

Oculo-cerebro-renal syndrome

Report of a case in a baby girl

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The oculo-cerebro-renal syndrome of Lowe is characterized by failure to thrive, mental retardation, hypotonia, cataracts, glaucoma, amino-aciduria, and decreased renal ammonia formation (Lowe, Terrey, and MacLachlan, 1952). A single report of a female with these findings exists in the literature (Švorc, Masopust, Komárková, Macek, and Hyánek, 1967). In all other characteristic cases, the genetic pattern has been consistent with an X-linked recessive mode of inheritance. Consequently, only males have been afflicted with this condition (Chutorian and Rowland, 1966; Schwartz, Hall, and Gabuzda, 1964; Švorc and others, 1967). Moreover, to the best of our knowledge, no case has been reported in a Negro subject.

We have had the opportunity to study a Negro female child with clinical and laboratory findings consistent with the diagnosis of Lowe's syndrome. The current report is concerned with these findings and a discussion of the implication.

Case report

A 10-day-old female infant was first admitted to the Flower and Fifth Avenue Hospitals Division of the New York Medical College with bilateral cataracts and megalocornea. The family history and pregnancy were entirely unremarkable. The general physical examination disclosed only ocular abnormalities which consisted of enlarged oedematous corneae. Examination under general anaesthesia revealed the corneal diameters of both eyes to be 11 mm. Posterior synechiae were noted in both eyes and scale readings with the Schiøtz tonometer with the 7.5 g. weight were recorded as 4.5 and 7.5 mm. Hg on the right and left respectively. Laboratory studies disclosed 3+ proteinuria and generalized amino-aciduria. Blood amino acid levels were normal.

Chromosome studies revealed a normal female karyotype. A bone marrow biopsy was negative for cystine crystals. Urine tests for cytomegalic inclusion disease and blood tests for rubella antibodies both gave negative results. Investigations for toxoplasmosis and mucopolysaccharidosis also gave negative results.

The patient was again admitted to hospital 5 months later, when she was noted to be small, underdeveloped, hypotonic, and hypoactive (Figure), having gained only 6 lb. in the first 8 months of life. The ocular findings at this time were unchanged, but mild hepatosplenomegaly and motor and mental retardation were observed. Urine was negative for galactose but showed generalized amino-aciduria and revealed the presence of proline and hydroxyproline. A bone survey at this time showed no evidence of rickets. An ammonium loading test was performed and showed normal renal production of ammonia in response to an induced metabolic acidosis. Examination under general anaesthesia revealed corneal diameters of 12.5 and 13 mm. on the right and left respectively. Schiøtz tonometer readings with 7.5 g. weight were 3.0 and 3.5 mm. Hg on the right and left respectively. A direct goniotomy was performed at this time on the right eye.



FIGURE A 6-month-old female child with the oculo-cerebro-renal syndrome

A follow-up in the ensuing 11 months has shown this child to be hyporeflexic, mentally retarded, and in the lower 3 percentile in growth and development. She has had frequent intercurrent infections which have responded to antibiotics.

More recent examination under anaesthesia showed the corneal diameter to be 12.5 and 13 mm. on the right and left respectively. Schiøtz readings with the 7.5 g. weight were 3.0 and 4.0 mm. Hg on the right and left respectively. A-scan ultrasonography disclosed axial lengths of 24 mm. bilaterally. Lens diameters were 2 mm. bilaterally.

Ocular examination of the mother and female siblings failed to disclose punctate lenticular opacities or any other ocular abnormality.

Discussion

Lowe and others (1952) first described three unrelated males with glaucoma, cataracts, mental retardation, and hypotonia. All were acidotic and had amino-aciduria with decreased renal ammonia production in response to an induced metabolic acidosis. The pattern of inheritance indicated an X-linked recessive mode of transmission and therefore only males were affected clinically (Chutorian and Rowland, 1966; Schwartz and others, 1964; Wilson, Richards, and Donnell, 1963).

Ocular pathological changes in Lowe's syndrome may be so specific as to be virtually diagnostic. The important findings in this regard are exceedingly thin cataractous crystalline lenses (Curtin, Joyce, and Ballin, 1967). Ultrasonography in the present case confirmed the presence of buphthalmos, but more significantly, demonstrated the presence of small thin lenses. This finding in a child with glaucoma, hypotonia, mental retardation, and amino-aciduria is certainly suggestive of the syndrome described by Lowe.

Several objections might be raised to the inclusion of this patient in the category of Lowe's syndrome. Foremost amongst these is the fact that the mode of inheritance is believed to correspond to an X-linked recessive pattern. If this is correct, only males will be affected with the clinical syndrome. Švorc and others (1967) have, however, reported a proven female with cataracts, mental and motor retardation, hypotonia, and amino-aciduria. As in the present case the relatives showed no abnormality.

As with a number of other heritable states, the female carrier has been shown to possess certain subclinical findings. More prominent amongst these are non-progressive punctate lenticular opacities which do not impair visual acuity. Amino-aciduria induced by orinithine loading has also been documented in female carriers of this condition (Chutorian and Rowland, 1966; Schwartz and others, 1964).

The patient reported here is unequivocally female on the basis of chromosome studies. It is of interest to note, however, that a significantly high incidence of cryptorchidism occurs in Lowe's syndrome. In one series, this approached an incidence of 80 per cent. (Chutorian and Rowland, 1966). Despite this observation, chromosome studies have not been routinely reported and it is therefore possible that a few misdiagnosed females have been included in the literature.

Bilateral posterior synechiae were noted in the present case. Although this finding has not been previously noted, not all patients reported in the literature have been subjected to biomicroscopy, so that it could have been overlooked. Moreover, in the histological study of this entity by Curtin and others (1967), the anterior chamber was filled with proteinaceous material. Clinically, this finding has been felt to be a prerequisite for synechia formation.

Initially, Schwartz and others (1964) reported derangements in ornithine metabolism as a prime defect in this condition. This finding was confirmed by Sidbury and McCarty (1963). However, later studies in patients with similar clinical findings have failed to confirm this specific pattern of amino-aciduria. Moreover, recent reports have shown that the pattern of amino-aciduria in a given patient is highly variable, both during the course of any one day and from day to day. In fact, in patients with amino-aciduria from any cause, the urinary excretion of amino acids depends on the dietary intake of protein (Chutorian and Rowland, 1966; Worthen and Good, 1958). Certainly, then, amino-aciduria is a *sine qua non* of the oculo-cerebro-renal syndrome, but the specific pattern of excretion requires further elucidation.

The patient here reported had no demonstrable defect in renal ammonia production when challenged with an induced metabolic acidosis. The three related children reported by Schwartz and others (1964) did not have this defect either, but they were felt to be representative of Lowe's syndrome.

Certainly, the basic metabolic and biochemical defects in Lowe's syndrome are not known, and it is thus impossible to define the condition precisely. Our patient has the clinical manifestations of an oculo-cerebro-renal syndrome, and as in those presented by Schwartz and others (1964), there is no defect in ammonia production. The spectrum of the oculo-cerebro-renal syndrome encompasses a number of different biochemical defects, and until these can be precisely determined, it may be well to group all such patients under this general heading.

References

- CHUTORIAN, A., and ROWLAND, L. P. (1966) *Neurology (Baltimore)*, **16**, 115
 CURTIN, V. T., JOYCE, E. E., and BALLIN, N. (1967) *Amer. J. Ophthalm.*, **64**, 533
 LOWE, C. U., TERREY, M., and MACLACHLAN, E. A. (1952) *Amer. J. Dis. Child.*, **83**, 164
 SCHWARTZ, R., HALL, P. W., and GABUZDA, G. J. (1964) *Amer. J. Med.*, **36**, 778
 SIDBURY, J. B., and MCCARTY, K. (1963) *Sth. med. J. (Bgham, Ala.)*, **56**, 1441
 ŠVORC, J., MASOPUST, J., KOMÁRKOVÁ, A., MACEK, M., and HYÁNEK, J. (1967) *Amer. J. Dis. Child.*, **114**, 186
 WILSON, W. A., RICHARDS, W., and DONNELL, G. N. (1963) *Arch. Ophthal. (Chicago)*, **70**, 5
 WORTHEN, H. G., and GOOD, R. A. (1958) *Amer. J. Dis. Child.*, **95**, 653