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CASE REPORT

Posterior reversible encephalopathy syndrome in a uremic patient with autosomal recessive polycystic kidney disease

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Abstract Posterior reversible encephalopathy syndrome (PRES) is characterized by headache, seizures, altered mental status, and visual disturbance. It is diagnosed by the presence of both clinical symptoms and radiographic findings on the parietal–occipital lobes. We here report a 61-year-old woman with non-compensative liver cirrhosis and chronic kidney disease, presenting with uremia-induced PRES. She expressed loss of consciousness and subsequent visual disturbance, during the progression of uremia. She was treated with hemodiafiltration therapy, and the symptoms of PRES fully improved. The case is of particular interest, in that the appearance of abnormal findings on magnetic resonance imaging was delayed more than 2 weeks, as compared to that of clinical symptoms. The etiology of chronic kidney disease in the patient was considered to be autosomal recessive polycystic kidney disease, and we performed DNA sequencing analysis on the polycystic kidney and hepatic disease 1 gene. Two homozygous missense mutations were found in the patient and may combinatorially affect the disease. This case raises a possibility that the incidence of PRES is much higher if the radiological examination is performed more frequently.

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Introduction

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome, is characterized by headache, seizures, altered mental status, and visual disturbance, associated with abnormal radiographic findings on the parietal–occipital lobes [1, 2]. It is caused by a number of clinical conditions, such as severe hypertension, eclampsia, immunosuppressive therapy, post-renal transplantation, and nephrotic syndrome [3]. It is diagnosed by the presence of both clinical and radiographic findings, and the prompt diagnosis and appropriate therapies can result in a complete recovery within a few weeks.

Herein, we report a case of uremia-induced PRES, in which the appearance of abnormal findings on magnetic resonance imaging (MRI) was delayed, as compared to clinical symptoms. Although the diagnosis of PRES was delayed in the case, hemodiafiltration therapy against uremia fully improved the symptoms. In this report, we have also described the results of DNA sequencing analysis on the polycystic kidney and hepatic disease 1 (*PKHD1*) gene in the patient, because the etiology of uremia was thought to be autosomal recessive polycystic kidney disease (ARPKD).

Case report

A 61-year-old woman with non-compensative liver cirrhosis and chronic kidney disease was admitted to our hospital on March 19th for the examination and treatment

of massive ascites. She had been suffering from abdominal distension, appetite loss, and shortness of breath. Her body weight and height were 47 kg and 154 cm, respectively. Physical examination revealed a blood pressure of 95/62 mmHg, heart rate of 86 beats/min, and body temperature of 36.5 °C. She showed no signs of an enlarged jugular vein or pitting edema, but exhibited anemia, a fluid wave, and splenomegaly. Her mental status on admission was normal. Her hemoglobin was 7.3 g/dL, and platelet count was 58000/μL. Blood chemistry showed total protein of 5.7 g/dL, urea nitrogen of 67.7 mg/dL, creatinine of 6.0 mg/dL, Na of 137.6 mEq/L, K of 3.3 mEq/L, Cl of 108 mEq/L, aspartate aminotransferase of 9 IU/L, alanine aminotransferase of 11 IU/L, alkaline phosphatase of 665 IU/L, and γ-glutamyl transpeptidase of 71 IU/L. Serum hyaluronic acid and type IV collagen were 120.0 and 8.4 ng/mL, respectively, whereas both hepatitis B antigen and hepatitis C antibody were negative. Urinalysis showed a urinary protein of 1.21 g/gCr, and urinary red blood cells of 3–5/high-power field. A chest X-ray displayed a normal cardiothoracic ratio of 48 %.

For the control of ascites, she was treated with furosemide, spironolactone, and tolvaptan. Although the amount of ascites decreased, serum levels of urea nitrogen and creatinine were gradually elevated. On April 19th, she failed consciousness, and the laboratory data showed urea nitrogen of 106 mg/dL, creatinine of 7.8 mg/dL, and ammonia of 18 μmol/L. She was diagnosed as uremic encephalopathy, and hemodiafiltration therapy three times per week was thereby started from April 20th. Her consciousness level improved soon. However, she then complained of prolonged visual disturbance over a month. MRI on May 7th showed a hyperintense signal in the parietal and occipital lobes bilaterally in diffusion-weighed images, although the findings had not been observed on April 26th (Fig. 1). Abnormal MRI findings disappeared on June 27th, and her visual symptoms also improved. Throughout the course of the admission, her blood pressure was less than 120/80 mmHg. Retrospectively, abnormal neurological findings during her admission were considered to be caused by uremia-induced PRES.

Although PRES was recovered, she was required to continue the maintenance hemodiafiltration therapy 3 times per week for end-stage renal disease. Regarding the etiology of chronic kidney disease, abdominal ultrasonography revealed bilateral multiple renal cysts as well as diffuse increases in parenchymal echogenicity in the kidneys. The length of the right and left kidneys was 94 and 93 mm, respectively. In addition, her parents did not have chronic kidney disease, but their consanguineous marriage was recognized. Moreover, results of the liver biopsy which the patient underwent over 10 years ago showed hepatoportal sclerosis/fibrosis. These findings met the criteria for ARPKD [4, 5]. ARPKD is caused by mutations in the *PKHD1* gene, which consists of 86 exons that are variably assembled into a number of alternatively spliced transcripts [6]. The longest transcript, comprising 67 exons, encodes the protein, fibrocystin/polyductin. By obtaining an informed consent from the patient, genetic analysis was performed. DNA sequencing analysis of these 67 exons in the patient revealed two homozygous missense mutations (p.Leu1870Val and p.Gln4048Arg) (Fig. 2). Although the incidence of these mutations is relatively high [6–10], it is possible that these mutations may combinatorially affect the development and progression of late-onset ARPKD.

Discussion

Posterior reversible encephalopathy syndrome is a reversible syndrome first described in 1996 by Hinchey et al. [1]. It is well recognized to be accompanied by hypertensive encephalopathy, but the syndrome is indeed caused by numerous clinical conditions [3]. In our case, PRES was thought to be induced by uremia, because the patient did not exhibit hypertension and because hemodiafiltration therapy recovered the clinical and radiological findings. Although precise mechanisms remain undetermined, uremic toxin-induced endothelial dysfunction is likely to play an important role in the development and the progression of the disease [3]. For example, multiple cytokines, such as interleukin-1β and tumor necrosis factor-α, are elevated in end-stage kidney disease [11, 12]. These factors would contribute to the pathogenesis of PRES.

Two major mechanisms have been proposed for the pathogenesis of PRES [1–3]. One is the mechanism involving vasogenic edema, in which severe hypertension overwhelms the ability of the cerebrovascular autoregulation system, resulting in disruption of the blood–brain barrier and capillary leakage. The other involves cytotoxic edema accompanied by vasospasm and tissue ischemia. In the present case, PRES is thought to be caused mainly by the latter mechanism, rather than the vasogenic edema, because the patient did not exhibit hypertension. This notion is supported by the MRI findings, in which a hyperintense signal in the bilateral parietal and occipital lobes was detectable by diffusion-weighed images [2]. In addition, it is also supported by the fact that no abnormal findings were detected by fluid-attenuated inversion recovery images in the patient (data not shown).

In this case, the appearance of abnormal findings on MRI was delayed, as compared to that of clinical symptoms. This point is of particular interest, because it is the first report, to our knowledge, showing such a delay in PRES. Indeed, abnormal MRI findings suggest that PRES were undetectable 7 days after the onset of loss of

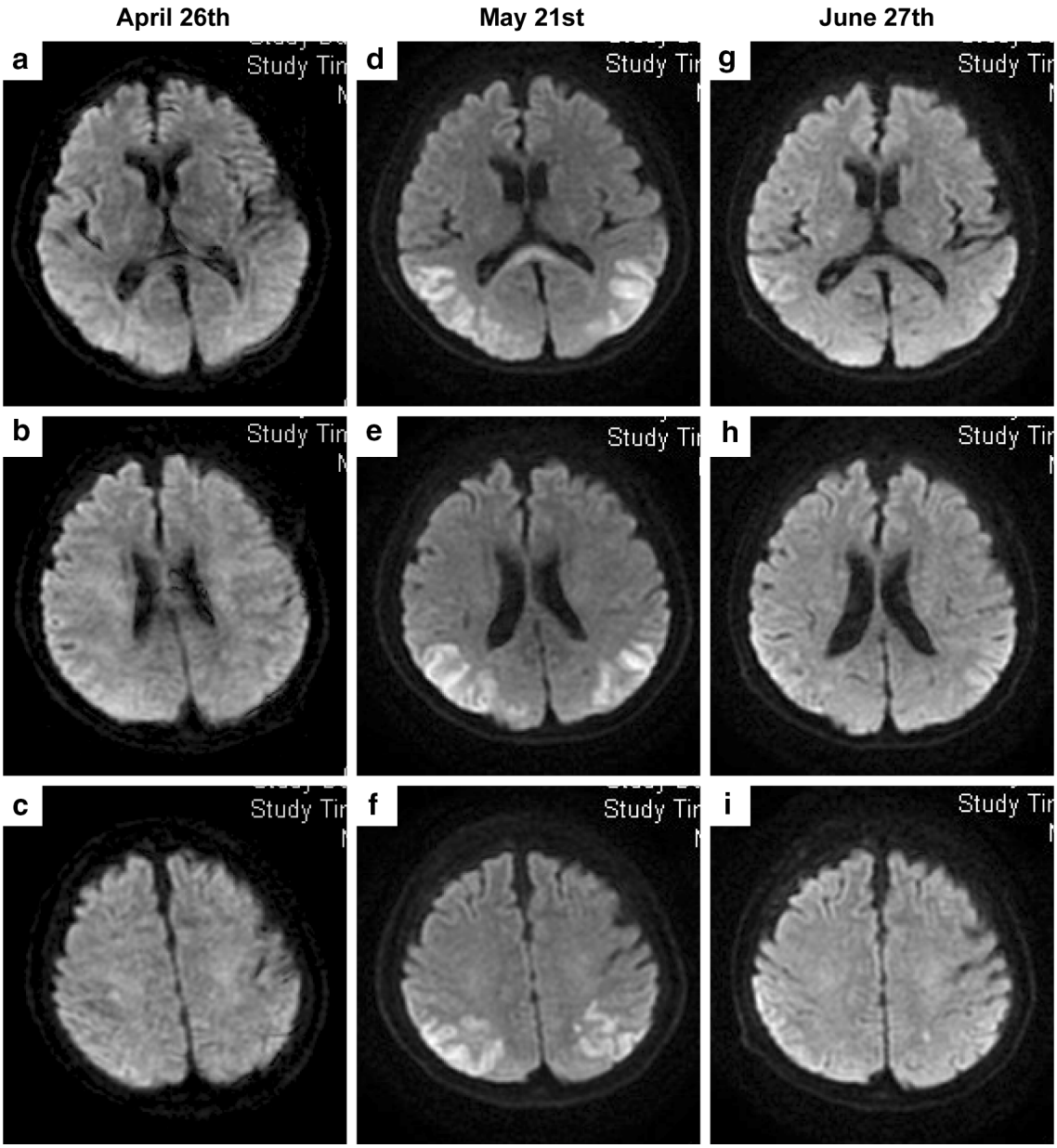

Fig. 1 Magnetic resonance imaging diffusion-weighed images on April 26th (**a**–**c**), May 21st (**d**–**f**), and June 27th (**g**–**i**). A hyperintense signal was detectable in the parietal and occipital lobes on May 21st, but not on April 26th and June 27th

consciousness, but detected 18 days later. Although the precise reasons why abnormal MRI findings were delayed in the case are unknown, it has been hypothesized that PRES has a spectrum of severity, ranging from an initially reversible phase of vasogenic edema formation to a later phase of cytotoxic damage [3, 13]. Only the later phase of cytotoxic damage was evident in the case. It is possible that the incidence of PRES is much higher than previously believed, if the radiological examination is performed more frequently.

ARPKD is an inherited disorder characterized by various combinations of bilateral renal cysts and congenital hepatic fibrosis [6, 14]. It has an estimated prevalence of 1 in 20000 live births. The clinical spectrum of ARPKD is widely variable: approximately 50 % of affected neonates die shortly after birth, whereas others survive to adulthood [14]. The minority of patients come to medical attention in adulthood with liver-related complications in association with mild kidney disease. The patient was considered to be adult-onset ARPKD, and we found two homozygous missense mutations (p.Leu1870Val and p.Gln4048Arg) in the *PKHD1* gene. However, results of previous studies suggest that both mutations are amino acid substitution polymorphisms, rather than the mutations causing ARPKD [6–10].

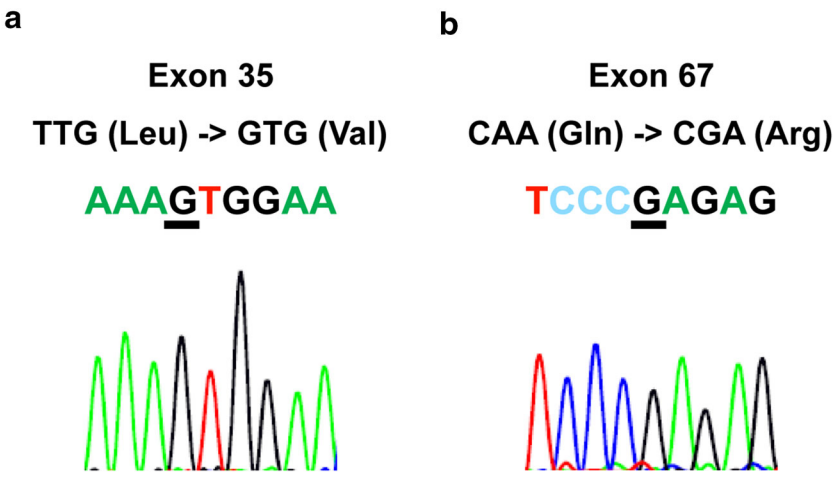

Fig. 2 DNA sequencing analysis in the *PKHD1* gene. The patient had two homozygous missense mutations: **a** the mutation from T to G in Exon 35 (p.Leu1870Val); and **b** the mutation from A to G in Exon 67 (p.Gln4048Arg)

Indeed, the frequency of p.Leu1870Val mutation is 0.8–4.5 % in the general population [7–10], and the alteration from Leucine to Valine is known as a conservative substitution. On the other hand, the frequency of p.Gln4048Arg mutation is 26–33 % [6, 7, 9, 10], but the change from glutamine to arginine is a non-conservative substitution. It is possible that coexistence of these two mutations affects the pathogenesis of ARPKD which exhibits the phenotype in the adulthood. To date, although more than 300 mutations were found in the *PKHD1* gene, no functional assays have been performed because of the long length of the gene. Further studies are required to determine the relationship between the *PKHD1* mutations and the activity of fibrocystin/polyductin.

Although uremia is one of the causes for PRES, it is unlikely that ARPKD-induced uremia is more related to PRES than other kidney diseases, because PRES as a complication of ARPKD has never been reported previously in the literature.

In summary, we experienced an ARPKD patient with PRES, in which the appearance of abnormal findings on MRI was delayed. It is possible that the incidence of PRES is much higher than previously believed. Intensive observation as well as more frequent radiological examinations are required to evaluate this possibility.

Conflict of interest The authors have declared that no conflict of interest exists.

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