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Case Report

Neuropathic Cystinosis: A Rare Case Report

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ABSTRACT

Cystinosis is a lysosomal storage disease characterized by an intracellular accumulation of cystine in different organs and tissues, leading to potentially severe organ dysfunction. The neurological manifestations in cystinosis are generally late and non-dominant. In this report, we described a case of infantile cystinosis with dominant neurological manifestations at the presentation. A three-and-a-half-year-old male baby was presented to the pediatric teaching hospital with a history of poor growth and delayed milestones. The condition started at the age of six months, with abnormal growth and development. Family history was positive for mental retardation. The child had a few dysmorphic features such as frontal bossing and wrist widening. The renal function tests were abnormal. Brain magnetic resonance image (MRI) revealed changes in bilateral frontal primitive gyral pattern. Bone marrow aspiration and liver biopsy were both in favor of cystinosis. Slit-lamp examination of the eyes demonstrated crystalline crystals and keratinopathy. A genetic study identified a mutation in the CTNS gene, which was consistent with the autosomal recessive nephropathic cystinosis. In conclusion, neurological manifestations could be one of the earlier presentations of infantile cystinosis.

Introduction

Cystinosis is a lysosomal storage disease characterized by an intracellular accumulation of cystine in different organs and tissues, leading to potentially severe organ dysfunction. It is an autosomal recessive disorder due to a mutation in the CTNS gene on chromosome 17. Its estimated incidence is 1 in 100,000 live births and is expected to be affected by the extent of consanguinity in the community (1,2).

Three clinical forms of cystinosis have been described based on the age of presentation: infantile, juvenile, and adult (2,3). Both the juvenile and adult types are rare and more indolent than the infantile form, and the adult form is sometimes called the ocular form because it is characterized by corneal cystine accumulation (3,4). The infantile type is by far the most common and severe form of cystinosis (1-3). It is also called nephropathic type, with a phenotype consisting of renal Fanconi syndrome, and a consecutively progressive loss of glomerular function leading to end-stage renal failure (2,4). On the other hand, the extra-renal manifestations are observed relatively late during the course of the disease, despite the early cystine accumulation. Nearly all untreated nephropathic cystinosis patients will develop an extra-renal involvement later in life. These manifestations are seen in almost all tissues and organs including the eyes, thyroid, pancreas, spleen, lymph nodes, bone marrow, and central nervous system (4,5).

Until recently, the central nervous system (CNS) has been considered clinically uninvolved in cystinosis (6,7). The involvement of the CNS in patients with cystinosis has been reported only recently (8,9). The first report of neurological clinical presentation of cystinosis was in 1982 (10). In this case report, we described a patient with infantile cystinosis who was dominantly presented with neurological manifestations.

Case report

A three-and-a-half-year-old male baby was presented to the pediatric teaching hospital with a history of poor growth and delayed milestones. The condition started at the age of six months, as noticed by his family that he had no normal growth and development like other babies of the same age. At that age, his mother mentioned that he had weak head control, unable to role, and had no social smile. At the age of one year, he could sit but with support, however, he couldn't crawl or walk and was unable to say any simple words. Also, the family noticed that he looked ill, and thin, and had a poor appetite and weight gain. The family started to consult private clinics and different lines of treatment, mainly tonics, were prescribed to him, but without any improvement in growth and development. At the age of 2.5 years, his condition got worse, His mother said that he looked confused and was sensitive to light and started to have attacks of fit. After medical consultation, he was diagnosed to have delayed milestone and was put on antiepileptic drugs. The baby gradually started to have vomiting, constipation, and abdominal distension, so he was referred to the GIT unit of the pediatric teaching hospital for further evaluation.

A detailed history was taken from the mother at the presentation. He was a full-term baby and delivered by cesarean section to a G5P2A3 mother. His birth weight was 3 kilograms. The prenatal, natal, and postnatal history was uneventful. His parents were first cousins. His older sister had the same presentation. There was a positive family history of mental retardation. On examination, the baby was conscious, ill looking, thin, pale but no jaundice or cyanosis. He had fair colored skin and hair, and no skin lesions were found. There were a few dysmorphic features like frontal bossing, wrist widening, and myopathic facies (figure 1). Systemic examination was generally normal, except for generalized hypotonia and hepatomegaly (10 cm below the costal margin). Body measurements (occipital-frontal circumference, body weight, and height) were below the third centile.

The first line of investigations revealed the following results. WBC=10.6 $x10^9$/L, PCV=31%, PLT= $313x10^9$/L,000, ESR= 32mm/ist hr, and normal blood film. Regarding renal function tests, the initial readings of blood urea and serum creatinine were 71 mg/dl and 0.67 mg/dl, respectively while the final readings were 54.2 mg/dl and 0.9 mg/dl, respectively Liver function tests showed the following results: serum ALT=31.9 U/l, AST=45.3 U/l, ALP=152.8 U/l, direct bilirubin= 0.088 mg/dl, and total bilirubin=0.203 mg/dl. Other biochemical tests were serum uric acid= 2.5 mg/dl, random blood sugar= 149 mg/dl, serum Na=131 mmol/l, serum K=2.4 mmol/l, serum Cl=98.1 mmol/l, serum phosphate=2.4 mg/dl. Blood gas analysis showed the following findings: PH=7.28, PCO2=33.4, Lactate=1.7, AG=14.6, HCO3=15.2, K=2.1, Na=133, Ca=0.76, Cl= 95. The coagulation study showed PT=13 s, PTT=35 s, and INR=1. General urine exam was normal apart from +++ of uric acid, and specific gravity of 1.010. Septic screen tests were negative. Abdominal ultrasound was normal apart from mild hepatomegaly. Echocardiography was normal while electroencephalography showed focal epilepsy. Magnetic resonance image (MRI) revealed changes in bilateral frontal primitive gyral pattern. There was a generalized decrease in white matter mantle with ill-defined peri-ventricular T2 and FLAIR hyper-intensity prominent around the dilated trigonal regions and around the dilated deep occipital horn. Such a combination of findings implied the presence of marked leukomalacia. In addition, there were features of hypoplastic pituitary gland and discrete regions of decreased or delayed myelination. Corpus callosum was normal, as well as the cingulate gyrus, posterior fossa structures, midline structures, and the structures at the cranio-cervical junction. No definite changes in old Kernicterus.

Based on the above findings, cystinosis was put on top of the differential diagnosis list. Accordingly, the second line of investigations was directed to exclude other differential diagnoses like galactosemia, tyrosinemia, hereditary fructose intolerance, Lowe syndrome, and Dent's disease. Bone marrow aspiration and liver biopsy were both in favor of cystinosis. Slit-lamp examination of the eyes detected crystalline crystals and keratinopathy. Finally, a genetic study was made and identified a loss of 9kb involving the CTNS gene, which was consistent with autosomal recessive nephropathic cystinosis.

Discussion

Interest in the clinical CNS manifestations in cystinosis was first noted in 1982, when Levine et al presented a 19-year-old cystinosis patient with neurological manifestations. The CNS involvement is considered one of the most recent and rare complications of cystinosis. This complication takes a long time to appear and generally develops after 10 years of age in cases where treatment is not initiated yet (8).

Early reports of clinical neurological manifestations in cystinosis were described in isolated case reports and generally thought to be secondary to systemic complications such as renal failure and other metabolic imbalances (11). The first study of detailed cognitive and neurological function in cystinosis reported gross and fine motor incoordination and generalized hypotonia in a majority of individuals with cystinosis, suggesting widespread, albeit nonspecific neurological involvement (12). The report also identified a specific cognitive deficit in visual spatial functioning in the 22 children and adults with cystinosis who participated in the study.

In contrary to what is published in the literature, our case report added a new case to the pool of case reports. The neurological manifestations appeared very early and rapidly in the first year of life, even before the renal involvement. The usual presentation in infantile cystinosis patients is renal Fanconi syndrome, however, in our patient, the CNS involvement was unusually dominant. Our aim in reporting the case report was to expand the clinical features of infantile cystinosis and consider CNS involvement as a potential early manifestation. We alert pediatricians to consider cystinosis as one of their differential diagnoses when challenging a patient with early progressing neurological manifestations, poor development, and

delayed milestones, especially if there is a positive family history of the same presentation.

Conclusion

Neurological manifestation could be one of the earlier manifestations of infantile cystinosis.

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Conflict of Interest

The authors have no conflict of interest and financial support to disclose.

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