into cervical canal (arrow). Line = foramen magnum.

Table 1

Subjects with cystinosis and Chiari I or tonsillar ectopia (TE).

Sex	Age at time of imaging	Pertinent History and Exam findings	Chiari I/TE finding	Other imaging findings
F	10y0m	Rickets, anemia	5 mm TE	--
M	14y6m	Presented at age 3 with severe headaches, dizziness, declining speech, loss of ability to walk, right sided weakness History of anemia, TPN dependency, motor delays, and cognitive delays	Chiari s/p occipital decompression	--
M	15y5m	No motor or cognitive delays reported At time of scan had moderate b/l sensorineural hearing loss, speech difficulty, and hemifacial hyperplasia	Chiari I	Mild volume loss
F	4y2m		>5 mm Chiari I, with a pointed configuration inferiorly	--
M	8y1m		5 mm TE	Mild volume loss
M	6y4m		7 mm right cerebellar TE	--
M	8y10m		Chiari I and cervical syringohydromyelia	Mild volume loss
F	18y10m	No motor or cognitive delays	Chiari I	--
F	5y11m		Chiari I with cervical cord syrinx	--