Case Report: Sequential Liver After Kidney Transplantation in a Patient With Sensenbrenner Syndrome (Cranioectodermal Dysplasia)

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Sensenbrenner syndrome, also known as cranioectodermal dysplasia (CED), is a rare ciliopathy clinically characterized by congenital craniofacial, skeletal, and ectodermal defects. Chronic kidney and liver insufficiency are also present in this disorder. Cranioectodermal dysplasia is an autosomal recessive and heterogeneous genetic disease. Six genes (IFT122, WDR35, IFT140, IFT43, IFT52, and WDR19) are known to be associated with this syndrome. Until 2021 more than 70 patients have been reported with CED, however, an orthotopic liver transplantation has been reported only in one case. Here, we present a case report of sequential liver-after-kidney transplantation in a male patient affected by CED. The kidney and liver transplantation was performed at the age of 7 and 12 years, respectively. Patients with Sensenbrenner syndrome require a multidisciplinary medical management and should regularly be followed-up by hepatologists and nephrologists, as the liver and kidney diseases are the major cause of morbidity and mortality.

Keywords: ciliopathy, Sensenbrenner syndrome (cranioectodermal dysplasia), renal failure, liver disease, kidney and liver transplantation

INTRODUCTION

Sensenbrenner syndrome, also known as cranioectodermal dysplasia (CED), is a rare and heterogeneous ciliopathy inherited in an autosomal recessive manner.

The characteristic clinical features include: craniosynostosis, dolichocephaly, facial dysmorphisms, growth retardation, short limbs, narrow chest, chronic kidney, and liver disease. To date, more than 70 patients with CED have been described and variants in six genes have been linked to this syndrome: IFT122, WDR35, IFT140, IFT43, IFT52, and WDR19 (1, 2). Changes in IFT122 and WDR35 account for approximately 70% of the incidence of this syndrome. Products of genes associated with CED belong to the intraflagellar transport (IFT) process, which plays an essential role in a proper cilia formation and function. Cilia are present in most types of human cells, including those localized in the kidneys, liver, eyes, heart, and limbs. Moreover, the cilia regulate diverse signaling pathways, such as the hedgehog (Hh) and Wnt-signaling (Wnt), which
play a crucial role in development and postnatal maintenance of organs and tissues. Therefore, ciliopathies are complex and multisystem diseases which involve all the major organs (3–5).

The main underlying cause of liver disease in ciliopathies is related to abnormal development of the bile ducts, which is often manifested as a congenital hepatic fibrosis (CHF), as well as Caroli’s disease (CD) or polycystic liver disease (PLD) (6,7).

In CED, hepatic lesions of a variable severity have been observed, ranging from hepatosplenomegaly, an increased echogenicity of the liver or a presence of liver cysts in imaging evaluations, to the severe liver failure with hyperbilirubinemia or cholestasis, requiring hospitalization as early as in the neonatal period. In contrast, a cirrhosis with severe cholestasis and biliary proliferation, as well as an acute cholangitis, has been described in infants, while in children aged 10 months, 3, and 4 years the presence of liver cysts have been confirmed (8, 9). Moreover, fatal outcome of two patients with CED at the age of 4 months, due to kidney and liver failure has been reported (1).

The intrahepatic biliary dilatation, biliary proliferation, and fibrosis were confirmed in the histopathological examination of the liver samples taken from the CED patients. Moreover, the elevated activity of hepatic enzymes may be also present (2). Affected individuals with kidney failure (KF), and end-stage liver disease (ESLD) may be the candidates for organ transplantation procedures, which are regarded as a life-saving management in relevant cases. The differential diagnosis of CED with Caroli’s disease/syndrome and ARPKD is presented in Table 1.

### CASE REPORT

Here, we present a 16-year-old male patient diagnosed with CED. The patient is a second child of the otherwise healthy, however consanguineous parents. He was delivered after uncomplicated pregnancy at 38 week of gestation. His birth weight was 3.54 kg (>50th percentile), birth length of 56 cm (>98th percentile), and occipital frontal circumference (OFC) 40.5 cm (>98th percentile). Apgar score was 7 at 1 min.

A clinical examination performed directly after birth, revealed the limb shortening, a narrow thorax, brachydactyly, large bilateral inguinal hernias, and dysmorphic features such as dolichocephaly, highly protruding auricles, small flat nose, and hypertelorism (Figure 1).

The clinical features observed in this patient were very similar to those presented by his older sister, who has also been diagnosed with Sensenbrenner syndrome.

A genetic analysis of the family identified a missense variant p.Val553Gly (c.1658T>G) in the IFT122 gene as previously described by Walczak-Sztulpa et al. (1). This change was the first variant found in the IFT122 gene in the family with Sensenbrenner syndrome. Based on the research project this gene has been shown to be associated with CED. p.Val553Gly change is consistent with the CED phenotype as both parents are the heterozygous carriers and two affected children are homozygous for the identified variant. The variant has been classified as likely pathogenic according to the ACMG guidelines (Varsome tool, the 16th January 2022) (10).

### TABLE 1 | Differential diagnostics CED with Caroli’s disease/syndrome and ARPKD.

| Cranioectodermal dysplasia | Caroli’s disease/syndrome | ARPKD |
|----------------------------|---------------------------|-------|
| Liver                      | Hepatosplenomegaly        | Liver lesions may not be visible at 1 year of age |
|                            | Liver cirrhosis           | Hepatosplenomegaly |
|                            | Acute cholangitis         | Hepatomegaly and symptoms of portal hypertension usually seen in older children |
|                            | Liver cyst                | The liver is always involved, but in the neonatal and infancy the picture of kidney disease predominates |
|                            | Histopathological examination—fibrosis, defective remodeling of the ductal plate (“DMP-like”), cholestasis | Histopathological examination—ductal plate malformation |
| Kidney                     | Kidney failure (usually occurs between 2 and 6 years of age) | Most present perinatally with enlarged kidneys |
|                            | Hypertension, proteinuria/hematuria | Systemic hypertension |
|                            | Histopathological examination—interstitial fibrosis with focal inflammatory cell infiltrates, tubular atrophy, glomerulosclerosis, occasional cysts | Cysts 1–2 mm in diameter arise due to dilatation of the collecting tubules of the nephron—may be poorly visible on ultrasound examination |
Functional studies performed in the skin fibroblasts harvested from the male patient revealed a significantly reduced cilia frequency and length, as compared to controls confirming abnormal primary cilia morphology and formation in the affected individual (1).

In infancy, the patient presented elevated creatinine serum concentration and later, over the following month a regular deterioration of the kidney function was observed. Finally he developed the KF at the age of 3.5 years, which required a chronic dialysis program. Consequently, he

**FIGURE 1** | Patient at the age of 1 year (A), 5 years (B), 9 years (C), and 16 years (D), respectively. CED characteristic dysmorphic features include dolichocephaly, high forehead, epicanthus, telecanthus, broad nasal bridge, hypertelorism, full cheeks, low set ears.
underwent a deceased-donor kidney transplantation at the age of 7 years and remained on a triple maintenance immunosuppression (steroids, tacrolimus, mycophenolic acid). At that time, the splenomegaly was diagnosed, however without significant complications of portal hypertension and synthetic liver function was preserved. Later he developed the esophageal varices requiring ligation, at 3 years after a kidney transplantation.
At the age of 12 years, due to, hepatic decompensation (increasing ascites), the patient was hospitalized in the local hospital. Laboratory tests showed elevated concentrations of urea and creatinine, hypoprothrombinaemia and hypoalbuminemia, abnormal coagulogram, anemia, and thrombocytopenia.

An abdominal ultrasound examination showed a large volume of fluid in the abdominal cavity, a reduced liver size with irregular outlines and features of the fibrosis and an enlarged spleen sized $14 \times 8$ cm (reference range: 8–9 cm). During hospitalization, the patient received red cell, platelets and albumin transfusions. A paracentesis was performed, yielding a total of approximately 4 L of ascitic fluid. Then the patient was transferred to our hospital. Laboratory tests showed elevated concentration of protein (increasing ascites), the patient was hospitalized in the local hospital. Laboratory tests showed elevated concentrations of urea and creatinine, hypoprothrombinaemia and hypoalbuminemia, abnormal coagulogram, anemia, and thrombocytopenia.

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On physical examination, he presented a large abdominal circumference and features of the fibrosis and an enlarged spleen sized $14 \times 8$ cm (reference range: 8–9 cm). During hospitalization, the patient received red cell, platelets and albumin transfusions. A paracentesis was performed, yielding a total of approximately 4 L of ascitic fluid. Then the patient was transferred to our hospital. Laboratory tests showed elevated concentration of protein (increasing ascites), the patient was hospitalized in the local hospital. Laboratory tests showed elevated concentrations of urea and creatinine, hypoprothrombinaemia and hypoalbuminemia, abnormal coagulogram, anemia, and thrombocytopenia.

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Table 2: Liver and kidney transplantation in Sensenbrenner syndrome.

| Gene | Sex | Age at transplantation (years) | Reference (No.) |
|------|-----|-------------------------------|-----------------|
| Liver |     |                               |                 |
| 1.   | WDR35 | Male | 7 | (10) |
| Kidney |     |                               |                 |
| 1.   | WDR35 | Female | 5 | (20) |
| 2.   | WDR35 | Male | 4 | (21) |
| 3.   | WDR35 | Female | 5 | (22) |
| 4.   | WDR35 | Male | 2.5 | (13) |
| 5.   | WDR35 | Male | 14 | (14) |
| 6.   | WDR35 | Female | 7 | (14) |
| 7.   | WDR35 | Male | 9 | (11) |
| 8.   | IFT140 | Female | 6 | (23) |
| 9.   | IFT140 | Male | 5 | (24) |
| 10.  | IFT144/WDR19 | Female | 14 | (19) |
| 11.  | IFT144/WDR19 | Female | 2 | (25) |
| 12.  | IFT144/WDR19 | Female | 2 | (14) |

DISCUSSION

Sensenbrenner syndrome is a rare genetic syndrome. The incidence in the US has been reported for <1:1,000,000 live births. Usually symptoms manifest themselves in the first years of life (11). To date, 41 families with confirmed diagnosis of CED by genetic analysis have been reported in the literature (9, 12–17). The diagnosis of Sensenbrenner syndrome is made based on characteristic clinical features and molecular genetic testing, usually in the first years of life. In affected patients mortality might be associated with kidney and liver insufficiency, respiratory and heart failure, and hypovolemic shock (1, 9).

Liver involvement of some degree is known to occur in approximately 40–50% of patients with Sensenbrenner syndrome, regardless of mutation status, also severe liver involvement is a less common feature (8). In rare cases KF may develop as early as in an infant period, due to congenital tubulointerstitial nephropathy (18), however progression to severe KF rather takes more time (a couple of years) in patients presenting nephronophthisis (16, 19).

The reported patient presented ultrasonography picture suggesting chronic tubulointerstitial lesions in the native kidneys, requiring the introducing of regular haemodialysis at the age of...
considered, but as the liver failure was more life-threatening, a simultaneous liver and kidney transplantation was initially proposed. The age at transplantation varied from 2.5 to 14 years. The genetic background included WDR35, IFT140, and IFT114/WDR19 genes mutations. The currently reported patient, who required sequential kidney and liver (after-kidney) transplantation presented IFT1122 mutation. To our best knowledge, this is the first report of a sequential liver-after-kidney transplantation, successfully performed in a pediatric patient with Sensenbrenner syndrome.

CONCLUSION

Patients with Sensenbrenner syndrome should be followed up by hepatologists and nephrologists on regular basis, as the liver and kidney diseases are the major causes of morbidity and mortality. The choice of transplantation procedure has to be individually assessed depending on the severity of kidney and liver damage over time.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article-supplementary material, further inquiries can be directed to the corresponding author(s).

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)’ legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JR, JW-S, PC, AL-B, AK, MS, WJ, RG, and JP: contributed interpretation of the data and critical revision of the article. All authors contributed to the article and approved the submitted version.

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