CASE REPORT

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Lowe Syndrome. Case report of a patient with a missense mutation in the OCRL1 gene

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ABSTRACT

Oculocerebrorenal or Lowe Syndrome is characterised by bilateral congenital cataracts, renal tubular dysfunction and hypotonia. It is a rare X-linked disorder caused by mutations of the OCRL1 gene located at Xq26.1, resulting in phosphatidylinositol 4,5-bisphosphate (PIP_2) 5 phosphatase deficiency. The diagnosis is based on morphological characteristics. Pre- and postnatal diagnosis is made by enzymatic and molecular analysis. Several mutations have been described in Lowe Syndrome and are related to heterogeneous phenotypical spectrum. The authors report a five year-old patient with mild Lowe Syndrome phenotype including congenital cataracts, glaucoma, hypotony and mental retardation, as well as proximal tubulopathy including generalised aminoaciduria and hypercalciuria but no phosphaturia or renal tubular acidosis. Clinical findings in this mild renal phenotype suggests that the gene product of the mutated allele (IVS12+5G>A) identified in the patient exhibits some residual function.

Key-words:
Congenital cataracts; mental retardation; missense mutation; oculocerebrorenal syndrome; proximal tubulopathy.

INTRODUCTION

Lowe syndrome (LS) was first described in 1952 by Lowe and colleagues[1]. Classically characterised by congenital cataracts, hypotonia, development delay, poor growth and renal tubular dysfunction, it was associated in 1954 to renal Fanconi syndrome[2]. It is a very rare disease with an estimated prevalence of 1 in 500,000 in the general population. It has been known since 1965 to be an X-linked recessive disorder[3], but only in the nineties was the underlying gene OCRL1 cloned[4]. This gene contains 24 exons and encodes a phosphatidylinositol 4,5-bisphosphate (PIP_2) 5 phosphatase found in the trans-Golgi network[5]. The clinical spectrum manifests when the enzyme activity is below 10% in fibroblasts resulting in the accumulation of its main substrate and leading to the mutual disequilibrium of the phosphoinositides that play a role in cytoskeleton remodelling and membrane traffic[6]. To date several mutations have been described[7]. *De novo* mutations were identified in 30% of affected males and somatic (only in some foetal line cells) and germline (in oocytes) mosaicism in 4.5% of the patients. Although it is an X-linked disorder usually affecting males, rare cases of females with X-autosome translocations or single base-pair mutation have been identified[8].

The clinical diagnosis of LS requires ocular, central nervous system and kidney involvement. Assessment of aminoaciduria has been the traditional method of screening for proximal tubular function in suspected patients. An early diagnosis based only on clinical criteria can be difficult and may not be confirmed for several years as the clinical features can be nonspecific or absent during the early stages[9].

Treatment is currently limited to the management of ocular abnormalities, developmental rehabilitation and correction of the metabolic disturbances arising from renal tubular dysfunction.

CASE REPORT

The patient is the second child of apparently unrelated young parents, with a healthy seven-year-old sister. Pregnancy was normal and birth was near term by spontaneous vaginal delivery. Physical examination revealed prominent frontal bossing, congenital bilateral cataracts, palpebral ptosis, unilateral cryptorchidism, hyporeflexia and hypotonia. Based on these clinical findings, a diagnosis of LS was considered. At the age of five weeks the child underwent surgical correction of the cataracts, with the late development of glaucoma.

Heart and brain ultrasounds were both normal. MRI of the brain revealed global subcortical and corpus callosum atrophy, with mild left temporal lobe hypoplasia. The karyotype was 46, XY. Molecular screening for Myotonic dystrophy and for long-chain fatty acids was negative. Electromyography was normal.

At nine months of age mild polyuria was noticed. Laboratory investigation showed normal renal function, normal serum electrolyte and bicarbonate levels, mild hypercalcemia (2,65 mmol/L) with hypercalciuria (UCalcium/UCreatinine ratio=4.9 mmol/mmol), and normal urinary excretion of phosphate, sodium and magnesium. The urinalysis failed to show evidence of proteinuria but a urinary inborn errors of metabolism screening indicated moderate generalised aminoaciduria (elevated aspartate, asparagine, glutamine, proline, glycine, valine, methionine, isoleucine, tyrosine, phenylalanine, ornithine, lysine and histidine). At two years of age the patient underwent renal ultrasound, which showed signs of incipient nephrocalcinosis. There were no clinical or radiological signs of rickets.

The diagnosis of LS was confirmed at two years of age by molecular analysis, with the identification of a missense mutation IVS12+5G>A on exon 12 of the OCRL1 gene. The mother, asymptomatic to date, was evaluated by a slit-lamp eye test and did not present lens opacities. However, she was a carrier of the same mutation which was absent in the grandmother, who also underwent molecular study.

The patient falls within the range of mild/moderate development delay in developmental milestones. He started walking independently around the age of 2.5 years, showing mild hypotonia and ligamentous hyperlaxity. He said his first words at 19 months of age, and at the age of four years his speech was immature but perceptible. Somatic growth was satisfactory up to the age of six months and afterwards below the 5th percentile. At present, he is five years old, maintains polyuria, stable nephrocalcinosis, hypercalciuria with borderline hypercalcemia (2.52-2.62 mmol/L) and proteinuria (urine protein/ creatinine ratio=765 mg/mmol) with normal proteinaemia (79.8 g/L) and albuminaemia (44.2 g/L). He preserves normal urinary excretion of phosphate (TRP=85%), normal serum phosphate and normal renal function (serum creatinine=37,7 umol/L), lacking metabolic acidosis. His blood pressure has remained within the normal range for age (‹90th percentile). To date he remains without specific management, apart from glaucoma control and rehabilitation therapy.

DISCUSSION

The typical features of LS include congenital cataracts, development delay and renal tubular dysfunction. Renal tubular dysfunction generally includes polyuria, tubular proteinuria with generalised aminoaciduria, proximal tubular acidosis, phosphaturia and rickets. Our patient presented with generalised aminoaciduria, without any of the other metabolic disturbances described in Fanconi syndrome, also classically associated to LS. He also presented with hypercalciuria and nephrocalcinosis, both infrequent signs, but previously reported[10]. OCRL1 mutations

(rather than in the CLCN5 gene) have also been recently detected in patients with Dent's disease, another rare X-linked proximal tubulopathy characterised by low molecular weight proteinuria, hypercalciuria, and nephrocalcinosis, but without ocular or brain involvement[11]. There is increasing evidence that patients with LS do not have renal Fanconi syndrome but a selective proximal tubulopathy, variable in extent and dominated by low molecular weight proteinuria, hypercalciuria, and nephrocalcinosis. This phenotypic heterogeneity is poorly understood, but the overlap of symptoms suggests that the similar reabsorption pathways in the proximal tubule are somewhat involved in both LS and Dent's disease[12].

To date several mutations have been described in LS: truncation mutations (nonsense, splice-site, frame-shift), missense mutations occurring in or outside the catalytic domain of the OCRL1 gene and rarely larger deletions[7]. Earlier case reports described different degrees of phenotype severity resulting from different types of mutations. The deletion of the entire OCRL1 gene or larger deletions have been previously found in affected males with severe features of LS[13]. A mild phenotype including incomplete opacities of the lenses was described in a 35-year-old patient, with a splice-site mutation (IVS19+1G>A)[14]. A missense mutation IVS12+5G>A on exon 12 of OCRL1 gene was identified in our patient, who presented with a mild renal phenotype. This is a mutation in a preserved region (+5 position), so quite safely the cause of LS. A pathogenic mutation on the exon 12 was previously described by Addis M *et al.*[15]. Clinical findings suggest that the gene product of the mutated allele exhibits some residual function.

In our case, the mother was identified as the carrier. Female carriers of LS are detected in 94% of cases by slit-lamp examination because of the presence of significantly punctiform white to grey lens opacities.[8] The carrier mothers are not affected in 6% of the cases and an explanation for that is the inactivation of the X with the mutation. This is one of the rare cases where the mother's slit-lamp examination was normal. Only molecular study allowed her to be identified as a carrier. We can presume that this was due to a *de novo* mutation owing to the grandmother's "germline mosaicism", as the latter did not present the mutated allele in the molecular blood study.

Identification of the mutation not only confirms diagnosis, but it is also essential for genetic counselling. Prenatal or preimplantation molecular diagnosis should be offered to this family, as the mother has a 25% possibility of having an affected boy and a 25% possibility of having a carrier daughter.

In severe phenotypes, death may occur in infancy, as a consequence of the renal disease, hypotonia or susceptibility to infection. Death usually occurs between the second or fourth decade of life, and the most frequent causes are respiratory illness, epileptic seizures and sudden death, often while sleeping. The less likely cause of death is due to renal tubulopathy, which progressively evolves into chronic kidney failure[8]. Our patient, now five years old, continues to present a stable renal status, lacks tubular acidosis or phosphate wasting and has no neurological or infectious complications, all predictive of a more benign and slow progressive disease.

CONCLUSION

All male infants with hypotonia and bilateral congenital cataracts should have LS as a possible diagnosis considered. Early diagnosis may be difficult due to several factors: the characteristic phenotype may not be present or may be difficult to identify until several years later, the lack of opacities in maternal lenses and the nonspecific hypotonia. Several mutations have been described in LS related to a phenotypically heterogeneous spectrum. Genetics play an important role in the atypical forms of hereditary diseases, as in this LS case, as it allows for the correct diagnosis, family study and provides crucial prognostic information.

Conflict of interest statement. None declared.

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