Complete oculocerebrorenal phenotype of Lowe syndrome in a female patient with half reduction of inositol polyphosphate 5-phosphatase

Katsusuke Yamamoto^{1,2} · Yasuhiro Hasegawa¹ · Yasuhisa Ohata^{1,3} · Kenichi Satomura^{2,4} · Yoshimi Mizoguchi¹ · Tsunesuke Shimotsuji¹ · Takehisa Yamamoto¹

Received: 14 January 2019 / Accepted: 29 October 2019 / Published online: 9 November 2019
© Japanese Society of Nephrology 2019

Abstract

The oculocerebrorenal disorder of Lowe syndrome is an X-linked mutation in the gene *oculocerebrorenal syndrome of Lowe 1 (OCRL)*, characterized by the triad of congenital cataracts, severe intellectual impairment, and renal tubular dysfunction. Manifestations of phenotype in female carriers and patients are extremely rare. We present a female case with congenital cataracts, severe intellectual impairment, sensorineural hearing loss, and renal tubular dysfunction as Lowe syndrome. A 9-year-old Japanese girl visited our hospital due to prolonged proteinuria. Her renal biopsy revealed diffuse mesangium proliferation, sclerosis and dilatation of renal tubules, and mild IgA deposition in the mesangial region. Furthermore, she had congenital cataracts, severe intellectual impairment, and sensorineural hearing loss. Genetic screening did not identify mutations of the *ORCL* gene encoding inositol polyphosphate 5-phosphatase (IPP-5P) (46 XX, female). However, we found the reduction of enzyme activity of IPP-5P to 50% of the normal value. Furthermore, her renal function had deteriorated to renal failure within a decade. Finally, she received peritoneal dialysis and renal transplantation. We present the oculocerebrorenal phenotype of Lowe syndrome in a female patient with reduced activity of IPP-5P without *OCRL* gene mutation.

Keywords Oculocerebrorenal · Lowe syndrome · OCRL gene · Inositol polyphosphate 5-phosphatase · Renal tubular dysfunction

Introduction

Lowe syndrome [oculocerebrorenal syndrome (OMIM #309,000)] is an X-linked recessive disorder which is caused by a mutation of the *oculocerebrorenal syndrome of Lowe 1 (OCRL)* gene on chromosome Xq26.1, encoding inositol polyphosphate 5-phosphatase (IPP-5P), characterized by the

triad of congenital cataracts, intellectual disability, and renal tubular dysfunction, first described in 1952 [1] by Lowe et al. Its prevalence in the general population is estimated to be approximately 1 in 500,000 [2]. A previous report suggested that about two-thirds of Lowe cases are transmitted by maternal carriers [3]. Female carriers with Lowe syndrome may show a mild phenotype, as in other X-linked disorders. Furthermore, female cases of Lowe syndrome are extremely rare because of its inheritance pattern. It has been reported that heterozygous females may manifest a more complete phenotype, and a total of ten cases have been reported in the literature [4]. Of these cases, three patients had cytogenetic abnormalities, whereas the causative defect was not ascertained in the other seven [4]. On the other hand, detail with IPP-5P activity was not described in the literature.

Recently, we had an opportunity to investigate the *OCRL* gene and activity of IPP-5P in a female patient who showed Lowe-like clinical findings. We found a 50% decreased level of enzyme activity responsible for Lowe syndrome, although direct analysis of the sequence revealed no mutations in the *OCRL* gene. We demonstrated the oculocerebrorenal

✉ Takehisa Yamamoto
t.yamamoto@minoh-hp.jp

¹ Department of Pediatrics, Minoh City Hospital, 5-7-1 Kayano, Minoh City, Osaka 562-8562, Japan

² Department of Pediatric Nephrology and Metabolism, Osaka Women's and Children's Hospital, 840 Murodo, Izumi City, Osaka 594-1101, Japan

³ Department of Pediatrics, Osaka University Graduate School of Medicine, 1-1 Yamadaoka, Suita City, Osaka 565-0873, Japan

⁴ Division of Internal Medicine, Meisei Daini Hospital, 1-19-20, Higashi-Obase, Higashinari, Osaka City, Osaka 537-0024, Japan

phenotype of Lowe syndrome in a female patient without *OCRL* gene mutation.

Case report

A Japanese girl presented with a very low birth weight (1248 g) and preterm birth (28 weeks). She had received mechanical ventilation due to her prematurity and developed renal dysfunction for some unknown reasons during infancy. Furthermore, she had bilateral congenital cataracts without Torch infection and other virus infection, and received lens extraction within the first year of life. There was no notable family history or consanguinity. She had been administered sodium bicarbonate (3.0 g/day) for distal renal tubular acidosis (RTA) and visited our hospital due to prolonged proteinuria at 9 years old.

Renal function

On the first visit to our hospital, she developed mild renal dysfunction with mild elevation of serum creatinine (Cr) and blood urea nitrogen (BUN) (Table 1). Urine examination showed proteinuria and elevation of excretion of β_2 -microglobulin (BMG) without elevation of *N*-acetyl- β -D-glucosaminidase (Table 1). Although normal values of fractional urine excretion of bicarbonate were obtained on treatment with sodium bicarbonate, ruling out the presence of a proximal RTA, there was still a possibility of impaired acidification at distal renal tubules.

When she was 12 years old, her renal function gradually progressed (Tables 2 and 3). Furthermore, we found heavy proteinuria (4725 mg/day). To examine the cause of renal dysfunction, we performed renal biopsy. We found that her histological findings of renal biopsy showed diffuse mesangium proliferation, sclerosis, and dilatation of renal tubules

(Fig. 1a–c). Immunofluorescence study for the presence of moderate IgM depositions and mild IgA depositions in the mesangial region (Fig. 1d, e), suggested that her renal dysfunction was caused by IgA depositions as IgA nephropathy. Her renal function was markedly reduced at the age of 20, with further elevations of serum levels of Cr (5.0 mg/dL) and BUN (48 mg/dL) (Table 2). Serum levels of intact parathyroid hormone (PTH) and $1,25(\text{OH})_2\text{D}$ were 39 and 45 pg/mL, respectively. Also, blood lactate and pyruvate concentrations were 10.4 and 0.8 mg/dL respectively. We administered enalapril and absorbent carbon; however, they did not prevent the progression of the renal function. As shown in Table 2, she developed renal failure at the age of 23 and began to receive peritoneal dialysis. Subsequently, she received a living renal transplantation.

Neurological findings

She had a very low intelligence quotient (39), and severe sensorineural hearing loss (> 80 dB), which was confirmed based on the auditory brain stem response, although there were no notable findings on neurological examination and a neuroimaging test.

Genetic screening and enzyme assay

Chromosome examination by a high-resolution chromosome banding technique showed normal 46XX. Furthermore, we performed a gene analysis of *OCRL*. We used a direct sequencing technique to analyze *OCRL* gene-coding sequence. The conditions of genetic analysis of *OCRL* were the same as those described previously [6]. However, we did not detect mutation of *OCRL* genes. We performed skin biopsy to collect samples from the forearm and establish skin fibroblasts in culture at the age of 12. Then, we measured the activity of IPP-5P as an enzyme responsible for

Table 1 Laboratory data on the first visit

Venous blood gas		Complete blood count		Biochemistry		Urinalysis	
pH	7.362	WBC	7000/ μL	Sodium	137 mEq/L	Protein	90 mg/dL
pCO ₂	40.3 mmHg	RBC	566 $\times 10^4$ / μL	Potassium	3.7 mEq/L	Occult blood	Not detected
pO ₂	38.0 mmHg	Hb	15.8 g/dL	Chloride	100 mEq/L	Glucose	Not detected
HCO ₃ [−]	22.3 mmol/L	Ht	43.6%	BUN	26 mg/dL	pH	6.5
BE	− 2.4 mmol/L	Platelet	29.8 $\times 10^4$ / μL	Cr	1.0 mg/dL	Specific gravity	1.006
sO ₂	80.5%			Ca	9.7 mg/dL	Cr	27 mg/dL
				IP	4.3 mg/dL	Ca	0.9 mg/dL
				UA	4.3 mg/dL	BMG	5510 $\mu\text{g/L}$
				Intact-PTH	27 pg/mL	NAG	4.7 U/L
							Ca/Cr 0.033
							20,407.4 $\mu\text{g/gCr}$
							17.4 U/gCr

BE base excess, BMG β_2 -microglobulin, BUN blood urea nitrogen, Ca Calcium, Cr creatinine, Hb hemoglobin, HCO₃[−] bicarbonate, Ht hematocrit, IP inorganic phosphorus, NAG *N*-acetyl- β -D-glucosaminidase, pCO₂ carbon dioxide partial pressure, pH potential of hydrogen, pO₂ oxygen partial pressure, PTH parathyroid hormone, RBC red blood cell, sO₂ saturated oxygen, UA urea acid, WBC white blood cell

Table 2 Renal function test of the patient

	9 y.o	10 y.o	11 y.o	12 y.o	13 y.o	14 y.o	15 y.o	16 y.o	17 y.o	18 y.o	19 y.o	20 y.o	21 y.o
Serum Cr (mg/dL)	1.0	1.1	1.6	1.5	2.0	1.9	2.1	2.3	2.6	2.8	5.4	5.0	5.7
BUN (mg/dL)	26	30	23	38	39	40	50	44	30	45	49	48	61
HCO ³⁻ (mmHg)	22.3	22.2	7.5	16.1	20.4	16.2	19.3	21.4	26.5	18.1	26.0	15.7	n.d
Urine BMG/uCr (μg/gCr)	20,407.4	29,428.6	32,330.2	43,309.1	47,315.2	17,447.2	20,823.7	18,365.8	37,633.3	25,750.0	81,479.2	81,710.9	49,532.1
Urine NAG/uCr (U/gCr)	17.4	12.9	11.6	13.6	n.d	7.2	7.1	6.3	8.8	6.5	16.7	10.5	n.d
eGFR (mL/min/1.73m ²)	45.1	43.5	32.9	36.3	n.d	30.3	n.d	25.7	23.1	21.7	12.7	13.5	12.3

eGFR is calculated as previously described [5]

BMG β2microglobulin, BUN blood urea nitrogen, Cr creatinine, n.d. no data, eGFR estimate glomerular filtration rate, NAG N-acetyl-α-D-glucosaminidase, n.d. no data, uCr urine creatinine, y.o. years old

Lowe syndrome in skin fibroblasts by thin-layer chromatography as previously described [7]. We found that the activity of the enzyme was almost half that of normal controls: 3.2 vs. 6.8 ± 0.9 (mean $\pm$ standard deviation) nmol/min/mg protein, respectively (Table 4). We did not measure IPP-5P enzyme activity in renal biopsy sample in this study.

Taken together, because of bilateral congenital cataracts, her renal dysfunction, severe intellectual impairment, and low activity of IPP-5P, we diagnosed her with the oculocerbrorenal phenotype of Lowe syndrome in a female patient.

Discussion

Lowe syndrome first described in 1952 as a X recessive disorder of mutation of the *OCRL* gene, resulting in reduced activity of IPP-5P, characterized by the triad of congenital cataracts, severe intellectual impairment, and renal tubular dysfunction with slowly progressive renal failure [1, 2]. Almost all patients with Lowe syndrome are male, except very few case reports of affected female patients with Lowe syndrome [4, 8–12]. It was considered that the cytogenic abnormalities of affected female patients with Lowe syndrome involve infelicitous lyonization [8], a 45, X karyotype, uniparental disomy, or an extremely skewed X-inactivation [4, 12].

Due to the mutation of the *OCRL* gene, activity of IPP-5P as an enzyme responsible for Lowe syndrome in soluble extracts of cultured skin fibroblasts derived from patients with Lowe syndrome is drastically reduced [13]. It was reported less than 10% activity in patients with Lowe syndrome [13, 14]. However, we found that the activity of the enzyme was only almost half that of normal controls in our case, although she had triad of congenital cataracts, renal tubular dysfunction, and developmental disability. On the other hand, in vitro, it was reported that the value of Ca²⁺ uptake which was associated with OCRL function showed inversely linear relation with the level of total 5-phosphatase activity [15]. On the other hand, a screening with Fabry disease which is an X-linked lysosomal α-galactosidase A deficiency, based on the measurement of the enzymic activity. Plasma enzymatic activity in female carriers might be within the normal range, compared with in male patients who usually present with very low enzymatic activity [16]. This phenomenon might explain at least in part of the discrepancy between this case and previous report. Moreover, the presence of this case might suggest the possibility that IPP-5P does not always represent the complete phenotype of Lowe syndrome. Thus, this is possible to suggest the presence of another gene than OCRL that is associated with the expression of the phenotype of Lowe syndrome. And the half reduction of IPP-5P is speculate to the opportunistic finding, whose function is to be elucidated in future.

Table 3 Laboratory data at the time of renal biopsy

Venous blood gas		Complete blood count		Biochemistry		Urinalysis	
pH	7.309	WBC	6700/ μ L	Sodium	140 mEq/L	Protein	4725 mg/day
pCO ₂	33.1 mmHg	RBC	$517 \times 10^4/\mu$ L	Potassium	3.9 mEq/L	pH	6.5
pO ₂	43.8 mmHg	Hb	14.2 g/dL	Chloride	112 mEq/L	Specific gravity	1.006
HCO ₃ ⁻	16.1 mmol/L	Ht	41.1%	BUN	38 mg/dL		
BE	- 8.8 mmol/L	Platelet	$31.1 \times 10^4/\mu$ L	Cr	1.5 mg/dL		
sO ₂	79.5%			Ca	8.4 mg/dL	Cr	33 mg/dL
				IP	4.6 mg/dL	Ca	1.5 mg/dL
				Intact-PTH	58 pg/mL	BMG	14,292 μ g/L
				IgA	175 mg/dL	NAG	4.5 U/L
							Ca/Cr 0.045
							43,309.1 μ g/gCr
							13.6 U/gCr

BE base excess, BMG β_2 -microglobulin, BUN blood urea nitrogen, Ca calcium, Cr creatinine, Hb hemoglobin, HCO₃⁻ bicarbonate, Ht hematocrit, IgA immunoglobulin A, IP inorganic phosphorus, NAG N-acetyl- β -D-glucosaminidase, pCO₂ carbon dioxide partial pressure, pH potential of hydrogen, pO₂ oxygen partial pressure, PTH parathyroid hormone, RBC red blood cell, sO₂ saturated oxygen, UA urea acid, WBC white blood cell

Fig. 1 Histological findings on renal biopsy. Low-magnification hematoxylin-eosin stain. **a** Original magnification, $\times 100$. High-magnification hematoxylin-eosin stain. **b** Original magnification, $\times 400$.

Periodic Acid-Schiff stain. **c** Original magnification, $\times 400$. Anti-IgM antibody staining (**d**). Anti-IgA antibody staining (**e**). Original magnification, $\times 400$

Table 4 Activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in skin fibroblasts

	Patient	Normal control
Phosphatidylinositol 4,5-bisphosphate 5-phosphatase (nmol/min/mg/protein)	3.2	6.8 ± 0.9

Mean $\pm$ standard deviation

Renal biopsy in patients with Lowe syndrome shows a characteristic course [2], with tubular dilation and proteinaceous casts at age 3–5 years and increased glomerular cellularity and focal glomerular sclerosis as well as

diffuse tubulointerstitial fibrosis in older children with Lowe syndrome [17–19]. Furthermore, there is an enlarged basement membrane, effacement of foot processes, and basement membrane thickening based on EM [19]. We

performed renal biopsy at the age of 12 when she developed mild renal dysfunction with mild elevations of serum Cr and BUN (Tables 2 and 3). We found a diffuse mesangium proliferation, sclerosis, and dilatation of renal tubules (Fig. 1a–c). It had been absent tubulointerstitial fibrosis and thickened basement membranes is known to be features of histological findings in patients with Lowe syndrome [17–19]. On the other hand, we also found mild IgA depositions (Fig. 1d, e). Her renal function had deteriorated gradually with age. Finally, she developed renal failure at the age of 21, when she received peritoneal dialysis and then renal transplantation. In general, children with IgA nephropathy show a relatively good renal prognosis. It was reported that 9% of patients had developed chronic renal failure by 15 years [20]. On the other hand, several studies suggested that heavy proteinuria at the time of biopsy [20] and familial IgA nephropathy predict a poor outcome [21]. Furthermore, the degree of proteinuria is correlated with the severity of morphologic glomerular lesions [19]. In our case, heavy proteinuria (4725 mg/day) at the time of biopsy as well as a low enzyme level with Lowe-like syndrome might be linked to the poor prognostic factors. Although the pathogenesis of progressive renal failure in Lowe syndrome is not clear [2], it was considered that the development of renal failure in our case was correlated in part with the IgA deposition as advanced IgA nephropathy.

There are three limitations of this study. First, we could not detect any exon mutation of the *OCRL* gene in our case. And, we did not sequence all intronic regions and perform RNA assay including northern blot and quantitative and semi-quantitative PCR targeting *OCRL* transcript. Furthermore, we had not performed high-resolution G-band human chromosomes karyotypes to clarify whether it is balanced translocation or not, although the previous report presented a girl with manifestations of Lowe syndrome who has a de novo balanced X/autosome translocation [22]. Second, we could not show the distinct loss of function of *OCRL* using IPP-5P activity and a close genocopy of Lowe syndrome due to a defect in a gene other than *OCRL* or highly skewed X-inactivation in whom the mutation was missed. Further study might be necessary to elucidate the molecular basis of a pathophysiology for the renal failure of this patient. Third, unfortunately, it was insufficient in information during perinatal period, and thus, we could not discuss whether it was deterioration of renal function by treatment such as indomethacin leading kidney damages or not.

In conclusion, we described the oculocerebrorenal phenotype of Lowe syndrome in a female patient showing reduced activity of IPP-5P without *OCRL* gene mutation. Renal dysfunction in this patient may have been deteriorated by IgA deposition.

Acknowledgements We are grateful to the past Dr. Youichi Mizusawa at Tokyo Medical and Dental University for enzyme assays and the past Dr. Takashi Sekine at The University of Tokyo for genetic investigations. We also thank Dr. Makoto Ishida at Ishida Clinic and Dr. Hidehito Kondou at Japanese Red Cross Kyoto Daiichi Hospital for useful discussions and Dr. Mai Ihashi, other pediatricians, and many medical staff working in Minoh City Hospital for their clinical co-operation.

Funding This research was not supported by any funds.

Availability of data and materials Data and materials are available from our hospital.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from patient and her parent included in the study.

References

1. Lowe CU, Terrey M, MacLachlan EA. Organic-aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation; a clinical entity. *Am J Dis Child*. 1952;83(2):164–84.
2. Bökenkamp A, Ludwig M. The oculocerebrorenal syndrome of Lowe: an update. *Pediatr Nephrol*. 2016;31(12):2201–12.
3. Hichri H, Rendu J, Monnier N, et al. From Lowe syndrome to Dent disease: correlations between mutations of the *OCRL1* gene and clinical and biochemical phenotypes. *Hum Mutat*. 2011;32(4):379–88.
4. Recker F, Reutter H, Ludwig M. Lowe syndrome/Dent-2 disease: a comprehensive review of known and novel aspects. *J Pediatr Genet*. 2013;2(2):53–68.
5. Uemura O, Nagai T, Ishikura K, et al. Creatinine-based equation to estimate the glomerular filtration rate in Japanese children and adolescents with chronic kidney disease. *Clin Exp Nephrol*. 2014;18:626–33.
6. Sekine T, Nozu K, Iyengar R, et al. *OCRL1* mutations in patients with Dent disease phenotype in Japan. *Pediatr Nephrol*. 2007;22(7):975–80.
7. Zhang X, Jefferson AB, Auethavekiat V, Majerus PW. The protein deficient in Lowe syndrome is a phosphatidylinositol-4,5-bisphosphate 5-phosphatase. *Proc Natl Acad Sci USA*. 1995;92(11):4853–6.
8. Svorc JM, Masopust J, Komárková A, Macek M, Hyánek J. Oculocerebrorenal syndrome in a female child. *Am J Dis Child*. 1967;114(2):186–90.
9. Harris LS, Gitter KA, Galin MA, Plechaty GP. Oculo-cerebrorenal syndrome. Report of a case in a baby girl. *Br J Ophthalmol*. 1970;54(4):278–80.
10. Hodgson SV, Heckmatt JZ, Hughes E, Crolla JA, Dubowitz V, Bobrow M. A balanced de novo X/autosome translocation in a girl with manifestations of Lowe syndrome. *Am J Med Genet*. 1986;23(3):837–47.
11. Mueller OT, Hartsfield JK, Gallardo LA, et al. Lowe oculocerebrorenal syndrome in a female with a balanced X;20 translocation: mapping of the X chromosome breakpoint. *Am J Hum Genet*. 1991;49(4):804–10.
12. Cau M, Addis M, Congiu R, et al. A locus for familial skewed X chromosome inactivation maps to chromosome Xq25 in a

- family with a female manifesting Lowe syndrome. *J Hum Genet.* 2006;51(11):1030–6.
13. Pirruccello M, De Camilli P. Inositol 5-phosphatases: insights from the Lowe syndrome protein OCRL. *Trends Biochem Sci.* 2012;37(4):134–43.
 14. Suchy SF, Olivos-Glander IM, Nussbaum RL. Lowe syndrome, a deficiency of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in the Golgi apparatus. *Hum Mol Genet.* 1995;4(12):2245–50.
 15. Wu G, Zhang W, Na T, Jing H, Wu H, Peng JB. Suppression of intestinal calcium entry channel TRPV6 by OCRL, a lipid phosphatase associated with Lowe syndrome and Dent disease. *Am J Physiol Cell Physiol.* 2012;302(10):C1479–1491.
 16. Monserrat L, Gimeno-Blanes JR, Marín F, et al. Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2007;50(25):2399–403.
 17. Abbassi V, Lowe CU, Calcagno PL. Oculo-cerebro-renal syndrome. A review. *Am J Dis Child.* 1968;115(2):145–68.
 18. Tricot L, Yahiaoui Y, Teixeira L, et al. End-stage renal failure in Lowe syndrome. *Nephrol Dial Transplant.* 2003;18(9):1923–5.
 19. Witzleben CL, Schoen EJ, Tu WH, McDonald LW. Progressive morphologic renal changes in the oculo-cerebro-renal syndrome of Lowe. *Am J Med.* 1968;44(2):319–24.
 20. Nakanishi K, Yoshikawa N. Immunoglobulin a nephropathies in children (includes HSP). In: Avner ED, Harmon WE, Niaudet P, editors. *Pediatric nephrology.* Springer: Heidelberg; 2016. p. 983–1033.
 21. Schena FP, Cerullo G, Rossini M, Lanzilotta SG, D'Altri C, Manno C. Increased risk of end-stage renal disease in familial IgA nephropathy. *J Am Soc Nephrol.* 2002;13(2):453–60.
 22. Hodgson SV, Heckmatt JZ, Hughes E, Crolla JA, Dubowitz V, Bobrow M. A balanced de novo X/autosome translocation in a girl with manifestations of Lowe syndrome. *Am J med Genet.* 1986;23:837–47.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.