

### Nephrotic Syndrome with X-linked Ichthyosis, Kallmann Syndrome and Unilateral Renal Agenesis

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*We describe a 10-year-old boy with X-linked ichthyosis, Kallmann Syndrome and unilateral renal agenesis who presented with nephrotic syndrome. DNA analysis revealed deletion of the Steroid Sulfatase (STS) gene. STS deficiency in X-linked ichthyosis leads to cholesterol sulfate accumulation, which induces transglutaminase-1 dysfunction. Since the slit diaphragm of the glomerular epithelial cell is a modified adherens junction, the accumulation of cholesterol sulfate could interfere with the normal slit diaphragm function of the glomerular visceral epithelial cell, resulting in nephrotic range proteinuria. The child went into remission on oral prednisolone.*

**Key words:** X-linked ichthyosis, Kallmann syndrome, Nephrotic syndrome, Steroid sulfatase gene.

X-linked ichthyosis (XLI) is a disorder of keratinization caused by Steroid Sulfatase (STS) deficiency. The STS gene is located on the short arm of X Chromosome (Xp22.3). When XLI is caused by deletion of the STS gene, it may be associated with other contiguous gene syndromes such as Kallmann syndrome. We describe a 10-year-old boy with X-linked ichthyosis, Kallmann

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syndrome and unilateral renal agenesis who developed steroid responsive nephrotic syndrome.

#### Case Report

A 10-year-old boy was brought with swelling over body for 5 days, first noticed in the periorbital region followed by progression over the next 4 days to anasarca. There was no history of oliguria, jaundice, diarrhea or dyspnea, and no significant past history. The child was a product of nonconsanguineous marriage and had dry, thickened and scaly skin since birth. Similar ichthyotic skin was seen in the maternal uncle and in two sons of the sister of the maternal grandmother. There was no history of renal disease in the family. Anthropometrical evaluation revealed a proportionate short stature with height of 117 cm (below 5th percentile). Blood pressure was 122/90 mmHg (consistently more than 95th percentile). On examination, the boy was found to have anasarca, but no pallor, icterus, lymphadenopathy or hepatosplenomegaly. Large polygonal dark brown scales were seen over the extensor and flexor aspects of the lower limbs giving a "fish-scale" appearance. Flexural areas were spared. On further clinical examination, the child was found to have anosmia (There was similar history of anosmia in relatives affected with ichthyosis). Right testes was not palpable in the scrotum or the inguinal canal; left testes was atrophic with volume of less than 1 mL. Investigations revealed proteinuria 2.2 g/day, serum albumin 2.3 g/L and cholesterol 260 mg/dL. Kidney function tests were normal. Urine microscopic examination and C3 levels were normal.

Hepatitis B surface antigen (HbsAg), anti-HCV antibodies and antinuclear antibody were negative. Ultrasonography of the abdomen revealed absent left kidney, while the right kidney showed compensatory hypertrophy. Left kidney agenesis was confirmed by DTPA scan. Ophthalmological examination and audiometry were normal. Serum LH level was < 0.07 mLU/mL, FSH was 0.28 mLU/mL, testosterone level was 5.1 ng/dL (normal

prepubertal value 10-30 ng/dL). Molecular DNA analysis revealed deletion of the STS (Steroid sulfatase) gene.

The child was diagnosed as nephrotic syndrome with X linked ichthyosis with Kallman syndrome and started on prednisolone tablets at 2 mg/kg/day, on which he went into remission on the sixth day. Hypertension was controlled on enalapril. He was discharged on prednisolone. He is presently in remission and under follow-up.

### Discussion

X-linked ichthyosis is a genodermatosis caused by Steroid Sulfatase deficiency. Steroid Sulfatase hydrolyses cholesterol sulfate to cholesterol. In STS deficiency, cholesterol sulfate accumulates in the stratum corneum; causing hyperkeratoses. The STS gene is located on the short arm of the X chromosome (Xp22.3)(1,2). Most XLI patients exhibit large deletions of the STS gene and flanking sequences(1), as in our case.

The association of hypogonadotropic hypogonadism with anosmia characterizes Kallmann syndrome. The X-linked disorder is caused by mutations of the KAL gene at Xp22.3. Unilateral renal agenesis has been described as an uncommon association with Kallmann syndrome(3,4). This is because the KAL gene is also expressed in the mesonephros and metanephros(5). The association of X-linked ichthyosis and Kallmann syndrome has been described earlier(3,4).

The association of nephrotic syndrome with ichthyosis has been described in only 2 cases in the literature. McGrae, *et al.*(6) described the concurrence of acquired ichthyosis and nephrotic syndrome in a 24 year-old woman with Keratitis, Ichthyosis and Deafness (KID syndrome). Our patient did not have keratitis or deafness. Matsukura, *et al.*(7) have described the second case in an 8-year-old boy who presented with Steroid Resistant Nephrotic Syndrome (SRNS) associated with X-linked Ichthyosis. Kidney biopsy findings were compatible with minimal change disease (MCD). Despite immunosuppressants and prednisolone, no clinical response was achieved. He rapidly reached end-stage renal failure and underwent renal transplantation. It was proposed

that SRNS should be considered one of the highly variable phenotypes associated with XLI. This was the first case describing nephrotic syndrome in association with X-linked ichthyosis.

Currently published evidence suggests that X-linked ichthyosis is a consequence of cholesterol sulfate induced transglutaminase 1 (TGM-1) dysfunction(8). TGM-1 is expressed in large amounts in epithelial tissues of the skin, lung, liver, and kidney. Formation of covalently cross-linked multi-molecular complexes by transglutaminase type 1 is an important mechanism for maintenance of the structural integrity of simple epithelial cells, especially at cadherin-based adherens junctions between epithelial cells of the lung, liver and kidney(9). Since the slit diaphragm of the glomerular visceral epithelial cell is a modified adherens junction(10), it has been postulated that cholesterol sulfate accumulation could interfere with normal slit diaphragm function, resulting in proteinuria(10).

In conclusion, we endorse the view of Matsukura, *et al.*(7) that nephrotic syndrome should be considered one of the highly variable phenotypes of X-linked ichthyosis. However, further research would be required to delineate this postulated mechanism, both at the molecular and biochemical level.

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## Severe Hypertriglyceridemia in an Infant with Red Cell Pyruvate Kinase Deficiency

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*Severe hypertriglyceridemia has been observed in infants with  $\beta$ -thalassemia major, an association termed hypertriglyceridemia-thalassemia syndrome. The pathophysiological basis for this association has remained unclear. We describe 6-month-old American girl with red cell pyruvate kinase (PK) deficiency, failure to thrive, and marked hypertriglyceridemia ( $=1500$  mg/dL). The hyperlipidemia resolved with hypertransfusion therapy. At age 18 months she underwent a splenectomy and has remained transfusion-independent with normal serum triglyceride levels. We suggest that severe hemolysis and chronic wasting are probably responsible for the hypertriglyceridemia seen in infants with thalassemia or PK deficiency.*

**Key words:** Hemolytic anemia, Hyperlipidemia, Thalassemia.

Hypertriglyceridemia may be familial or acquired and may reflect increased hepatic

synthesis or decreased catabolism. A variety of diseases have been linked to secondary hypertriglyceridemia, including infection, renal insufficiency, and diabetic ketoacidosis. Hypertriglyceridemia may accompany acute, massive hemolysis(1). With the exception of infants with  $\beta$ -thalassemia major(2-5), however, there are no reports of hypertriglyceridemia associated with chronic hemolytic anemia. We describe an unusual case of severe hypertriglyceridemia in an infant with red cell pyruvate kinase (PK) deficiency and failure to thrive.

### Case Report

A 6-month-old girl was referred to our hematology clinic for chronic anemia, jaundice, and poor growth. She was the 3.5 kg term product of a

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