

Long-term kidney function of Lowe syndrome: a nationwide study of paediatric and adult patients

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To the Editor,

The oculocerebrorenal syndrome of Lowe (Lowe syndrome, OMIM 309000) is an X-linked genetic disorder that is characterized by three major abnormalities: ocular disease, central nervous system (CNS) disorder and kidney disease [1, 2]. The clinical symptom of kidney disease is Fanconi syndrome, which causes rickets, kidney calcification, acidosis and progressive chronic kidney disease (CKD) [2]. Lowe syndrome is caused by pathogenic variants of the OCRL gene [3]. OCRL encodes inositol polyphosphate 5-phosphatase (OCRL1), which affects cellular functions such as kidney tubular endocytosis [4]. Kidney disease is one of the major prognostic factors of Lowe syndrome [2]. Zaniew et al. [5] found kidney outcomes and correlations between the estimated glomerular filtration rate (eGFR) and clinical prognostic factors in childhood in an international cohort. However, there are no studies analysing the progression of CKD in patients with Lowe syndrome who survived into adulthood.

We conducted a multicentre, retrospective study of a nationwide cohort of paediatric and adult Lowe syndrome patients. Clinical diagnosis of Lowe syndrome was based on the presence of all three of the following: congenital cataracts, Fanconi syndrome and CNS involvement [6, 7] and patients who did not have genetic data were clinically diagnosed. A total of 54 patients from 51 families were analysed in the study. eGFR was calculated using the original Schwartz method [8], but with a revised k-value of 26 (when serum creatinine is in the $\mu\text{mol/l}$ range) for patients with Lowe syndrome, as suggested previously [9]. This method is not validated in adult patients, but eGFR formulas such as the Chronic Kidney Disease Epidemiology Collaboration and Cockcroft–Gault are not suitable for patients with Lowe syndrome due to their low muscle mass. Therefore, we used the Schwartz formula with a k-value of 26 for both paediatric and adult patients. Details of the study design are described in the [Supplementary Data](#). Clinical characteristics of the cohort are detailed in Table 1. All patients had congenital cataracts and CNS involvement. Fanconi syndrome with extremely high levels of urine β_2 -microglobulin was present in all 46 patients with available data, thus meeting the criteria for the clinical diagnosis of Lowe syndrome. The remaining patients with missing urine β_2 -microglobulin data had

pathogenic variants in the OCRL gene. Genetic test results were obtained from 40 of 54 patients (74%). All 40 patients had pathogenic variants in the OCRL gene. The details of the variants are shown in [Supplementary Table S1](#). Genetic testing was not performed in the remaining 14 patients, because informed consent could not be obtained. Phenotypes of these 14 patients are shown in [Supplementary Table S2](#). All patients had congenital cataracts, CNS involvement and Fanconi syndrome, with extremely high levels of urine β_2 -microglobulin, thereby meeting the criteria for the clinical diagnosis of Lowe syndrome.

A scatter plot of eGFR versus age at the last visit is shown in Fig. 1A. There was a strong negative correlation between age at the last follow-up and eGFR ($r = -0.80$, $P < .0001$). During childhood (age <20 years), CKD stages G2–3 and G4–5 were observed in 97% (34/35) and 3% (1/35) of patients, respectively (Fig. 1A). In adult (age ≥ 20 years) patients, CKD stages G4–5 were observed in 84% (16/19) of patients (Fig. 1A). Eight patients developed end-stage kidney disease (ESKD) at the median age of 32 years [interquartile range (IQR) 25–39]. ESKD was observed in 67% (6/9) of patients when the analysis was restricted to those ≥ 30 years of age. Three patients underwent kidney replacement therapy. Next, we plotted the time course of the eGFR from each patient and smoothed the scatterplots using LOESS regression analysis. The eGFR of the entire cohort was found to deteriorate steeply after 10 years of age (Fig. 1B).

Associations of clinical data and manifestations with the eGFR at the last follow-up are shown in [Supplementary Tables S3 and S4](#). Univariate analysis showed that age and urine protein:creatinine ratio were significantly correlated with the eGFR at the last follow-up ([Supplementary Table S3](#)). The eGFR was higher in patients with hypercalciuria than in those without ([Supplementary Table S4](#)). Multiple regression analysis including features of clinical importance (age at last follow-up, hypercalciuria, metabolic acidosis, nephrocalcinosis/nephrolithiasis and urine protein:creatinine ratio) showed that only age was significantly correlated with the eGFR ([Supplementary Table S5](#)). The eGFR values at last follow-up according to variant type are shown in [Supplementary Fig. S1](#). Age in the present study was not significantly different among variant types. There were no significant

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Table 1: Clinical characteristics of the entire cohort (N = 54).

Characteristics	Values	Range
Male, n (%)	54 (100)	–
Age at diagnosis (months) (n = 44), median (IQR)	9 (6–16.8)	0–170
Age at last follow-up (years), median (IQR)	14.5 (8.8–23)	2–45
Height SDS, median (IQR)	–3.7 (–5.1 to –3.0)	–11.3 to –0.5
Growth retardation, n (%)	48/ (89)	–
Congenital cataracts, n (%)	54 (100)	–
Central nervous system involvement, n (%)	54 (100)	–
Nephrocalcinosis/nephrolithiasis, n (%)	19 (35)	–
Rickets, n (%)	23 (43)	–
eGFR (ml/min/1.73 m ²), median (IQR)	44.3 (22.2–55.4)	4.4–70.4
CKD stage 1, n (%)	0 (0)	–
CKD stage 2, n (%)	10 (19)	–
Age at CKD stage 2 (years), median (IQR)	9 (6.5–10)	3–15
CKD stage 3, n (%)	27 (50)	–
Age at CKD stage 3 (years), median (IQR)	11 (7–18)	2–22
CKD stage 4, n (%)	9 (17)	–
Age at CKD stage 4 (years), median (IQR)	27 (22.5–36)	18–45
CKD stage 5 ^a , n (%)	8 (15)	–
Age at CKD stage 5 (years), median (IQR)	32 (24.8–38.5)	20–42
Serum albumin (g/dl) (n = 50), median (IQR)	4.3 (4.1–4.5)	3.1–5.0
Serum phosphate (mg/dl) (n = 53)	3.9 (3.1–4.8)	2.2–6.9
Serum phosphate SDS (n = 53), median (IQR)	–0.8 (–2.2–0.3)	–5.0–6.5
Hypophosphataemia, n/N (%)	13/53 (25)	–
Alkaline phosphatase ^b (n = 52), median (IQR)	901 (565–1294)	63–2923
Bicarbonate concentration (mmol/l) (n = 47), median (IQR)	22.3 (20.1–25.3)	16.8–28.9
Metabolic acidosis ^c , n/N (%)	39/53 (74)	–
Proteinuria, n/N (%)	49/49 (100)	–
Urine β_2 -microglobulin (μ g/l) (n = 46), median (IQR)	75 312.0 (53 562.3–129 802.5)	5995.0–350 000.0
P:Cr ratio (mg/mg) (n = 44), median (IQR)	3.9 (2.4–7.3)	0.0–18.5
Hypercalciuria, n/N (%)	33/43 (77)	–

Laboratory data including eGFR were collected at the last follow-up.

^aThree patients underwent kidney replacement therapy. One patient started haemodialysis (HD) at age 22 years using a tunnelled cuffed catheter and has been on HD for 11 years with the use of sedation during HD sessions. One patient started HD at age 40 years using an arteriovenous fistula and has been on HD for 5 years without the use of sedation during HD sessions. One patient underwent kidney transplantation. A detailed clinical course after kidney transplantation was not available.

^bJapanese Society of Clinical Chemistry method.

^cMetabolic acidosis was defined when receiving supplementation and/or with decreased blood bicarbonate levels (<22 mmol/l).

SDS: standard deviation score; P:Cr ratio: protein:creatinine ratio.

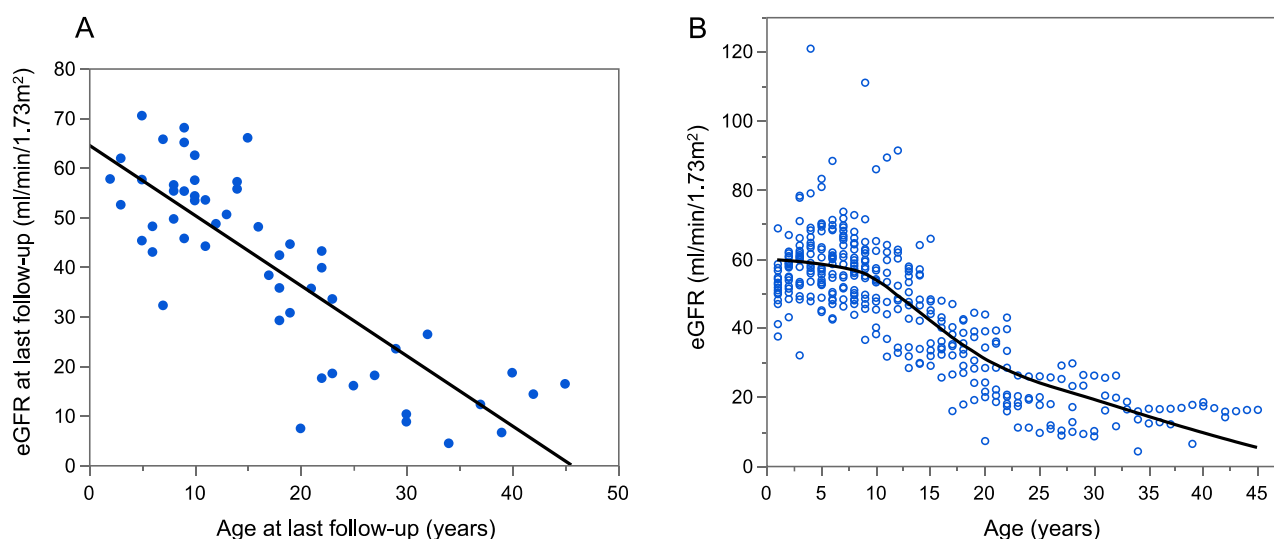


Figure 1: (A) Scatterplot of correlation between eGFR and age at the last follow-up (N = 54). There was a significant negative correlation between the eGFR and age ($r = 0.80$, $P < .0001$). CKD stages G4–5 were observed in 16/19 (84%) patients after 20 years of age and in 8/8 (100%) after 30 years of age. (B) Longitudinal analysis of eGFR versus age in the cohort patients. Longitudinal eGFR data are plotted and the scatterplot was smoothed using LOESS regression analysis. CKD progressed steeply after 10 years of age. eGFR deteriorated less steeply after 20 years of age, but this result could have been affected by censored ESKD cases.

differences in the eGFR between non-truncating and truncating variants (Supplementary Fig. S1). The variants were also tested for their position along the gene and were used to classify the patients into four groups, which refer to the respective OCRL1 domains. There were no significant differences in age in the present study among the domains. The eGFR was not significantly different between patients with variants in the 5-phosphatase domain (exons 9–15) and those in the RhoGAP domain (exons 21–24) (Supplementary Fig. S2).

In 2018, Zaniew *et al.* [5] analysed CKD progression during childhood in a large cohort of patients with Lowe syndrome. They found that CKD stages G2–5 and G4–5 were observed in 82% and 9% of patients, respectively. In the present study, most paediatric patients developed moderate CKD, as previously reported [5]. Charnas *et al.* [10] first reported that the kidney function of Lowe syndrome linearly decreased with age >10 years and Zaniew *et al.* [5] reported that a clear breakpoint in eGFR decline occurred at the age of 10 years. Similarly, our study showed that the eGFR deteriorated steeply after 10 years of age (Fig. 1B), which is consistent with previous reports [5, 10]. In contrast, there are limited data regarding the long-term kidney outcomes of adult patients. Bökenkamp *et al.* [11] reported that adult Lowe syndrome patients develop ESKD in the second to fourth decade of life. We analysed CKD progression in Lowe syndrome patients including 19 adults (≥ 20 years of age), which is the largest cohort of adult Lowe syndrome patients reported thus far. We found that 84% of patients developed CKD stages G4–5 after 20 years of age and 67% of patients developed CKD stage G5 after 30 years (Fig. 1A). These results suggest that most patients with Lowe syndrome develop ESKD by their fourth decade of life.

Zaniew *et al.* [5] also reported that the position of pathogenic variants was not associated with kidney outcomes. In the present study, the eGFR was not significantly different between patients with 5-phosphate domain variants and those with RhoGAP domain variants. Previous studies analysed the factors associated with eGFR deterioration and showed that only age was significantly correlated with the eGFR [5, 12]. Our study also showed that only age was significantly correlated with the eGFR in the multivariate analysis.

It has been described that nephrocalcinosis may potentially contribute to CKD progression [5]. However, the abovementioned studies showed that nephrocalcinosis and hypercalciuria were not associated with eGFR deterioration [5, 12]. Bockenhauer *et al.* [9] reported that nephrocalcinosis was not associated with hypercalciuria and age. Similarly, the present study showed that nephrocalcinosis and hypercalciuria were not associated with eGFR deterioration. Because nephrocalcinosis is usually assessed by ultrasound, hyperechogenic kidneys may be diagnosed with nephrocalcinosis, which can result in overestimation. In addition, our results suggest that hypercalciuria is reduced in older patients (Supplementary Table S4), although the mechanism is unknown. Studies of pathological examinations suggest that tubulointerstitial fibrosis [13] and podocyte injury [14] may be associated with decreased kidney function. Further genetic and pathological analyses are required to determine the factors associated with the progression of kidney dysfunction in Lowe syndrome.

Our study has several limitations. The present study is a retrospective analysis of a nationwide cohort with a relatively small sample size. However, collecting a larger number of patients including adult individuals is very difficult due to its rarity. Our study is also limited by the use of the Schwartz formula with a different k-value, which is not validated in adult patients with Lowe syndrome. Rickets, nephrolithiasis and nephrocalcinosis were not

defined at the time of the questionnaire survey. Genetic tests were not performed in one-fourth of the patients. Furthermore, limited data were available for the univariate and multivariate analyses of factors associated with eGFR.

In conclusion, CKD progressed steeply after 10 years of age and 84% of patients developed CKD stages G4–5 after 20 years of age. Nephrocalcinosis and hypercalciuria did not show a significant impact on the eGFR.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](https://ndt.oup.com/ndt/article/39/8/1360/7640030) online.

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AUTHORS' CONTRIBUTIONS

T.A. was responsible for the conceptualization, data curation, formal analysis, investigation, methodology, visualization and writing of the original draft. K.M. was responsible for the conceptualization, data curation, formal analysis and review and editing. T.Y., K.H., R.H. and K.I. were responsible for data curation, investigation, methodology and review and editing. Y.S. and K.I. were responsible for data curation and review and editing. S.K. and Y.H. were responsible for the investigation, methodology and review and editing. E.I. was responsible for the methodology, statistics supervision and review and editing. M.H. was responsible for supervision and review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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