Case Report

Bartter syndrome associated with nephropathic cystinosis

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ABSTRACT

Bartter syndrome is a rare inherited defect in the thick ascending limb of the loop of Henle. It is characterized by low potassium levels (hypokalaemia), increased blood pH (alkalosis) and normal to low blood pressure. There are three types of Bartter syndrome: neonatal, the classic type and Gitelman syndrome. Nephropathic cystinosis is an autosomal recessive disorder characterized by accumulation of free cystine in lysosomes due to disorder of lysosomal transport that can lead to end stage renal failure within 10 years and multiorgan impairment. We report a 5 year 9 month old child with Bartter syndrome associated with nephropathic cystinosis, hypothyroidism and rickets. Hitherto, only a handful of similar cases have been reported in the literature.

Keywords:

Bartter syndrome; Nephropathic cystinosis; Hypothyroidism; Rickets; Child.

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INTRODUCTION

Bartter syndrome is a rare inherited defect in the thick ascending limb of the loop of Henle. It is characterized by low potassium levels (hypokalaemia), increased blood pH (alkalosis) and normal to low blood pressure. There are three types of Bartter syndrome: neonatal, the classic type and Gitelman syndrome [1]. Nephropathic cystinosis is an autosomal recessive disorder characterized by accumulation of free cystine in lysosomes due to disorder of lysosomal transport that can lead to end stage renal failure within 10 years and multiorgan impairment [2]. Patients with classic Bartter syndrome may have symptoms in the first two years of life, but they are usually diagnosed at school age or later. They present with polyuria, polydipsia, and a tendency to dehydration, but normal or just slightly increased urinary calcium excretion without the tendency to develop kidney stones. These patients also have vomiting and growth retardation. Kidney function may continue to be normal if the disease is treated but occasionally patients proceed to end-stage renal failure [3].

The diagnosis of cystinosis can be missed in infants, because not all signs of renal Fanconi syndrome are present during the first months of life. In older patients, cystinosis can mimic idiopathic nephrotic syndrome [4].

CASE REPORT

A 5 year 9 month old Sudanese child presented to King Salman Hospital, Riyadh, Saudi Arabia, with history of polyuria, polydipsia and short stature, which were noticed for the last three years. He was delivered by normal vaginal route at term with birth weight of 3.4 kilogram. The pregnancy and his neonatal period were uneventful. His parents are first-degree cousins, they have other three daughters ages 16, 13 and 12 years, all are alive and well. There is no family history of note. He looked normal up to the age of 3 years when he started to have frequent vomiting, which was not projectile with watery non-offensive diarrhoea that contained no mucus or blood. He was not thriving well with poor appetite. There were no other significant complains. His parents sought medical advice at different hospitals where he was admitted once at another hospital few months earlier with the same problem.

On examination, he was severely stunted with a weight of 11 kg (3^{rd} – 4^{th} SD) below the mean and his height 89 cm (4th – 5^{th} SD) below the mean. His blood pressure was normal. He was pale, not cyanosed or jaundice with subtle dysmorphic features including large eyes, drooping mouth and thin sparse hair. His sclerae were clearly injected with remarkable photophobia. The cardiovascular and respiratory systems were normal. He had a distended abdomen with multiple cautery marks, but had neither hepatosplenomegaly nor abdominal masses. His muscles were wasted but with normal tone and reflexes.

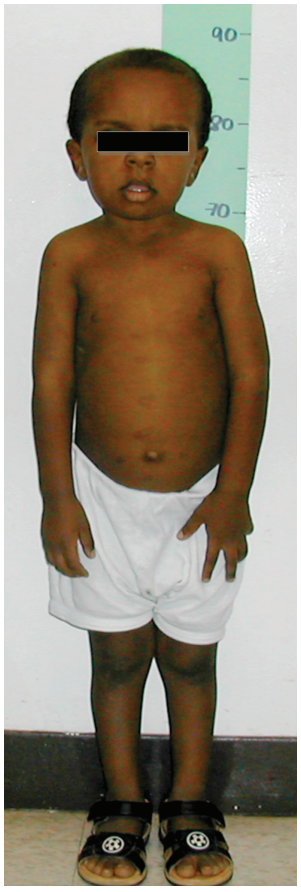

Figure 1 – The Patient at the age of 5 years and 9 months was severely stunted and had subtle dysmorphic features. He had a distended abdomen with multiple cautery marks.

Biochemical investigations included blood gas analysis, full blood count, renal and liver function tests, lipid profile and baseline endocrine and metabolic investigations (Table 1).

Table 1 - The biochemical results of the patient

Test	Result	Normal range
Hb	12.8 gm /dl	11.5 -15.5
WBC	7100 cells	5.500-11.500 (differential normal)
HCT	39.4 %	35-45
MCV	78.4 fl	77-95
MCH	25 pg/cell	25 -33
PLT	$240x10^9$	150-400 $x10^9$
ESR	15	0 -10
BUN	43 mg/dl	20-40
Creatinine	1.0 mg/dl	3 -1
Random blood sugar	78 mg/dl	50-126
Sodium	129 mEq/l	138 – 145
Potassium	2.1 mEq/l	3.5 – 4.5
Chloride	91 mEq/l	98 – 106
Osmolality	272 mOsmol/l	275 -295
Calcium	4.5 mg/dl /dl	8.8-10.8
Phosphorus	2.75 mg/dl	3.7-5.6
Magnesium	1.9 mg/dl	1.5- 2.3
Total serum bilirubin	0.352 mg/dl	less than 1
AST	66 IU/L	15 – 55
ALT	41 IU/L	5- 45
Alkaline Phosphatase	693 IU/L	145 -420
Total protein	72 gm/l	6.1 -7.9
Albumin	41 gm/l	4.0 -5.2
Cholesterol	456.3 mg/dl	109 -189
Triglyceride	194.9 mg/dl	31 -108
High density lipoprotein	125 mg/dl	35 -84
Tandem MS screen	normal	-
TSH	100 mlU/l	0.27 –7.1
Parathyroid	14.72 mlU/l	1.6 – 6.9
Cortisol	408.5 ug/dl	171 – 539
Arterial blood gas	PH 7.48, PCO2 28.7mmHg, PO2 81.5 mmH, HCO3 27.5mEq/l	PH (N 7.35 -7.45), HCO3 (N 21 -27)

ALT – Alanine transferase, AST – Aspartate transferase, BUN – Blood urea nitrogen, ESR – Erythrocyte sedimentation rate, Hb – Haemoglobin, HCT – Haematocrit, MCV – Mean corpuscular volume, MCH – Mean corpuscular haemoglobin, MS – Mass spectrometry, PLT- Platelets, WBC – White blood cells.

Abdominal ultrasound showed mild hepatomegaly. Twenty four hour urine volume 1760 ml (3 ml /kg/hr), urine protein in 24 hours was 1.09 gm/day. Glomerular filtration rate was 29.18 ml/min/1.73m^2.

Further work up with ophthalmological evaluation and slit lamp examination (Figures 2 and 3) revealed heavy cystine crystals in the anterior chamber and sclera.

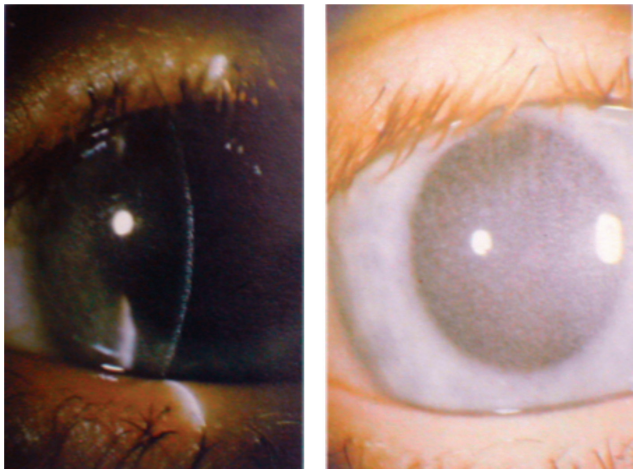

Figure 2 - Slit lamp examination showed crystals diffusely present throughout the corneal surface.

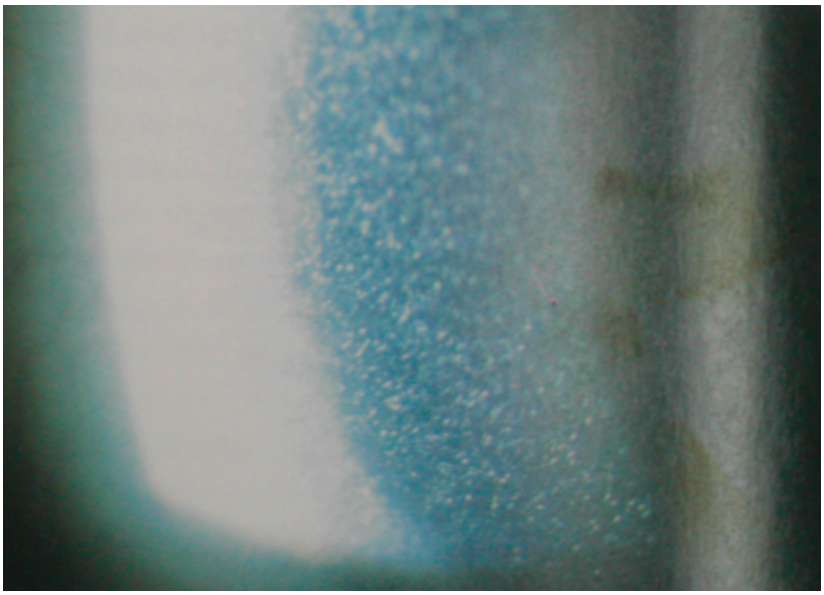

Figure 3 - Slit lamp examination revealed the punctate needle-shaped crystals.

Cystine level in leucocytes was requested and sample was sent to an international laboratory in Germany where the result showed a very high concentration of cystine that confirmed the diagnosis of cystinosis.

The management was started with correction of fluids and electrolytes replacement mainly with potassium chloride, treatment of hypothyroidism with L-thyroxine and treatment of rickets with alfacalcidol. Restriction of cystine and methionine in diet was applied and the specific treatment with Cysteamine (Cystagon) tab of 150 mg four times daily, and cystagon eye drops were initiated.

DISCUSSION

Bartter syndrome, originally described by Bartter and colleagues in 1962, represents a set of closely related, autosomal recessive renal tubular disorders characterized by hypokalaemia, hypochloraemia, metabolic alkalosis, and hyperreninemia with normal blood pressure [5]. The underlying renal abnormality results in excessive urinary losses of sodium, chloride, and potassium. Bartter syndrome has been traditionally classified into three main clinical variants: neonatal (or antenatal) Bartter syndrome, classic Bartter syndrome and Gitelman syndrome [6]. Advances in molecular diagnostics have revealed that Bartter syndrome results from mutations in numerous genes that affect the function of ion channels and transporters that normally mediate transepithelial salt reabsorption in the distal nephron segments. Several mutations have been identified to date. Such advances may result in the development of new therapies.

The first case of nephropathic cystinosis was reported in 1903, clinical understanding matured after 1930 by Fanconi in Switzerland .The modern era in investigation began in 1967 when amino acid analysis by ion exchange chromatography became sensitive enough to measure minute amount of cystine [7]. The incidence is estimated to be 1 case per 100,000 to 200,000 live birth. About 400 cases of classic nephropathic cystinosis were reported in North America with about 15 new cases diagnosed each year. The responsible gene is CTNS at chromosome 17p13 [8,9]. All patients appear to have mutations in CTNS, and more than 50 different CTNS mutations have been described. The gene CTNS encodes for protein cystinosin, which is deficient in cystinosis and is needed for the transport of lysosomal cystine to cytosol. Therefore, cystine increases inside the lysosomes 50-100 times leading to crystals formation and cell damage. The clinical manifestations appear several months after birth with variable symptoms and signs. Kidney involvement is the foremost clinical characteristic as renal Fanconi's syndrome (polyuria, polydipsia, aminoaciduria, proteinuria, glucosuria, and phosphaturia and electrolyte imbalance).

The classic (infantile) nephropathic cystinosis accounts for 95% and is the most severe one [10]. The intermediate (late onset) or (juvenile) has a slower rate of progression. There is an ocular non-nephropathic (benign) form with ocular manifestations, and lacking all systemic symptoms [11].

Diagnosis is confirmed by measuring the leukocyte cystine content [12], followed by molecular genetic testing. Prenatal diagnosis is also possible biochemically, by detecting elevated cystine concentrations in both chorionic villi and amniocytes. Established treatment is mainly supportive with unrestricted intake of water and salt [13]. The specific treatment is cysteamine, which depletes cells of cystine. The administration of cysteamine at 1.3–1.9 g/m^2 in four daily doses drastically lowers the cystine content of the lysosomes, postpones or even prevents the deterioration of renal function and the development of extra-renal complications. Furthermore, cysteamine treatment improves growth. Cysteamine should be administered as soon as the diagnosis of cystinosis is made, and continued life long, even after renal transplantation to protect the extra-renal organs.

Many patients have survived into the third decade of life without the need for renal transplantation if diagnosed early and treatment is established before symptoms develop.

CONCLUSION

Cystinosis is the major cause of inherited Fanconi syndrome, and should be suspected in young children with failure to thrive and signs of renal proximal tubular damage.

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