Atypical haemolytic uraemic syndrome in a Japanese patient with DGKE genetic mutations

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Dear Sirs,

Atypical haemolytic uraemic syndrome (aHUS) is characterised by thrombosis in the microvasculature and is caused by dysregulation of the complement alternative pathway via mutations or autoantibodies. Recessive mutations in the diacylglycerol kinase ε gene (DGKE) were recently identified in aHUS patients under two years old (1, 2) as well as in patients with membranoproliferative glomerulonephritis, membranoproliferative-like glomerular microangiopathy, or thrombotic microangiopathy (TMA) (3, 4). A clinical feature of patients with homozygous or compound heterozygous DGKE mutations is initial acute kidney injury, typically in children less than one year old. The aHUS caused by DGKE mutations is independent of complement dysregulation (5) and the exact mechanism is not known. Loss of DGKE expression in endothelial cells showed a proinflammatory and prothrombotic phenotype, with increased expressions of ICAM-1 and tissue factor (6).

To obtain additional clinical information for aHUS patients with DGKE mutations, we performed a genetic analysis of DGKE in Japanese patients with an aHUS onset in the first two years of life. Japan’s Nara Medical University has functioned as a TMA referral centre since 1988 (7), and has collected 1,122 Japanese TMA patients until the end of 2013. The database includes 77 patients with aHUS, which is defined by acute renal failure, thrombocytopenia, and microangiopathic haemolytic anaemia, with no severe ADAMTS13 activity deficiency or Shiga toxin-producing Escherichia coli infection. Patients with organ or haematopoietic stem cell transplantation were excluded from aHUS. Some of genetic analyses of aHUS have been previously reported (8, 9). From the database, we selected 14 aHUS patients with a disease onset in the first two years of life. Direct sequencing of the polymerase amplification reaction products was performed using the 3730xl DNA Analyzer (Applied Biosystems Japan, Tokyo, Japan) (8). The study protocol was approved by the Ethical Committee of the National Cerebral and Cardiovascular Center, the Hiroshima Prefectural Hospital, and Nara Medical University, and written informed consents for genetic analysis were obtained. Among the 14 selected patients, we identified one patient who had a splice site mutation c.1213–2A>G derived from his father and a frameshift mutation c.71delT encoded with p.Leu24Cysfs*145 derived from his mother (Figure 1). Both mutations are likely deleterious for the DGKE function and pathogenic loss-of-function mutations. Neither genetic mutation was detectable (<20 mg/dl), and he had high lactate dehydrogenase and creatinine levels. He received repeated plasma infusions and nine sessions of plasmapheresis. However, no treatment was effective for his haemolytic and renal failure. His severe hypertension did not initially respond to fluid removal by haemodialfiltration and was also refractory to treatment with a large intravenous dose of nicardipine chloride, peroral enapril, and losartan. Finally, treatment with the complement C5 blockade drug eculizumab every three weeks for 17 months resulted in the control of severe hypertension and the cessation of peritoneal dialysis (12). After the administration of eculizumab, the platelet counts and C3 level increased and the lactate dehydrogenase levels decreased.

The number of aHUS patients with DGKE mutations who were treated with eculizumab at the acute phase and as maintenance therapy is limited. At the acute phase, one patient showed a negative
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Adzhubei IA, Schmidt S, Peshkin L, et al. A
Ozaltin F, Li B, Rauhauser A, et al. DGKE variants
George JN, Nester CM. Syndromes of thrombotic
Matsumoto T, Fan X, Ishikawa E, et al. Analysis of
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response and another showed a positive response (1, 2). Lemaire et al. reported seven aHUS patients with DGKE mutations treated with eculizumab (1). None of the patients showed an abnormality in the complement system. In that study, one patient with DGKE mutations had aHUS recurrences even after eculizumab treatment. The genetic study of a Spanish aHUS registry reported an aHUS patient with concurrent DGKE and C3 mutations who was treated with eculizumab (2). After presenting with aHUS at eight months of age, she had several aHUS recurrences, and bi-weekly plasma infusions were effective in normalising blood parameters; subsequent eculizumab treatment resolved the infection-associated edemas that were typical in this patient. Sanchez Chinchilla et al. suggested that the association of DGKE mutations concomitant with a C3 gene mutation in this particular patient possibly contributed to more severe disease with chronic activation of TMA and a positive response to eculizumab treatment.

We report here a patient with DGKE mutations who presented plasmapheresis-resistant aHUS and severe hypertension in the first year of life. We did not identify mutations predisposing for aHUS in 6 complement genes in the patient, however he was successfully treated with eculizumab. The treatment strategy for aHUS patients with DGKE mutations is not yet settled (1, 2, 5). Further studies are needed to identify the appropriate therapeutic strategies for aHUS patients with DGKE mutations.

Conflicts of interest

T. Miyata has received lecturing fees from Bayer, Daiichi Sankyo, Boehringer Ingelheim, Shino-Test, Kyowa Kirin and Bristol-Myers. T. Ohta has received lecturing fees from Asahikasei Pharma, Pfizer, Alexion Pharma, Daiichi Sankyo, Kyowa Kirin and Kyorin. Y. Fujimura is a recipient of research grant from Alexion Pharmaceuticals. None of the other authors declares a conflict of interest.

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