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A First Reported Case of Oculocerebrorenal Syndrome of Lowe in Hong Kong and Review of Literature

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Abstract Oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked recessive disorder characterised by congenital cataracts, mental retardation, and renal tubular dysfunction. OCRL is caused by mutations in the *OCRL* gene, which encodes for an enzyme phosphatidylinositol 4,5-biphosphate 5-phosphatase [PtdIns (4,5)P2-5ase]. Deficiency of this enzyme impairs proper intracellular protein sorting, especially in the organs of high requirement of PtdIns(4,5)P2-5ase, namely eyes, brain and kidneys. Treatment is system-specific and death usually occurs in the second or third decade of life, mainly due to progressive renal failure. Here we describe the clinical and investigation findings of the first reported case of OCRL in Hong Kong, who presented with congenital cataracts, mental retardation, epilepsy and renal tubular acidosis. Mutational analysis identified a novel hemizygous c.2145_c.2146insTT mutation in the *OCRL* gene of the proband and his mother. Management of this disease is also discussed.

Key words Congenital cataracts; Mental retardation; *OCRL* gene; Oculocerebrorenal syndrome of Lowe; Renal tubular dysfunction

Introduction

Oculocerebrorenal syndrome of Lowe (OCRL) was initially described in 1952 by Lowe, Terrey, and MacLachan, who reported the triad of congenital cataracts, mental retardation and generalised amino-aciduria.[1] Due to the X-linked inheritance, the vast majority of patients are males, though female cases have been reported,[2] who had X autosome translocations involving the *OCRL* locus. The *OCRL* gene was cloned in 1992[3] and mapped to Xq24-26 in 1997.[4] It encodes a 105-kD enzyme, phosphatidylinositol phosphatase 4,5-biphosphate 5-phosphatase [PtdIns(4,5)P2-5ase].[5,6] A loss or reduction (<10% of normal) of the enzyme activity has been demonstrated in cultured skin fibroblasts of affected subjects.[5-7] Most of the mutations consist of deletions involving one or a few nucleotides, missense, nonsense and frameshift mutations.[8-11] PtdIns(4,5)P2-5ase is a critical metabolite involved in Golgi vesicular transport.[3,5] It affects actin polymerization which plays a key role in the formation, maintenance, and proper function of tight junction and adherens junction. All these have been demonstrated to be critical in renal proximal tubule function and in the differentiation of the lens.[12] The cardinal features of OCRL are congenital cataracts, mental retardation and renal tubular dysfunction. We report a case of OCRL with typical clinical features and a novel mutation was identified. Its management issue will be discussed.

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Patient

A 6-year-old boy initially presented to our unit at the age of 3 with seizure. He was born full term, delivered by normal spontaneous delivery with a birth weight of 3.5 kg in the mainland China. Parents were non-consanguinous. He was the first and sole child in the family. The antenatal care in China was claimed to be uneventful and a negative family history was noted. He was noticed to have bilateral cataracts and floppiness at 3 months of age. His cataracts were operated later on. Developmental delay was noted and he started to develop seizure at around 18 months of age. The seizure was mainly generalised tonic seizure of limbs with up-rolling eyes, cyanosis and post-ictal drowsiness, duration of 1 minute. Frequency of attacks ranged from once per several days to several times per day. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of brain showed a pineal cyst only while electroencephalography (EEG) was also performed but the result was not available to us. He was started on topiramate empirically in China and remained seizure free for about 13 months.

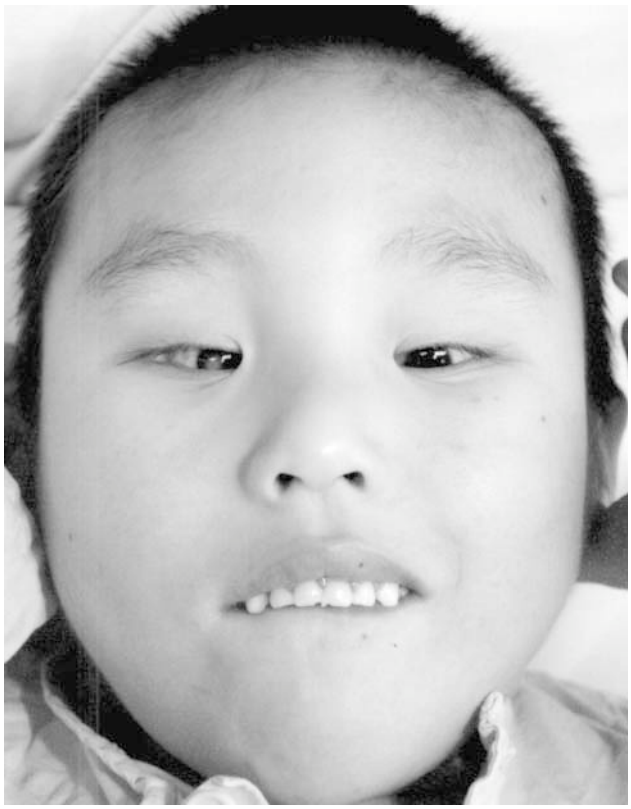

Figure 1 Facial appearance of the patient at 6 years of age: frontal bossing, bilateral enophthalmos with corneal clouding of the right eye and prominent epicanthic folds are obvious. Strabismus was induced with near accommodation only.

He came to Hong Kong at 31 months of age. He was admitted to our unit because of seizure attacks after he ran out of anti-epileptic medication. On physical examination, his weight and head circumference were both at 25th centile while his height was 2 cm below 3rd centile. No hypertension was noticed. He had frontal bossing, bilateral enophthalmos with corneal clouding of the right eye, prominent epicanthic folds (Figure 1) and bilateral clinodactyly. He had hypotonia with hyporeflexia. Visual function including follow and fixation was present. Significant developmental delay was noticed. He could walk for a few steps, reach out and pick up objects with palmer grasp but clumsy in targeting due to his visual problem. He had babbling only and could not wave bye-bye. He could not feed himself nor indicate any toilet need. No stranger anxiety was noted. His developmental age was 1 year in gross motor aspect, and 6 months in fine motor, speech and social aspects. Biochemistry showed an almost normal blood gas with pH of 7.34, base excess of minus 4.8 mmol/L and bicarbonate of 19.7 mmol/L. There was a mild increase of aspartate amino-transferase (AST) to 92 IU/L in liver function test. Other blood results including complete blood count, renal function, sodium, potassium, calcium, thyroid function test were normal. Metabolic screening including serum lactate, pyruvate, ammonia, carnitine and amino acid profile, urine for metabolic screen, organic acid and amino acid assay were all normal. EEG showed very frequent left frontal epileptic discharge with right frontal involvement occasionally. He was continued with topiramate alone in view of previously good seizure control. Visual evoked potential showed absence of P100 of the left side. Brainstem auditory evoked potential, nerve conduction study and electromyography were all normal. Ophthalmological assessment showed visual acuity less than 6/120 bilaterally and bilateral posterior chamber intraocular lens and posterior capsular opacification. MRI brain showed global cerebral atrophy, bilateral micro-ophthalmos and enophthalmos with slightly deformed globes, a homogenous cystic suprapineal structure, most probably an arachnoid cyst or a normal variant.

His seizure control was good with only 2 breakthrough attacks till 6 years of age. Abnormal manneristic behaviour of compressing his neck against hard objects was noticed at age of 6. This manneristic behaviour was difficult to control despite behavioural therapy or physical restraint. At the age of 6, he developed status epilepticus with tonic seizure of limbs and rhythmic eye movement to right side for more than 30 minutes, which required intravenous phenytoin loading and intensive care. His drug compliance of

topiramate was good at the dose of 4.7 mg/kg/day. No other herbs or medications were taken. There was no systemic upsets prior to the development of status epilepticus. EEG showed intermittent spikes over left centroparietal region. Carbamazepine was added on top of topiramate. He then remained seizure free with this regimen of anti-epileptic drugs. His latest developmental levels were as follow: he could run, scribble freely. However, he spoke no words at all and could not tell body parts of the body. His activity of daily living was totally dependent and he just started to study in a special school.

During that admission, he was found to have persistent severe proteinuria, up to 103 mg/m^2/hr protein excretion while the serum albumin level remained normal. His glomerular filtration rate was normal, 125 ml/min/1.73m^2. There was no oedema clinically. His height was 5 cm below 3rd centile while the weight and head circumference was at 25th and 10th centile respectively. Blood gas showed compensated metabolic acidosis of pH 7.28, base excess of minus 8.9 mmol/L and bicarbonate of 16.9 mmol/L. Serum sodium was 136 mmol/L, potassium was 3.6 mmol/L, calcium was 2.3 mmol/L, phosphate was 1.1 mmol/L, free carnitine was 19.7 umol/L, all were within normal range. AST, creatine kinase, alkaline phosphatase and HDL cholesterol were raised to 83 IU/L, 266 mmol/L, 435 IU/L and 2.7 mmol/L respectively. Serum para-thyroid hormone was normal. X-ray of wrists and knees did not show any features of rickets. Bone age was 4½-year-old at the chronological age of 6 years and 4 months. Repeated urine for amino acid assay showed a generalised amino-aciduria with sparing of branched-chain amino acids. Urine calcium excretion was raised to 1; sodium excretion was normal while phosphate reabsorption was decreased to 77%. Urine for microglobulin was markedly elevated to >100 ug/ml. Sodium bicarbonate loading test confirmed proximal renal tubular acidosis. Ultrasound of kidneys showed a few tiny hyperechoic foci in both kidneys suggestive of early findings of medullary nephrocalcinosis. He was started on sodium citrate, potassium citrate, sodium phosphate and vitamin D supplement. His mother was referred for ophthalmological evaluation with normal examination.

Mutational Analysis

Genomic DNA was extracted from peripheral blood of the proband and the mother using the Qiagen DNA blood mini kit (Hilden, Germany), following the protocol from the manufacturer. Each exon and exon-intron boundaries of the *OCRL* gene were amplified by polymerase chain reaction (PCR). The primer sequences for exons 1 to 23 were designed from the *OCRL* genomic sequence NC_000023, using Primer 3 online software. These primer sequences and the PCR conditions are available upon request. The PCR products were purified and sequenced using either forward or reverse primer with the BigDye Terminator cycle sequencing kit (Applied Biosystem, CA, USA). The DNA sequencing products were analyzed on the ABI PRISM 3100 Genetic Analyzer (Applied Biosystem, CA, USA). The reference sequence is the human *OCRL* mRNA sequence (GeneBank accession number NM_000276).

Results

With comparison to a normal human control DNA sequence (Figure 2A), a novel hemizygous c.2145_c.2146insTT mutation was detected in the *OCRL* gene of the proband (Figure 2B). This is a frameshift mutation that leads to miscoding of 9 amino acids starting from codon 716 (Leu) and eventually a premature termination of translation at codon 725. His mother was confirmed to be a heterozygous carrier (Figure 2C).

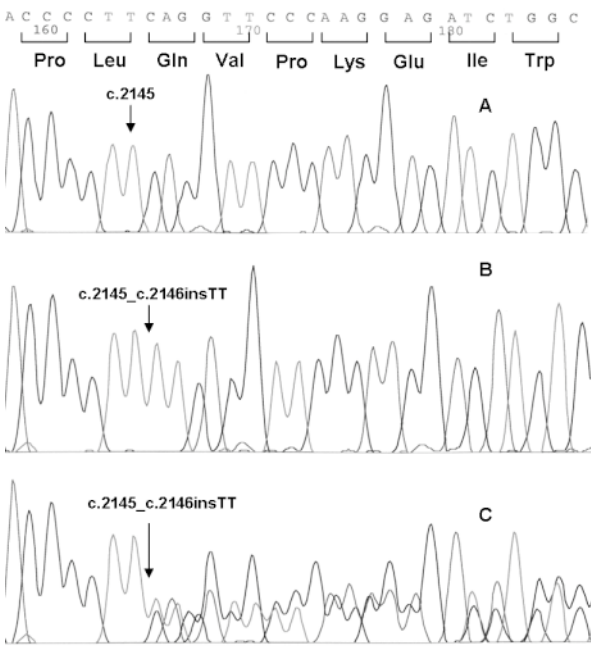

Figure 2 (A) A normal control DNA sequence, showing the position of c.2145. (B) A hemizygous c.2145_c.2146insTT was detected in the *OCRL1* gene of the proband. (C) The mother is heterozygous of the c.2145_c.2146insTT insertion.

Discussion

The differential diagnoses include other syndromal disease or inborn errors of metabolism, such as Zewellger syndrome, Fabry disease, Lesch-Nyhan syndrome and galactosaemia. Zewellger syndrome usually does not survive beyond 1 year of age and typical facial appearances will be easily appreciated. Fabry disease was unlikely as the patient did not have angiokeratoma at all. As the patient had normal serum level of uric acid and negative reducing substance in urine, Lesch-Nyhan syndrome and galactosaemia were ruled out.

OCRL is a very rare genetic disease. Its estimated prevalence in Western populations is 1-5 per million, according to the French Lowe Association.[13] It affects multiple systems, namely ocular, central nervous system, renal and skeletal systems. In ocular system, various manifestations can be seen in OCRL, including cataracts, glaucoma, corneal keloids, strabismus and nystagmus.[14] Cataracts are a hallmark of OCRL and always present at birth. Glaucoma, with or without buphthalmos, occurs in about 50-60% of boys with OCRL and usually is bilateral. Typically it is diagnosed in the first year of life but may be present at any age. Corneal keloids, occurring in 25% of patients, cause significant visual impairment. They are scarlike opacifications of the cornea that can develop spontaneously or following trauma.[15] They usually develop in children older than 5 years, and are bilateral in about half of them. Removal of cataracts as early as possible is recommended though the expected visual acuity is not good anyway.[16] Glaucoma in OCRL patients typically is difficult to treat. Surgical implantation of artificial valve to control the release of intraocular fluid is often required. Treatment of corneal keloid consists of surgical removal of scar tissue or radiation therapy.

Developmental delay, mental retardation, seizure and behavioural problems are common neurological manifestations. Most of them have moderate mental retardation and about one third have profound mental retardation. Intelligence is stable over the life span. Supervised functioning in daily activities and meaningful language acquisition commonly occur.[17] Early intervention programmes for Lowe patients can be extremely beneficial for improving function. Swimming and water sports are helpful to improve their muscle tone. In a survey of 54 patients with OCRL, Charnas[18] found 33% patients with a clinical history of seizure. The most common type was generalised tonic-clonic seizure, other was infantile spasm, staring spells, and mixed staring and generalised tonic-clonic seizure. Ono[19] reported phenytoin to be effective in treatment of seizures in 2 OCRL patients though they had different seizure types. There is a high prevalence of maladaptive behaviours, including episodic outbursts (Lowe tantrum), stubbornness, and stereotypy. Problems were first noted at the age of 5, worsened at an average age of 8, and then improved in two thirds of patients at a mean age of 14.[20] Kenworthy[21] found the following 5 behaviours appeared more often in OCRL patients when compared to subjects with matched intelligence quotient: temper tantrums; irritablity; stereotypy/mannerisms; obsessions/unusual preoccupations; and negativism. Treatment of behavioural problems includes both medication (neuroleptics, stimulants, carbamazepine) and behavioural modification, though they are usually not effective. In our patient, he had mannerism of compressing his neck to hard objects and it was refractory to both behavioural therapy and physical restraint.

The renal involvement of OCRL usually starts to manifest within the first year of life. It comprises of tubular dysfunction, with proteinuria, generalised amino-aciduria progressing to the renal Fanconi syndrome, and later glomerular disease. Fanconi syndrome is failure in reabsorption of water, electrolytes, bicarbonate, glucose, calcium, phosphorus and small molecules, such as amino acids and carnitine. This explains the polyuria and susceptibility to hypovolaemia with intercurrent illness, metabolic acidosis, and hypophosphataemia with resultant poor growth and rickets. In our case, urine for amino acid assay was performed at 3 years of age and the result was normal. Another one was repeated only when he was admitted for status epilepticus at the age of 6. It illustrates the importance of performing urine for amino acid assay from time to time if the other two systems (central nervous system and eye) were also involved. It may enable an early diagnosis be made. Renal tubular dysfunction presents early, with slow progress glomerular dysfunction and gradual decline in glomerular filtration rate. Renal failure is expected by the fourth decade of life.[22] The oldest OCRL patient in literature was a 49-year-old gentleman who has been put on ambulatory peritoneal dialysis.[13] Hypercalciuria and its sequelae (nephrocalcinosis or nephrolithiasis) may occur commonly in patient with OCRL as a component of tubular dysfunction or a complication of Vitamin D and calcium therapy.[23] Careful monitoring of acid base status and electrolyte levels is required. Sodium citrate and citric acid (Bicitra) or sodium citrate and potassium citrate (Polycitra) is necessary to maintain serum bicarbonate level greater than 20 mmol/L. Potassium, calcium, carnitine, phosphate, and Vitamin D supplements may be required if

serum level is low. Precaution should be taken to ensure adequate fluid intake during intestinal upset or severe heat. Regular renal ultrasound to look for complications of hypercalciuria is recommended.

A wide variety of skeletal problems are encountered in OCRL patients. Some may be just the associated features, but the others are complications of hypophosphataemia and hypotonia. Associated features are joint swelling, arthritis, tenosynovitis, and scoliosis. The proper management of joint swelling is less clear, but minimisation of discomfort, maintenance of mobility, and judicious use of surgery are reasonable guidelines. Hypophosphataemia leads to osteopenia or even rickets and renders the child prone to fractures. Osteopenia and fractures can be prevented by optimal management of the associated renal disease.

The onset and progression of puberty occurs at a normal age in OCRL patient.[17] Fertility may be reduced due to the peritubular fibrosis and azospermia associated with OCRL. The frequency of unilateral or bilateral cryptochidism in OCRL has been reported from 17-40%.[17, 24]

Clinically, patient may be found to have corneal clouding at birth or early infancy. Feeding difficulties (due to hypotonia) and delayed motor development are the other common presenting problems in early infancy, while seizure, polyuria and polydipsia develop later on. Typical facial features are noted with microcephaly, frontal bossing, deep-set eyes, fair skin complexion and baldness. Short stature is common due to the various skeletal involvements. Developmental delay, hypotonia, areflexia, and proteinuria may be obvious in physical examination.

Laboratory investigations review significant metabolic acidosis due to the urinary loss of bicarbonate. Clinically significant hypokalaemia, hyponatraemia and hypocalcaemia are rare. Serum carnitine may be low depending on the amount lost in urine. Serum creatinine will be raised if creatinine clearance declines. Alkaline phosphatase, AST, lactate dehydrogenase, creatine kinase, HDL cholesterol, thyroxine, and erythrocyte sedimentation rate may be elevated. Urinalysis shows generalised amino-aciduria with sparing of branched-chain amino acids, phosphaturia, calciuria and proteinuria. X-ray of long bone may reveal typical features of rickets including metaphyseal flaring, osteopenia and renal ultrasound may show nephrocalcinosis or nephrolithiasis. MRI brain may show marked heterogenicity in the white matter changes, ranging from diffuse high intensity signal to no demonstrable changes.[19]

Surgery precaution should be exercised for OCRL patients. Chronic metabolic acidosis may be the most important component affecting anaesthetic management. Any agent that rapidly decreases sympathetic tone, in the presence of acidosis, may potentiate circulation depression. Therefore, agents that minimally affect the circulation should be used and intra-operative monitoring is important. The principle anaesthetic problem of the existing hypokalaemia is serious cardiac arrhythmia. The aim of serum potassium is 3.5-4.5 mmol/L.[25] Because of increased sensitivity, the dose of neuromuscular blocking agents should be reduced by 25-50% and a nerve stimulator used to follow the degree of paralysis and adequacy of reversal. Dextrose containing solutions should be avoided, as hyperglycaemia and secondary insulin secretion may further lower serum potassium. Hyperventilation is to be avoided to prevent further decrease in serum potassium.

Referral of patient's mother for detailed ophthalmological assessment is a must for the sake of genetic counselling. Laube[26] showed 7 out of 13 mothers examined had typical lens opacities. Four types of lens opacities occur in OCRL heterozygotes: punctate cortical opacities, linear cortical opacities, subcapsular plaques, and posterior polar cataracts. The typical findings are numerous punctate lenticular opacities or a single dense posterior polar cataract. Renal and nervous system manifestations are uncommon. In our case, the mother is asymptomatic and no characteristic lens manifestation is detected. Hence, molecular analysis of the OCRL gene is a more definitive way to diagnose female carriers. Prenatal diagnosis is possible for at risk pregnancies, either by biochemical assay of the activity of [PtdIns(4,5) P2-5ase] in cultured amnoicytes, or direct mutational analysis of the *OCRL* gene.

In conclusion, the diagnosis of OCRL is not obvious especially when the patient is in early infancy. Therefore, this diagnosis should be considered in all male infants with hypotonia and bilateral congenital or early onset cataracts. Urine for amino acid assay should be performed from time to time to look for amino-aciduria even with normal result previously. Obtaining a proper family history is crucial for genetic counselling of OCRL. Ophthalmological examination of patient's mother is necessary. Mutation analysis of *OCRL* gene is more definitive in confirming the diagnosis and identification of female carriers.

Remarks: The Lowe Syndrome Association (LSA) was founded in 1983. It maintains an international registry of affected individuals, disseminates information about OCRL, and supports and encourages medical research into the disorder. Website as follows: www.lowesyndrome.org

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