CASE REPORT

Association of Nephropathic Cystinosis and Pseudotumor Cerebri with Bilateral Duane Syndrome Type I

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ABSTRACT

A 15-year-old girl, a known case of nephropathic cystinosis with a history of kidney transplantation, presented for evaluation of lid drooping in lateral gaze and a recent-onset headache. Examination of ocular movements showed bilateral limitation of abduction combined with narrowing of palpebral fissure in adduction. Deposition of polychromatic crystals in the conjunctiva and corneal stroma of both eyes was evident. Both optic discs were oedematous and intracranial pressure was 270 mm CSF, which responded to oral acetazolamide. The patient developed metabolic imbalances and multiple organ failure, from which she expired 3 months after presentation.

Keywords: Cystinosis, Duane syndrome, pseudotumor cerebri

INTRODUCTION

Cystinosis is a rare autosomal recessive disorder characterised by the accumulation of the amino acid cystine within lysosomes. It affects 1 infant in 100,000 to 200,000 births.¹ Cystinosis has been mapped to chromosome 17p13; the defective gene is *CTNS*.² It is a systemic metabolic defect that can present in three forms: infantile, intermediate, or adult. The infantile, or nephropathic, form features include dwarfism and progressive renal dysfunction, with deposition of fine polychromatic cystine crystals in the conjunctiva, corneal stroma, and other parts of the eye. In the natural history of untreated nephropathic cystinosis, renal failure generally occurs within the first decade of life. Renal and ocular involvements are less severe in the intermediate or adolescent form. In the adult form, life expectancy is normal, with no kidney involvement.² Association with multi-organ involvements such as delayed puberty, hypothyroidism, pancreas and liver diseases, distal myopathies, hypophosphatemic rickets, failure to thrive, and, relevant to our patient, central nervous system (CNS)

involvement such as calcification, atrophy, and pseudotumor cerebri (PTC) have been reported.^{1–3}

In this report, we present a rare case of cystinosis associated with PTC and bilateral Duane syndrome type I.

CASE REPORT

A 15-year-old girl was referred for evaluation of ptosis on lateral gaze; she also complained of headaches beginning 6 months prior to presentation. Family history was significant for a consanguineous relationship between her parents. The patient's brother and sister had both died in childhood because of renal failure, presumably also due to cystinosis.

She had a history of hypertension and hypothyroidism and had undergone kidney transplantation when she was 9 years old. She had an extensive medication regimen, including prednisolone, mycophenolate mofetil (CellCept), cystagon, rapamycin (sirolimus), nortriptyline, amlodipine, furosemide, atenolol, levothyroxine, ranitidine, vitamin D,

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FIGURE 1 The patient is orthotropic in primary position with limitation of movements in abduction; globe retraction and narrowing of palpebral fissure in adduction.

FIGURE 2 Polychromatic cystine crystals in the corneal stroma.

ferrous sulphate, atorvastatin, and cysteamine eye drops.

On general examination she was found to be obese and she had short stature and moon face. Her best-corrected visual acuity was 20/20 in both eyes. She was orthotropic in primary position, with bilateral limitation of movements on lateral gaze. Globe retraction and narrowing of palpebral fissure were evident in adduction in both eyes, compatible with bilateral Duane syndrome type I (Figure 1).

Her pupils were normal, reactive to light, and no afferent pupillary defect was detected. Slit-lamp examination revealed deposition of fine polychromatic cystine crystals in the conjunctiva and corneal stroma of both eyes (Figure 2). On fundus examination media were clear and optic discs were swollen (Figure 3).

Brain computed tomography (CT) scan, magnetic resonance imaging (MRI), and magnetic resonance venography (MRV) were all normal. She underwent lumbar punctures twice, which were reported normal. On peripapillary optical coherence tomography (OCT) true optic disc oedema was confirmed in both eyes, and nerve fibre layer thickness were reported to be 242 and 320 μm in right and left eyes, respectively (normal range: $91 \pm 8 \mu\text{m}$).⁴

One month later, she suffered from severe headaches, dizziness, and ataxia. During this episode, intracranial pressure was detected to be elevated (270 mm CSF) and based on medical history and physical examination, the diagnosis of PTC associated with nephropathic cystinosis and bilateral Duane syndrome type I was confirmed; oral acetazolamide 500mg was started. After 1 month, papilloedema

diminished significantly and her headache, ataxia, and dizziness improved. She passed away because of metabolic disturbances in the setting of multiple organ failure 3 months later.

DISCUSSION

The three disorders nephropathic cystinosis, PTC, and Duane syndrome are rare, with an estimated incidence of 1 in 100,000 to 200,000 live births for cystinosis,¹ and 1 in 100,000 persons for PTC.⁵ About 1% of children have congenital strabismus.⁶ Of those 1–4% suffer from Duane syndrome.⁷ Statistically speaking, only 1 out of 10 trillion should be stricken with all three of cystinosis, Duane syndrome, and PTC.¹

The elevated intracranial pressure without a space-occupying lesion in this case was presumed to be idiopathic; however, some underlying mechanisms could be suggested. A postulated mechanism for PTC in patients with cystinosis is that they are hypercoagulable as a complication of renal failure. Thrombophilia can cause arachnoid villi thrombosis and decreased cerebrospinal fluid reabsorption leading to increased intracranial pressure (ICP).⁸ Another possible mechanism for PTC is cystine accumulation and deposition in the choroidal plexus, meninges, and brain parenchyma.^{8–10} It is thought that cystine deposition in meninges might interfere with cerebrospinal fluid (CSF) outflow by obstructing the arachnoid villi, causing PTC;¹ however, this mechanism was unproven due to lack of brain biopsy. One interesting point in this case is that despite the clinical picture of PTC on three occasions, raised ICP was only detected during the third lumbar puncture.

Irrespective of the patient's cystinosis, other possible causes for the increased intracranial hypertension include medications. Several reports have claimed that using medications such as prednisone, growth hormone, cyclosporine, oral contraceptives, vitamin D, and levothyroxine are risk factors for PTC.^{11–16} Our patient had been taking prednisolone, vitamin D, and levothyroxine.

Kidney transplantation in patients with infantile cystinosis corrects kidney failure and prolongs survival. The disease does not recur in the graft (the donor parenchymal cells are not homozygous for the

FIGURE 3 Fundus photograph of both eyes show optic disc swelling.

genetic defect and are therefore able to transport cystine from the lysosomes). However, transplantation does not prevent progression of the disease in nonrenal organs and cystine continues to accumulate in other tissues, giving rise to such complications as ocular involvement (e.g. severe photophobia, corneal ulceration, retinal blindness), delayed puberty, hypothyroidism, pancreatic disease, liver disease, distal vacuolar myopathy, swallowing difficulties, and CNS involvement (e.g. calcification, atrophy, and pseudotumor cerebri). Therefore, therapy with oral cysteamine is indicated in patients after kidney transplantation.³ Management of cystinosis with oral cysteamine must be initiated as soon as diagnosis of cystinosis is made. Cysteamine ophthalmic solution is useful when cystine crystals accumulated in the eye.³ Posterior segment manifestations such as pigmentary retinopathy and optic nerve oedema may be treated with oral cysteamine.²

In addition to highlighting a rarer complication of cystinosis, this case also is unique in that this patient had Duane syndrome associated with cystinosis. Most cases of Duane syndrome are sporadic, but about 5–10% show autosomal dominant inheritance. The defective gene in Duane syndrome type I maps to chromosome 8q13.¹⁷ A higher prevalence in females and the left eye has been reported and about 15% of cases are bilateral. Duane syndrome presents in several ways, all of which are characterised by anomalous co-contraction of the medial and lateral rectus muscles, producing retraction of the globe in actual or attempted adduction. Type I Duane syndrome is the most common form (50–80% in several series) that refers to poor abduction, frequently with primary position esotropia. Even though most affected patients have Duane syndrome alone, many associated systemic defects have been observed, such as Goldenhar syndrome and Wildervanck syndrome;^{17–19} however, the association of Duane syndrome and cystinosis has not been reported yet.

In Duane syndrome, surgery is reserved for cases with a primary position deviation, a significant face turn, marked globe retraction, or large up shoots or down shoots.^{17–19} This patient had none of these signs.

It should be noted that limitation of abduction in bilateral sixth nerve palsy after increased intracranial pressure can cause palpebral fissure widening in abduction, but it will not cause globe retraction in adduction, which helps distinguish the two disorders. In addition, Duane syndrome would have been present since infancy, whereas sixth nerve paresis rarely presents congenitally and the patient would be more esotropic at distance.¹⁹

The patient expired due to multiple organ disorders despite successful kidney transplantation. Death of her siblings at lower ages reflects the severity of disease in her family and may be a complication of the consanguineous marriage of her parents.

In summary, the important aspect of this case is the need for high clinical suspicion for increased intracranial hypertension in individuals with cystinosis. This difficulty in diagnosis is highlighted in our case by the two prior normal lumbar punctures. In addition, this is the first case in the literature to report a patient simultaneously suffering from cystinosis and Duane syndrome, which is likely incidental, but unique.

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REFERENCES

- [1] Dogulu CF, Tsilou E, Rubin B, FitzGibbon EJ, Kaiser-Kupper MI, Rennert OM, Gahl WA. Idiopathic intracranial hypertension in cystinosis. *J Pediatr* 2004;145: 673–678.
- [2] Gahl W, Kuel EM, Iwata F, Lindblad A, Kupper MK. Corneal crystals in nephrotic cystinosis: natural history and treatment with cysteamine eye drops. *Mol Genet Metab* 2000;71:100–120.
- [3] Medscape. Homepage. ca. 1994–2013. Available at: <http://www.Emedicine.Medscape.com/article/981650-overview>. Accessed May 13, 2013.
- [4] Pakravan M, Pakbin M, Aghazadehamiri M, Yazdani S, Yaseri M. Peripapillary retinal nerve fiber layer thickness measurement by 2 different spectral domain optical coherence tomography machines. *Eur J Ophthalmol* 2013; 23:289–295.
- [5] Friedman DI. Pseudomonas cerebri. *Neurosurg Clin N Am* 1999;10:609–621.
- [6] Tychsen L. Infantile esotropia: current neurophysiologic concepts. In: Rosenbaum AL, Santiago AP, editors. *Clinical Strabismus Management Principles and Surgical Techniques*. Philadelphia: WB Saunders; 1999:117–138.
- [7] DeRespinis PA, Caputo AR, Wagner RS, Guo S. Duane's retraction syndrome. *Surv Ophthalmol* 1993;38: 257–288.
- [8] Casserly LF, Reddy SM, Dember LM. Venous thromboembolism in end-stage renal disease. *Am J Kidney Dis* 2000; 36:405–411.
- [9] Jonas AJ, Conley SB, Marshall R, Johnson RA, Marks M, Rosenberg H. Nephropathic cystinosis with central nervous system involvement. *Am J Med* 1987;83:966–970.
- [10] Vogel DG, Malekzadeh MH, Cornford ME, Schneider JA, Shields WD, Vinters HV. Central nervous system involvement in nephropathic cystinosis. *J Neuropathol Exp Neurol* 1990;49:591–599.
- [11] Cruz OA, Fogg SG, Roper-Hall G. Pseudotumor cerebri associated with cyclosporine use. *Am J Ophthalmol* 1996; 122:436–437.
- [12] Bulens C, De Vries W, Van Crevel H. Benign intracranial hypertension: a retrospective and follow-up study. *J Neurol Sci* 1979;40:147–157.
- [13] Rogers AH, Rogers GL, Bremer DL, McGregor ML. Pseudotumor cerebri in children receiving recombinant human growth hormone. *Ophthalmology* 1999;106: 1186–1190.
- [14] Walker AE, Adamkiewicz J. Pseudotumor cerebri associated with prolonged corticosteroid therapy. *JAMA* 1964; 188:779–784.
- [15] Amrani Y, Terriza F, Moreno C, Casado A. Pseudotumor cerebri caused by vitamin excess due to intake of milk enriched with A and D vitamins [letter]. *Rev Neurol* 1996; 24:1304–1305.
- [16] Raghavan S, DiMartino-Nardi J, Saenger P, Linder B. Pseudotumor cerebri in an infant after L-thyroxine therapy for transient neonatal hypothyroidism. *J Pediatr* 1997;130: 478–480.
- [17] Engle EC. The genetic basis of complex strabismus. *Pediatr Res* 2006;59:343–348.
- [18] Engle EC. Oculomotility disorders arising from disruptions in brainstem motor neuron development. *Arch Neurol* 2007;64:633–637.
- [19] Parks MM, Mitchell PR. Cranial nerve palsy. In: Tasman W, Jaeger EA, editors. *Clinical Ophthalmology*. Vol. 1. Philadelphia: JB Lippincott; 1991:1–17.