SHORT REPORT

Early proximal tubular dysfunction in Lowe's syndrome

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The early diagnosis of Lowe's syndrome can be difficult. Urinary excretion of retinol binding protein (RBP) and the lysosomal enzyme N-acetyl-glucosaminidase (NAG) were significantly increased in boys with Lowe's syndrome. Measurement of these urine parameters is recommended in suspected cases.

The oculo-cerebro-renal syndrome of Lowe is a rare X linked disorder characterised by congenital cataracts, developmental delay, and renal tubular dysfunction.[1] The underlying gene, OCRL-1, has been cloned and encodes a phosphatidylinositol (4,5) biphosphate 5-phosphatase.[2] Affected boys have evidence of proximal renal tubular dysfunction within the first year of life.[1]

Assessment of aminoaciduria has been the traditional method of screening proximal tubular function in at risk boys. However, the diagnosis may not be confirmed for several years, because the clinical features can be non-specific.

Low molecular weight proteins such as retinol binding protein (RBP) are freely filtered by the glomerulus and 99% reabsorbed in the proximal tubule.[3] N-acetyl-glucosaminidase (NAG), a lysosomal enzyme, is another sensitive marker of proximal tubular integrity.[4] The urinary excretion of RBP and NAG is a sensitive index of tubular function and normal ranges are described, not only in infants,[4] but also in neonates.[5] Recently, markedly increased urine levels of RBP have been shown in adult males with Lowe's syndrome.[6]

We reviewed presenting features of 14 patients with particular emphasis on the investigations used to confirm diagnosis. In eight of these patients we have additionally determined urinary excretion of RBP and NAG.

PATIENTS AND METHODS

The records of 14 patients with Lowe's syndrome seen in our hospital between 1975 and 2002 were reviewed. When assays became available in 1992 we measured urinary excretion of RBP and NAG in eight younger patients (five when diagnosis was suspected and three retrospectively).

NAG activity was determined by using a commercially available kit (Praill Price Richardson Diagnostics, London, UK); the unit used for NAG activity was µmol of 2-methoxy-4-(2'nitrovinyl)-phenol (MNP)/h per mmol. RBP was measured by enzyme linked immunosorbent assay (ELISA) using rabbit antisera (Dako, High Wycombe, UK). Since the urine RBP/Cr and NAG/Cr ratios are logarithmically normally distributed, the data were log transformed. Descriptive data are presented as geometric means and ranges, and compared using Student's two tailed *t* tests.

RESULTS

In seven children the diagnosis of Lowe's syndrome has either been made or confirmed by identification of a mutation in OCRL-1, in three by the presence of typical maternal lens opacities and in another three by a positive family history. The typical dysmorphic facies had only been noted in three infants. Other non-specific features were commonly seen (see table 1). The significance of maternal lens opacities was not recognised until 1980, but thereafter, this finding has helped to confirm diagnosis soon after presentation. Of the 13 mothers examined, seven had typical lens opacities. Where these lens opacities were present the diagnosis was made in the first weeks of life in those patients seen in the past 10 years, but later in earlier cases.

Importantly aminoaciduria was not detected on routine screening or was felt to be too mild for Lowe's syndrome in six children. The geometric mean urine RBP/Cr in eight patients was 43139 µg/mmol (range 16 783–103 482) which was significantly increased ($p < 0.001$) compared to normal amounts (3.1 µg/mmol, range 0.3–38.8). The geometric mean urine NAG/Cr in patients was 299 µmol MNP/h per mmol (range 117–7121) and also significantly higher than in controls (11.1 µmol MNP/h per mmol, range 3.4–35.5; $p < 0.001$) (fig 1). All boys had plasma creatinine concentrations within the normal age related reference ranges.

Mean age of diagnosis in patients without family history prior to use of RBP/NAG determinations was 25 months, whereas following introduction of tubular protein screening, mean age fell to 13 months. Factors which contributed to a delay in the diagnosis were lack of the characteristic facies, lack of maternal lens opacities, persistent hyaloid vessels of the lens (interpreted as a structural lens anomaly and not as a sign of metabolic disorder), and finally, early development not as severely impaired as predicted for Lowe's syndrome.

DISCUSSION

Typical clinical features of Lowe's syndrome include congenital cataracts, learning difficulties, and renal tubular dysfunction.[1] However, the characteristic phenotype is often difficult to identify in neonates.

In 11 of the 14 cases, the typical facies seen in older Lowe's boys, was not recognised at presentation. Additionally in six of 14 suspected patients the extent of aminoaciduria was

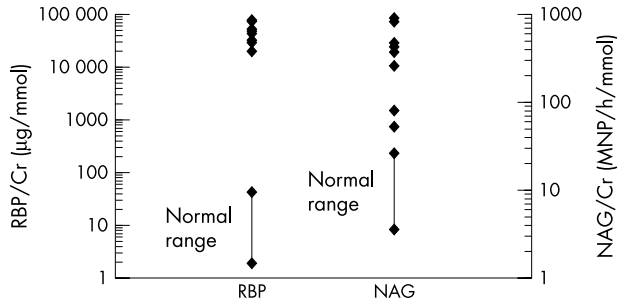

Figure 1 Urinary excretion of RBP and NAG in eight patients with Lowe's syndrome. Results are factored by urine creatinine to correct the variation in urinary concentration.

Table 1 Clinical features and mutations in 14 patients with Lowe's syndrome

Case	Age at diagnosis	Lens form	RBP and NAG measured	Presence of maternal lens opacities	General features	Genetics
1	70 mth	Lamellar	ND	Yes	Dysmorphic facies, seizures, developmental delay	ND
2	46 mth	Dense opacity	Yes	Yes	Hypotonia, severe growth retardation, developmental delay	ND
3	Birth	Dense opacity	Yes	Yes	Hypotonia, rickets, arthrogryposis, developmental delay	Nonsense mutation in exon 11 (OCRL shift)
4	5 mth	Intralenticular haemorrhage	ND	No	Hypotonia	ND
5	31 mth	Dense posterior central opacity	ND	No	Hypotonia	ND
6	1 mth	Dense opacity	ND	Yes	Hypotonia, developmental delay	ND
7	28 mth	Central posterior plaque	Yes	No	Severe growth retardation, hypotonia	Frameshift mutation in exon18
8	3 mth	Central posterior capsule defect	ND	Yes	Hypotonia	Missense mutation in OCRL-1 at codon 245
9	41 mth	Dense opacity	Yes	No	Dysmorphic facies, developmental delay, hepatosplenomegaly	Gln215stop (nt820CαT)
10	4 mth	Dense opacity	Yes	No	Hypotonia, rickets	Deletion of 4'UTR of the OCRL-1 gene
11	27 month	Dense opacity	Yes	No	Hypotonia, nephrocalcinosis, developmental delay	Shift in exon 16 amplimer of OCRL
12	Birth	Small lens, dense posterior opacity	ND	Yes	Hypotonia, distal hypospadias	ND
13	3 mth	Plaque in fetal nucleus	Yes	No	Very floppy, dysmorphic facies	Shift in amplimer for exon 21 of OCRL
14	2 mth	Dense opacity	Yes	Yes	Hypotonia	ND

ND, not done.

considered normal or too mild to be consistent with Lowe's syndrome. This may have been due to methodological problems or may have reflected low plasma amino acids secondary to poor protein intake. Other contributory factors delaying the diagnosis were the lack of opacities in maternal lenses, other possible causes for hypotonia, and persistent hyaloid vessel of the lens.

There was a significant increased level of RBP and NAG in the urine of all eight tested patients.

All male infants with hypotonia and bilateral congenital cataracts should have a diagnosis of Lowe's syndrome considered. Typical features such as dysmorphic facies and aminoaciduria may be absent. Their mother's lenses should be examined after dilation of the pupils, although clear maternal lens can occur if Lowe's syndrome has arisen from a new mutation, and there is also a small possibility of a carrier mother having a clear lens.[1] We recommend assessment of urinary RBP and NAG as sensitive tests for the mild Fanconi syndrome associated with early Lowe's syndrome. Subsequently the diagnosis can be definitely confirmed by mutation screening of OCRL-1.

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Enquiries about availability of urine RBP and NAG levels should be made to the duty Clinical Biochemist, Department of Biochemistry, Camelia Botnar Laboratories, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK; tel: ++44 (0)20 7405 9200, bleep 589.

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REFERENCES

1 **Charnas LR**, Bernardini I, Rader D, *et al*. Clinical and laboratory findings in the oculocerebrorenal syndrome of Lowe, with special reference to growth and renal function. *N Engl J Med* 1991;**324**:1318–25.
2 **Attree O**, Olivos IM, Okabe I, *et al*. The Lowe oculocerebrorenal syndrome gene encodes a novel protein highly homologous to inositol polyphosphate-5-phosphatase. *Nature* 1992;**358**:239–42.
3 **Tomlinson PA**. Low molecular weight proteins in children with renal disease. *Pediatr Nephrol* 1992;**6**:565–71.
4 **Dillon SC**, Taylor GM, Shah V. Diagnostic value of urinary retinal-binding protein in childhood nephrotic syndrome. *Pediatr Nephrol* 1998;**12**:643–7.
5 **Roberts DS**, Haycock GB, Dalton RN, *et al*. Prediction of acute renal failure after birth aspyxia. *Arch Dis Child* 1990;**65**:1021–8.
6 **Norden AG**, Lapsley M, Lee PJ, *et al*. Glomerular protein sieving and implications for renal failure in Fanconi syndrome. *Kidney Int* 2001;**60**:1885–92.