Clinical Kidney Journal, 2024, vol. 17, no. 4, sfae073

https://doi.org/10.1093/ckj/sfae073
Advance Access Publication Date: 22 March 2024
Exceptional Case

EXCEPTIONAL CASE

A 20-year follow-up study of identical twin sisters with immunoglobulin A nephropathy

Masahiro Okabe [1,2], Nobuo Tsuboi [1], Hiroyuki Ueda[1], Erika Hishida[3], Yoichi Miyazaki[1,2] and Takashi Yokoo[1]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan, [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine Daisan Hospital, Tokyo, Japan and [3]Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan

Correspondence to: Nobuo Tsuboi; E-mail: tsuboi-n@jikei.ac.jp

ABSTRACT

Immunoglobulin A nephropathy (IgAN) is characterized by diverse clinicopathological phenotypes. Herein we present a follow-up study of previously reported identical twin sisters with IgAN. The older sister exhibited more severe kidney histopathology and proteinuria and a lower birthweight than did her younger sister, and only the older sister experienced two childbirths. These raised concerns regarding her kidney outcomes. However, with timely multidisciplinary treatments, the older sister's kidney function remained preserved after 20 years of IgAN history. Our findings indicate the significant contribution of environmental/epigenetic factors to IgAN progression and the need for tailored medical care corresponding to life events.

Keywords: chronic kidney disease, IgA nephropathy, life event, monozygotic, twins

INTRODUCTION

The presence of immunoglobulin A nephropathy (IgAN) clusters in families suggests that genetic predisposition is involved in the development of IgAN. Environmental or epigenetic factors may play roles in individual differences in IgAN severity; however, the evidence is insufficient.

We previously reported identical twin sisters with IgAN who developed the disease at approximately the same age but showed discordance in clinicopathological severity [1]. In the present report, we describe the long-term clinical course of twins with IgAN over 20 years.

CASE REPORTS

The patients included in the present case report are identical twin sisters in their 40s. They grew up together, attended the same school until the age of 15 and lived together until they were married in their early 30s. The twins developed IgAN in their teenage years, but their clinical courses differed. Fig. 1 and Supplementary Table S1 present comparisons of the two cases. The older sister weighed less at birth than her younger sister (2330 versus 2745 g). None of the sisters had a history of habitual tonsillitis. The older sister exhibited more severe histopathological findings in the first and second kidney biopsies and required aggressive remission induction therapy, including two corticosteroid regimens and tonsillectomy. Furthermore, her urinary protein levels remained extremely higher than those of her younger sister (time-averaged values: 0.98 ± 0.64 versus 0.36 ± 0.18 g/day). Notably, both sisters discontinued angiotensin II receptor blockers (ARBs) during fertility treatment. Consequently, the older sister had two childbirths along with increased urinary protein. The resumption of ARBs and

Received: 16.3.2024; Editorial decision: 18.3.2024

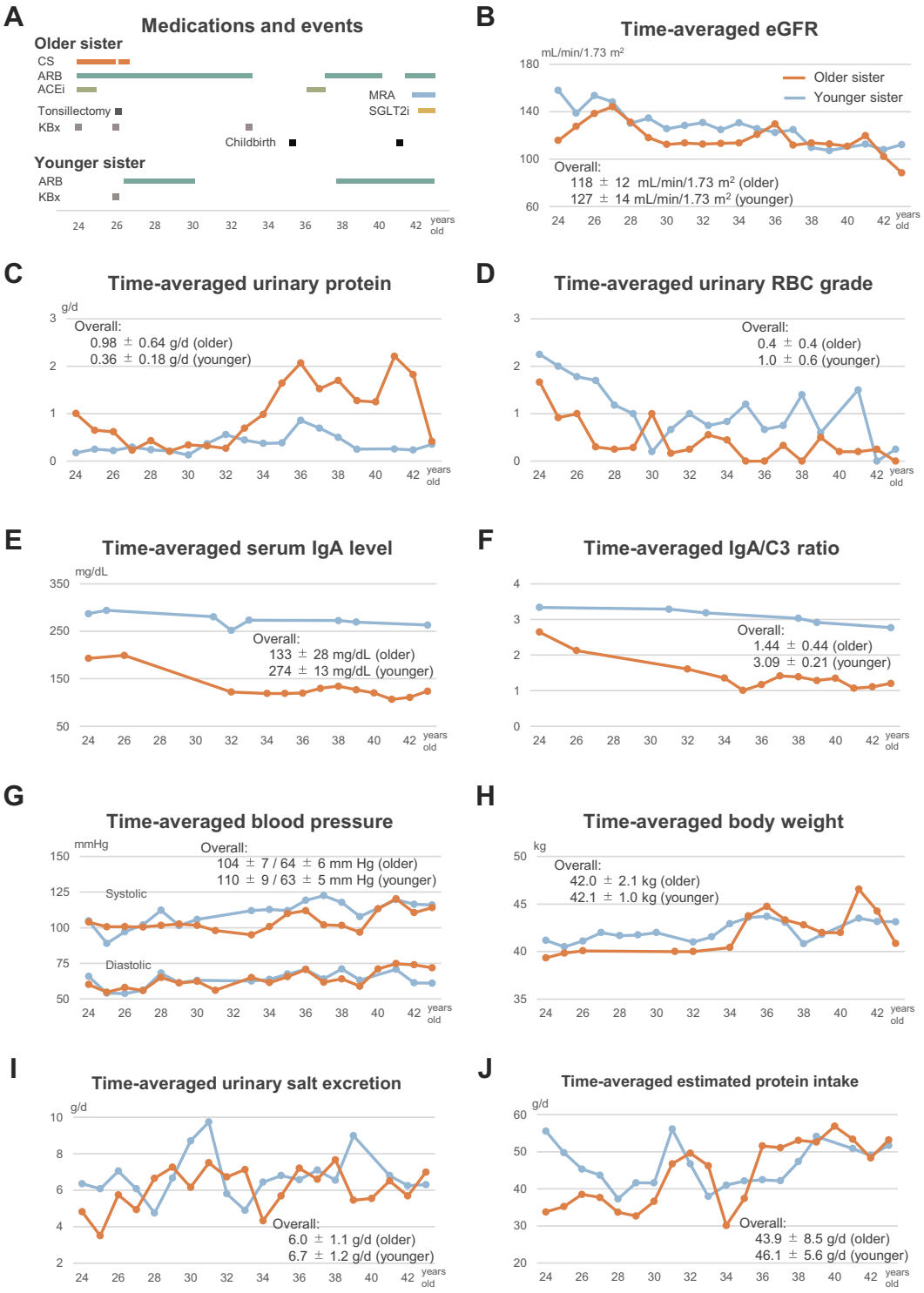

Figure 1: Clinical course of identical twin sisters with IgAN over 20 years. **(A)** Medications and events in the twins. The older twin was aggressively treated with two corticosteroid (CS) regimens (2-year oral corticosteroids and 6-month steroid pulse therapy) and tonsillectomy because of the highly active IgAN. ARBs were administered to the twins except during their infertility treatment or pregnancy, and mineralocorticoid receptor antagonist (MRA) and sodium–glucose co-transporter-2 inhibitor (SGLT2i) were sequentially administered to the older sister after two childbirths. Kidney biopsies were performed once in the younger sister and three times in the older sister. **(B–J)** Time-averaged values. The time-averaged values were calculated as a 1-year average of each measurement. Urinary protein level, salt excretion and estimated protein intake were calculated with 24-h urine collection. Haematuria was graded into four groups according to urinary sediment red blood cell (RBC) count: 0 [0–4 cells/high-power field (HPF)], 1 (5–19 cells/HPF), 2 (20–49 cells/HPF) and 3 (≥50 cells/HPF). Corticosteroid therapy combined with tonsillectomy improved kidney function, proteinuria, haematuria, serum IgA level and IgA:C3 ratio in the older sister; however, the urinary protein level was increased after ARB discontinuation and during pregnancies. In contrast, only a mild increase in urinary protein level was observed in the younger sister during ARB interruption. The older sister required further aggressive therapies using MRA and SGLT2i. There were no significant differences in the time-averaged values of blood pressure, body weight and salt and protein intakes between the twins. ACEi: angiotensin-converting enzyme inhibitor; eGFR: estimated glomerular filtration rate; KBx: kidney biopsy.

commencement of mineralocorticoid receptor antagonist and sodium–glucose co-transporter-2 inhibitor therapy contributed to proteinuria reduction. The younger sister showed less severe proteinuria during prolonged ARB interruption. The time-averaged values of factors that may affect IgAN progression, including body size, blood pressure and protein and salt intake, did not differ between the twins. The older sister had lower serum IgA levels and IgA:C3 ratios throughout the period. The glomerular volume of both sisters in the first kidney biopsy did not differ [1.58×10^6 (older sister) versus 1.61×10^6 μm^3 (younger sister)]. The glomerular volume of the older sister increased over time (1.17- and 1.73-fold in the second and third biopsies, respectively, compared with that of the first biopsy) (Supplementary Table S1); however, the kidney function of the twins remained similar.

DISCUSSION

In the present cases of identical twins with IgAN, the clinical presentations of the twins were discordant. Throughout the clinical course, the older sister exhibited more severe proteinuria, possibly due to a combination of several factors. Because the twins were identical, different exposures to environmental or epigenetic factors may have caused differences in the IgAN severity between the twins [2].

Low birthweight, which can be associated with a low nephron number [3], might have affected the clinical course of the older sister. However, the twins showed no difference in the glomerular volume in the first biopsy. This suggests that the difference in the nephron number, indicated by birthweight, may not have been sufficient to affect glomerular haemodynamics, at least at the time of the first diagnostic biopsy.

Throughout the clinical course, the older sister consistently showed lower serum IgA levels and IgA:C3 ratios, a surrogate for the disease activity of IgAN [4], than did the younger sister. Corticosteroid therapy and tonsillectomy in the older sister may have further influenced this trend.

While the disease activity of IgAN was attenuated by corticosteroid therapy combined with tonsillectomy in the older sister, her glomerular volume gradually increased over time. Notably, the further exacerbation of proteinuria after ARB discontinuation may be evidence of greater nephron loss in the older sister. In addition, the fact that both pregnancies of the older sister exacerbated proteinuria implies the involvement of haemodynamic effects [5]. Renin–angiotensin–aldosterone blockade and sodium–glucose co-transporter-2 inhibition adequately reduced urinary protein levels, probably by attenuating glomerular hyperfiltration.

In conclusion, we observed the clinical course of identical twin sisters with IgAN over 20 years. With timely multidisciplinary treatment for IgAN, the twins showed relatively good clinical courses. Our findings indicate that even when the genetic background is identical, IgAN severity can vary significantly because of various life events. These findings reaffirm the importance of tailored medical care for patients with IgAN, whose disease status continuously changes during the long-term clinical course.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

PATIENT CONSENT

The authors obtained written consent from all patients discussed in this report.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

M.O., N.T., H.U. and E.H. treated the patients. M.O., N.T. and E.H. collected the data. M.O. and N.T. drafted the manuscript and prepared the figure. H.U., E.H., Y.M. and T.Y. revised the manuscript. All authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

All authors declare no relevant conflicts of interest.

REFERENCES

1. Tsuboi N, Kawamura T, Okonogi H *et al*. Discordant clinicopathological features in monozygotic twins with IgA nephropathy. *Nephrol Dial Transplant* 2011;**26**:4146–8. https://doi.org/10.1093/ndt/gfr519
2. Jefferis J, Pelecanos A, Catts V *et al*. The heritability of kidney function using an older Australian twin population. *Kidney Int Rep* 2022;**7**:1819–30.
3. Luyckx VA, Brenner BM. Birth weight, malnutrition and kidney-associated outcomes—a global concern. *Nat Rev Nephrol* 2015;**11**:135–49. https://doi.org/10.1038/nrneph.2014.251
4. Yang D, Pei G, Wang S *et al*. Combined effects of the serum IgA/C3 ratio and glomerular C3 staining on the renal outcome in adult IgA nephropathy. *Kidney Blood Press Res* 2024. https://doi.org/10.1159/000536114
5. Neuringer JR, Brenner BM. Hemodynamic theory of progressive renal disease: a 10-year update in brief review. *Am J Kidney Dis* 1993;**22**:98–104. https://doi.org/10.1016/S0272-6386(12)70174-9

Received: 16.3.2024; Editorial decision: 18.3.2024