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Exceptional Case

EXCEPTIONAL CASE

Renal involvement and Strømme syndrome

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ABSTRACT

Strømme syndrome is a rare autosomal recessive congenital disorder involving multiple systems. Centromeric protein F (*CENPF*) is the causative gene of the disease, and variants are usually linked to lethal outcomes either during the foetal stage or in early life. We present a young adult with a genetic diagnosis of Strømme syndrome who—in addition to classic microcephalia, microphthalmia and intestinal atresia (apple peel-type)—experienced slow and unexpected evolution to end-stage renal disease (ESRD). In conclusion, Strømme syndrome is a complex multiorgan disease that needs multidisciplinary clinical management, and potential evolution to ESRD should be taken into account.

Keywords: centromeric protein F (CENPF), dialysis, end-stage renal disease, rare disease, Strømme syndrome

BACKGROUND

Strømme syndrome (OMIM #243605) is an autosomal recessive congenital disorder involving multiple systems that shares clinical features with ciliopathies. Affected individuals typically have intestinal atresia, variable ocular abnormalities, and microcephaly, and sometimes other systems are involved, including the kidney and heart. In some cases, the condition is lethal in early life, whereas other patients show normal survival with or without mild cognitive impairment [1].

CASE REPORT

Here, we report the case of a young man who has been followed by our hospital since he was born in 2000; in his first days of life, he needed abdominal surgery due to an intestinal apple peel-type atresia. Our patient presented a polymalformative context with microcephalia, microphthalmia, microcornea and corneal leucoma, preauricular chondroma and mild cognitive impairment. High-resolution karyotype, and renal and cardiac ultrasound, examinations were normal [2].

He was regularly followed up, and evaluated via twice yearly clinical visits and biochemical examinations, until he was 9 years old (see Figure 1). He then stopped attending regular check-ups every 6 months and did not present any notable medical occurrences until 2018, when he was admitted at our hospital's emergency department with hyporexia, weight loss, paleness, asthenia and halitosis. Biochemical examination showed: creatinine 13.02 mg/dL, urea 300 mg/dL, haemoglobin 5 g/dL, pH 7.235, serum bicarbonate 17.7 mEq/L, serum calcium 6.1 mEq/L, serum potassium 4.5 mEq/L and estimated glomerular filtration rate 5 mL/min/1.73 m^2. Blood pressure was 135/90 mmHg and there were no oedemas, proteinuria, haematuria or urinary crystals. Kidney sizes were 7 cm (right) and 7.5 cm (left).

He was immediately treated for renal failure and anaemia, and after that he was hospitalized for a specific diagnostic and

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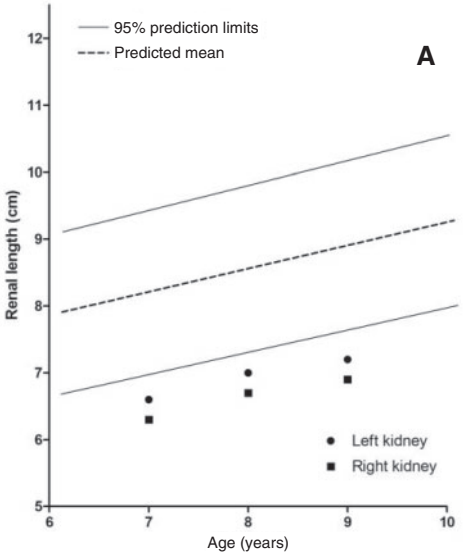

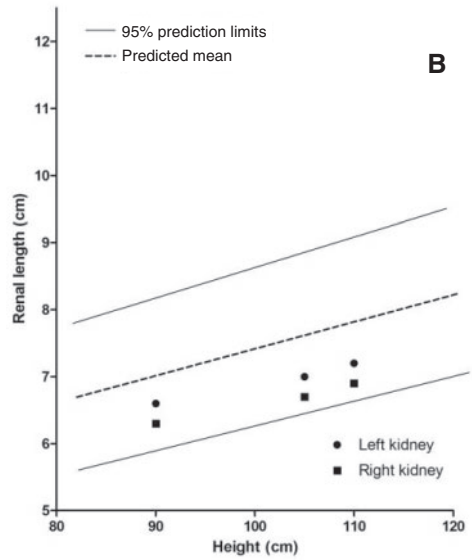

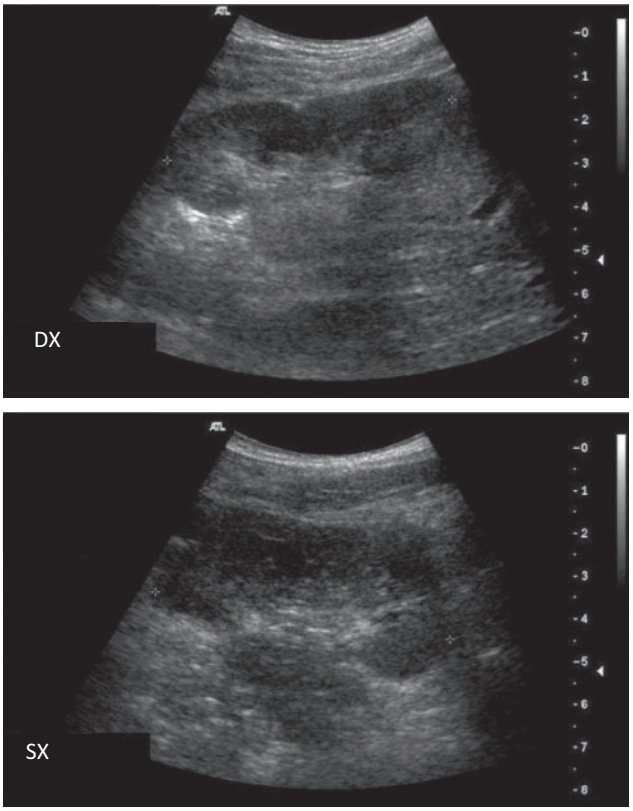

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Age (years)	Serum creat (mg/dL)	Height (cm)	GFR (mL/min/1.73 m^2)*
3	0.36	68	78
4	0.40	77	80
5	0.43	81	78
6	0.46	90	81
7	0.48	95	82
8	0.55	105	79
9	0.58	110	78

* Creatinine based 'Bedside Schwartz' equation (2009)

FIGURE 1: Renal length related to (**A**) patient age and (**B**) patient height (left kidney: circles and right kidney: squares). (**C**) Renal ultrasound at 7 years of age. (**D**) Summary table with available data for serum creatinine, height and glomerular filtration rates between the ages of 3 and 9 years.

therapeutic overview. Renal ultrasound revealed bilateral hypoplasia with hyperechoic kidneys and poor corticomedullary differentiation, and chronic haemodialysis was started.

After informed consent was obtained from all family members, considering the patient's medical history and phenotype, genetic counselling and testing were performed. Comparative genomic hybridization array (Agilent SurePrint G3 Human CGH Microarray 180 K) was normal and analysis of a panel of ciliopathy genes by next generation sequencing (PGM Ion Torrent) discovered two pathogenic loss-of-function (LoF) variants of centromeric protein F (*CENPF*), which were confirmed by Sanger sequencing: chr1-214802443-C-T(hg19), NM_016343.3: c.1123C>T, NP_057427.3: p.(Arg375Ter) inherited from the mother; and chr1-214819669-AG-A (hg19), NM_016343.3: c.6757del, NP_057427.3: p.(Glu2253AsnfsTer13) inherited from the father (see Supplementary Material). Neither variant has previously been described in the literature as causative of Strømme syndrome; no other significant variants were found. The patient recently received a transplant from a deceased donor and is in good health.

DISCUSSION

Variants in *CENPF* have recently been associated with Strømme syndrome in a subset of patients with ciliopathy and primary microcephaly [3]. *CENPF* encodes a protein involved in centromere–kinetochore complex formation, which plays crucial roles in chromosome segregation during mitosis, spindle orientation and primary cilia formation. *CENPF* knockdown in animal models results in ciliopathy phenotypes, as demonstrated in zebrafish [3], and *CENPF* cardiac myocyte-specific deletions lead to adult-onset dilated cardiomyopathy in mice [4]. The recently

described knockout murine model has revealed several structural kidney abnormalities including the loss of ciliary structures, tubule dilation and disruption of glomeruli, which suggest a specific role for CENPF protein in renal development [5].

To date, 11 individuals with LoF *CENPF* variants have been described, six of which died *in utero* and presented a classical Strømme phenotype associated with bilateral kidney hypoplasia (four cases in one family and two in another). The other five cases presented microcephalia, intestinal atresia and ocular abnormalities; three showed no kidney involvement and no clinical information was available for the other two (see Supplementary Material).

Here, we report a clinical and genetic case update for Strømme syndrome, and we believe that our experience underlines the need to perform renal follow-up in these patients. *CENPF* variants can cause kidney malformations, as has been previously shown in the literature [3] and in our unique case with evolution to end-stage renal disease during the second decade of life.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

Data sharing: genomic data reported here are available upon request. The pathogenic variants have been submitted to ClinVar NCBI resource (https://www.ncbi.nlm.nih.gov/clinvar/).

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CONFLICT OF INTEREST STATEMENT

None declared.

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