Intracranial Hypertension in Cystinosis Is a Challenge: Experience in a Children's Hospital

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Abstract *Background:* Cystinosis is a rare systemic lysosomal disease affecting mainly the kidney and eye. Ocular involvement in cystinosis is universal being the presence of cystine crystals in the cornea a diagnostic criterion and one of the earliest manifestations of the disease. Neuro-ophthalmologic manifestations are considered a rare and late complication in these patients. The aim of this article is to report the unexpectedly high incidence of intracranial hypertension in children with cystinosis at our centre.

Methods: This study included eight children (0–16 years of age) with cystinosis seen at the paediatric ophthalmology department, Hospital Universitari Vall d'Hebron (Barcelona, Spain), a tertiary hospital, over the last 5 years.

Results: Three girls and five boys, mean age: 9.6 years (range: 5–14 years), were studied. During follow-up, 4 out of 8 developed papilledema and confirmed high cerebrospinal fluid (CSF) pressure. The only symptomatic child presented an Arnold–Chiari anomaly with enlarged ven-

tricles, whereas the other three, all asymptomatic, were diagnosed by scheduled fundoscopy and had normal neuroimaging studies. All four patients had at least one known risk factor for developing intracranial hypertension: initiation of growth hormone therapy, tapering of corticosteroids, acute renal failure and Arnold–Chiari malformation. Two of them required a ventriculoperitoneal shunt.

Conclusions: Our results show that intracranial hypertension can occur more frequently than expected in patients with cystinosis. Furthermore, visual prognosis depends on early diagnosis and prompt treatment. A multidisciplinary approach is necessary, and we recommend fundoscopic examinations in all paediatric patients with cystinosis whether or not they present symptoms.

Abbreviations

CKD	Chronic kidney disease
CSF	Cerebrospinal fluid
GFR	Glomerular filtration rate
ICP	Increased intracranial pressure
IH	Intracranial hypertension
LP	Lumbar puncture
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
PTCS	Pseudotumor cerebri syndrome
rhGH	Recombinant human growth hormone
VA	Visual acuity

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Introduction

Cystinosis (OMIM #219800) is a rare systemic lysosomal disease that mainly affects the kidney and eye. It is an autosomal recessive disease caused by mutations of the

CTNS gene (Touchman et al. 2000), with an estimated incidence of 1 in 100,000 live births. Most patients present with severe Fanconi syndrome from infancy and progressive renal impairment. Neurocognitive involvement is generally mild but very frequent, even in children. The primary cognitive deficits in these patients occur in the areas of visual-spatial ability, visual-motor coordination and short-term visual memory (Viltz and Trauner 2013). Prognosis depends on early diagnosis, and the prompt initiation of cysteamine treatment (Gahl and Nesterova 2010).

Ocular involvement is universal in cystinotic patients. The presence of cystine crystals in the cornea is a diagnostic criterion and one of the earliest manifestations. Crystals are also deposited in other ocular structures such as the conjunctiva, iris, choroid and retina (Richler et al. 1991; Dureau et al. 2003; Tsilou et al. 2007). Neuro-ophthalmologic manifestations are considered a rare and late complication in these patients (Nesterova and Gahl 2008).

Increased intracranial pressure (ICP) in children is often secondary to traumatic brain injury, hydrocephalus, brain tumours or intracranial infections. However, pseudotumor cerebri syndrome (PTCS) is uncommon in childhood, with an estimated incidence of 0.1–1 per 100,000. PTCS is a condition defined by elevated ICP in the absence of clinical, laboratory or radiologic evidence of infection, vascular abnormality, intracranial space-occupying lesion or hydrocephalus (Rangwala and Liu 2007; Friedman et al. 2013). PTCS has been reported in few patients with cystinosis; however, its real incidence remains unknown (Dogulu et al. 2004; Rogers and McGregor 2010).

The aim of this study was to report the unexpectedly high incidence of intracranial hypertension (IH) in children with cystinosis followed at our centre. We would like to discuss why patients with cystinosis have a higher incidence of IH and why IH is more severe than in the normal paediatric population.

Methods

The study included eight children with cystinosis followed at the paediatric ophthalmology department of a tertiary hospital, over the last 5 years. Cystinosis was confirmed in all cases with a white blood cell cystine content >1 nmol/2 cystine/mg protein and a positive genetic diagnosis. There were three girls and five boys with a mean age of 9.6 years (range: 5–14 years). During their regular ophthalmologic follow-up, 4 out of 8 developed papilledema (Table 1). Brain magnetic resonance imaging (MRI) with magnetic resonance venography (MRV) was performed in all cases with papilledema and, unless contraindicated, cerebrospinal

fluid (CSF) pressure was measured by lumbar puncture (LP).

We had previously examined our patients annually; however, in January 2015 our protocol was changed to at least one visit every 3 months in five patients because they were enrolled in a clinical trial conducted locally to study the efficacy and safety of a new topical cysteamine formulation in viscous solution.

Results

Case 1: A 9-year-old girl was diagnosed with cystinosis at the age of 7 months. She had Fanconi syndrome and mild reduction in the glomerular filtration rate (GFR). Her chronic treatment included oral and topical cysteamine, vitamin D3, potassium and phosphate salt supplements, thiazides, carnitine, omeprazole, losartan and recombinant human growth hormone (rhGH) (0.34 mg/kg/week). She had been treated with rhGH for 3 years. Ophthalmologic examination 10 months previously had been unremarkable except for the presence of corneal crystals. She had complained of headache and loss of vision during the previous weeks as well as non-specific back pain. Ophthalmologic assessment showed visual acuity (VA) of 20/60 in her right eye and hand movements in her left eye, with a left relative afferent pupillary defect. Colour vision was severely impaired. Fundus examination revealed severe bilateral disc oedema (Fig. 1). MRI and MRV revealed an Arnold–Chiari anomaly and enlarged ventricles. Venous sinus thrombosis was ruled out. Owing to the Arnold–Chiari anomaly, an LP was not done and neurosurgeons performed a continuous recording of CSF pressure. ICP was 30 cm of water (the normal value in children is ≤ 25 cm of water) (Friedman et al. 2013). Blood pressure and extensive coagulation studies were strictly normal. She was diagnosed with “fulminant” intracranial hypertension. Owing to the severity of the papilledema and significant visual loss, the patient underwent ventriculoperitoneal shunting within 1 week of diagnosis. Treatment with rhGH had been stopped at presentation. Unfortunately, VA and visual fields were severely affected. Fundus examination revealed optic disc atrophy and right macular atrophy.

Case 2: A 10-year-old boy was diagnosed with cystinosis at the age of 12 months, with a successful kidney transplant 12 months previously. His medications prior to admission included oral and topical cysteamine, tacrolimus, mycophenolic acid, methylprednisolone (on a tapering dose), enalapril, omeprazole and rhGH (0.36 mg/kg/week). Regular treatment with rhGH had been stopped immediately after transplantation but was resumed 2 weeks before our visit. Ophthalmologic examination 7 months before had

Table 1 Characteristics of patients with cystinosis and intracranial hypertension

Patients	Age (years)	Gender/age at diagnosis (months)	Genetic diagnosis	Cystine levels nmol $\frac{1}{2}$ cys/mg prot	Serum Cr (mg/dL)	Renal status	BP (mmHg)	Risk factors IH
1	11	F/7	Homozygous/57Kbdel	1.75	0.86	CKD 2	116/63	Arnold–Chiari rhGH
2	10	M/12	Heterozygous/57Kbdel /297-312del16pb	2.7	1.6	K Tx (12 months before)	102/68	rhGH Corticosteroids (tapering) Acute renal failure
3	7	M/6	Homozygous/646dupA	4.09	0.66	K Tx (11 months before)	99/69	Corticosteroids (tapering)
4	6	M/20	Heterozygous 57Kbdel – c.682-1G>T	1.46	0.81	CKD 2	97/55	rhGH

BP blood pressure, CKD chronic kidney disease, Cr creatinine, cys cysteine, F female, IH intracranial hypertension, K Tx kidney transplant, M male, prot protein, rhGH recombinant human growth hormone

Fig. 1 Severe bilateral disc oedema with dilated veins, many exudates and multiple peripapillary and peripheral retinal haemorrhages in both eyes of Case 1 (right eye on the left and left eye on the right)

been unremarkable except for corneal crystals. The patient was evaluated by the ophthalmology department in order to be enrolled in our clinical trial. He often complained of epigastric pain, nausea and reflux and occasional headache that were attributed to the cystinosis itself or treatment-related side effects. Although ophthalmologic assessment showed normal VA, the optic discs were swollen. MRI and MRV revealed great distension of the perioptic subarachnoid space (Fig. 2). LP yielded an opening pressure of 36 cm of water with normal CSF composition. Routine laboratory tests revealed acute graft dysfunction attributed to acute rejection and treatment with rhGH was stopped.

The patient received three IV pulses of methylprednisolone and oral acetazolamide. However, the acetazolamide caused severe metabolic acidosis and had to be stopped. Corticosteroids were not sufficiently effective to control IH and the patient required ventriculoperitoneal shunting. Fortunately, his renal function improved. His VA is currently normal; however, the visual field shows an enlarged blind spot and fundus examination reveals mild optic disc atrophy.

Case 3: A 7-year-old boy was diagnosed with cystinosis at 6 months of age. He had had a successful kidney transplant 11 months before the visit. His medication included oral and topical cysteamine, tacrolimus, mycophenolic acid,

Fig. 2 MRI T2-weighted axial image showing distension of the perioptic subarachnoid space (*arrow*) and flattening of the posterior aspect of the globe in Case 2

methylprednisolone (on a tapering dose), losartan and labetalol. Ocular examination 2 months previously had been normal, except for corneal crystals. He was seen at a scheduled visit for our clinical trial with no visual or systemic complaints. His VA was normal but fundus examination showed bilateral optic disc swelling. MRI and MRV were unremarkable and LP revealed an opening pressure of 37 cm of water with normal CSF composition. Treatment was initiated with oral acetazolamide (8 mg/kg/day) b.i.d. and corticosteroids (0.5 mg/kg/day). Low doses of acetazolamide were administered as the patient developed severe metabolic acidosis requiring large doses of oral sodium bicarbonate. A follow-up visit 1 month later revealed normal optic discs. VA and visual field were also normal.

Case 4: A 6-year-old boy was diagnosed with cystinosis at the age of 20 months. His medication prior to admission included oral and topical cysteamine, vitamin D3, candesartan and rhGH (0.3 mg/kg/week) that had been started 4 weeks earlier. Ocular examination 1 month previously had been normal, except for corneal crystals. Papilledema was detected during a routine eye examination at a scheduled visit in our clinical trial. MRI and MRV were unremarkable except for mild distension of the perioptic subarachnoid space and a partially empty sella. LP revealed an opening

pressure of 25 cm of water with normal CFS composition. rhGH was stopped and treatment was initiated with oral acetazolamide (2.5 mg/kg/day) b.i.d. A follow-up visit 1 month later revealed normal optic discs and his VA was also normal. Visual fields were not performed because of his young age.

Discussion

Intracranial hypertension is considered a rare and late complication in patients with cystinosis. However, two reports suggested a higher incidence of PTCS in patients with cystinosis than in the general population: Dogulu et al. (2004) found an estimated frequency of 5% of PTCS in their study of approximately 150 patients and Rogers and McGregor (2010) reported three patients out of six with PTCS. In our series, 4 out of 8 children developed intracranial hypertension, three had PTCS and the fourth a pathologic MRI.

Cystinosis is a multisystemic disease and patients are treated with several different drugs. Many potential risk factors are associated with the development of secondary PTCS: renal failure, vitamin D deficiency, treatment with rhGH, thyroxine and calcineurin inhibitors, and tapering of

steroids. Also, cystinosis per se may play a primary role in the development of IH as the deposit of cystine in meninges and arachnoid villi may reduce CSF absorption (Viltz and Trauner 2013; Parnes et al. 2008; Ross et al. 1982). Furthermore, Rao et al. (2015) reported that children with cystinosis have a 12-fold higher prevalence of Chiari I malformations than the general paediatric population. Poor metabolic disease control may also contribute to IH, as observed in two of our patients (Cases 2 and 3) who maintained elevated cystine levels despite maximum cysteamine doses. A relationship between the preservation of renal glomerular function and compliance with cysteamine treatment has also been reported (Nesterova et al. 2015), and we thought it could also have a relationship with IH.

Furthermore, treatment with cysteamine may also contribute to IH development since it is described as a potential adverse effect on the prescription drug labelling (PRO-CYSBI® (cysteamine bitartrate) delayed-release capsules. Label information). However, in our opinion, it is difficult to establish a cause-and-effect relationship between cysteamine treatment and IH as many other risk factors coincide at the same time in these patients.

It is important to note the association of rhGH therapy and PTCS (Rogers et al. 1999). Reeves and Doyle (2002) reported the prevalence in the GH-treated population to be approximately 100 times higher than in the general paediatric population. Temporary discontinuation of rhGH is required, with a later prescription at a lower dose which usually prevents the reappearance of IH. Children with chronic kidney disease (CKD) treated with rhGH are more likely to develop PTCS than those with other primary diseases (Reeves and Doyle 2002; Koller et al. 1997; Blethen et al. 1996). It is postulated that the antidiuretic effect of rhGH could be the cause of IH and that effect could be more evident in patients with a decreased GFR (Souza and Collett-Solberg 2011). Alternatively, or in addition, GH may cross the blood–brain barrier and raise local levels of insulin-like growth factor I which, in turn, increases CSF production from the choroid plexus (Darendeliler 2009). In children with cystinosis, this mechanism could trigger other concurrent risk factors such as reduced posterior cranial space and CSF flow obstruction caused by cystine crystals.

Our patients were receiving rhGH doses between 0.3 and 0.36 mg/kg/week, the standard doses in children with CKD, owing to growth hormone resistance. Therefore, IH in cystinosis could be due not only to rhGH treatment but also to the higher doses used. This could explain why patients 2 and 4 developed IH within the first 4 weeks of rhGH treatment. However, patient 1 developed that complication after 3 years of rhGH treatment, and the causal relationship between rhGH and IH is thus difficult to establish in this case and could be related to Arnold–Chiari malformation.

Malozowski et al. (1995) reported that higher doses and increased frequency of administration since the introduction of rhGH in 1985 may be contributing to the development of IH in some patients. However, Reeves and Doyle (2002) found no relationship between the rhGH dose and IH development.

Severe growth retardation is a clinical hallmark in children with cystinosis. In the literature, rhGH treatment in those patients has been reported to be safe and effective (Wühl et al. 2001; Besouw et al. 2012); thus, the possible adverse effects of rhGH observable in a few patients should be weighed against the known treatment benefits before initiating therapy, and rigorous controls should be programmed.

Furthermore, patients with cystinosis have many risk factors and their renal disease may complicate the use of conventional IH treatment. Since acetazolamide in our patients caused significant metabolic acidosis owing to persistent or residual Fanconi syndrome, we recommend low doses. Half of our patients needed a ventriculoperitoneal shunt. Case 1 presented “fulminant” IH with acute presentation of profound vision loss and severe papilledema becoming legally blind despite prompt treatment. Overall, our results show that IH in patients with cystinosis is more aggressive than in paediatric patients with IH. Nevertheless, in Cases 3 and 4, prompt diagnosis led to the resolution of papilledema without visual damage with systemic treatment alone.

Another important issue we wish to emphasize is that some of the clinical manifestations in these patients may be attributable to their renal disease or their medications rather than to IH, which can delay the diagnosis. Nausea and vomiting could be non-specific symptoms of cystinosis secondary to the deposition of crystals in the digestive system. Side effects of oral cysteamine include nausea, vomiting and headache, with the latter also being a main complaint in IH. It is important to remember that, among young children with IH, headache is less common than in adults and they are more often asymptomatic.

An important limitation of our study was the small case series, and it cannot be assumed that all patients with cystinosis have the same risk.

Conclusion

Ophthalmologists are used to being concerned about cystine crystals in the cornea and retina; however, we must become more aware of the possibility of optic nerve disease.

Our results show that IH can occur more frequently than expected in patients with cystinosis. A multidisciplinary approach is necessary since these patients present many risk

factors and their renal disease may also complicate the use of conventional IH treatment. The prescription of rhGH in cystinosis is almost universal, but we recommend starting at the lowest effective dose, with gradual increases up to the therapeutic dose.

Visual prognosis depends on early diagnosis and prompt treatment which cannot rely on clinical symptoms alone. We recommend regular and standardized fundoscopic examinations especially in children with risk factors, such as initiation of rhGH, tapering of corticosteroids and treatment with calcineurin inhibitors after kidney transplantation.

Take-Home Message

Intracranial hypertension is an unexpected complication in patients with cystinosis and regular fundoscopic examinations are recommended to rule out papilledema.

Compliance with Ethics Guidelines

Conflict of Interest

Nieves Martín-Begué, Silvia Alarcón, Charlotte Wolley-Dod, Luis Enrique Lara, Álvaro Madrid, Paola Cano, Mireia del Toro and Gema Ariceta declare that we have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in this study. Additional informed consent was obtained from all patients (or from their parents) for which identifying information is included in this article.

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