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Case report

Alpers syndrome with prominent white matter changes

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Abstract

Alpers syndrome is a fatal neurogenetic disorder caused by the mutations in *POLG1* gene encoding the mitochondrial DNA polymerase γ (polγ). Two missense variants, c.248T > C (p.L83P), c.2662G > A (p.G888S) in *POLG1* were detected in a 10-year-old Chinese girl with refractory seizures, acute liver failure after exposure to valproic acid, cortical blindness, and psychomotor regression. The pathology of left occipital lobe showed neuronal loss, spongiform degeneration, astrocytosis, and demyelination. In addition, there were prominent white matter changes in a series of brain magnetic resonance imaging (MRI) and increased immunological factors in CSF.

Keywords: Alpers syndrome; *POLG1* mutations; Leukoencephalopathy

1. Introduction

Alpers syndrome is a rare autosomal recessive hepatocerebral syndrome characterized by intractable seizures, early onset progressive liver dysfunction leading to hepatic failure, psychomotor regression (OMIM#203700) [1,2]. The disease manifestation is usually in early childhood and progress to death [1]. Naviaux et al. first demonstrated the deficiency of mitochondrial DNA polymerase γ activity and mitochondria DNA (mtDNA) depletion in the muscle and liver tissue of a patient with Alpers syndrome [3]. Mutations in *POLG1* gene have also been reported to be responsible for autosomal recessive and autosomal dominant forms of progressive external ophthalmoplegia, juvenile spinocerebellar ataxia-epilepsy syndrome, sensory ataxia, neuropathy, dysarthria, and ophthalmoparesis (SANDO), Parkinsonism, male infertility as well as Alpers syndrome [4–12]. More than 83 point mutations, mostly missense mutations have been documented, but cases from Chinese have not been reported (http://dir-apps.niehs.nih.gov/polg/).

Alpers syndrome, as a neurodegenerative disease, affects mainly the gray matter. This report describes the first confirmed case with Alpers syndrome in China, who had prominent white matter lesion in MRI and high immunological factors in CSF.

2. Case report

The 10-year-old girl is a 4th grade elementary school student. She is the first child of healthy, nonconsanguineous parents. At 5 years of age, her hearing threshold was found to be a little bit elevated, otherwise she was

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healthy and developed normally until 9 years of age. Her school performance was below average. At 9 years of age, she developed multifocal partial seizures. The seizures usually generalized and progressed to status epilepticus. Serials EEGs showed slow activity and almost continuous spike wave over the central, parietal, and occipital regions of both hemispheres. She was treated with phenobarbital, carbamazepine, topiramate, vaproic acid (VPA), lamotrigine, and clonazepam. However, the seizures could not be controlled. VPA was used for 2 and half months and then was terminated due to acute liver failure. She developed edema and coagulopathy 52 days after starting VPA treatment. The investigation of the coagulative function at that time revealed decreased fibrinogen (1.56 g/L, normal range: 2.00–4.00 g/L). Three weeks later she developed jaundice and hepatomegaly. Liver function studies showed abnormalities of alanine transaminase, aspartate transaminase, total bilirubin, direct bilirubin, total protein, albumin, and fibrinogen with values of 64 μ/L (normal range: 0–40 μ/L), 215 μ/L (normal range: 0–45 μ/L), 145.6 μmol/L (normal range: 1.7–20 μmol/L), 113.1 μmol/L (normal range: 0–6 μmol/L), 44.35 g/L (normal range: 60–82 g/L), 28.8 g/L (normal range: 35–50 g/L), and 0.64 g/L, respectively. VPA treatment was stopped. The liver function improved and was near normal 6 months later.

Seven months after the onset of the disease, the patient developed episodes of visual loss. In the first two episodes, the vision recovered several days later. However, the visual loss persisted after the third episode. The simultaneous MRI showed high T2 and DWI signals in the occipital region (Fig. 1C). Visual evoked potentials were absent. The vision problem appeared to be cortical in origin. The patient developed psychomotor regression gradually. She could not walk and sit without support 4 months after the onset of the disease. Nine months after the onset of disease, she lost language and had poor response to commands. She had been in vegetative state since 1 year after the onset of the disease. Her symptoms did not respond to the treatment of intraveously immunoglobulin (2 g/kg), corticosteroids, as well as the above mentioned antiepileptic drugs.

Biochemical studies including lactate, pyruvate, and ammonia were normal. Plasma amino acids and urine organic acids were normal. CSF was investigated 8 times from the beginning of the disease to 13 months after the onset. The CSF was acellular but the protein concentration increased every time from 1.99 g/L to 2.28 g/L (normal range: 0.15–0.45 g/L). CSF glucose was normal. The immunological studies of CSF showed that oligoclone bands were positive from the very beginning to the last investigation. IgG synthesis rate increased from

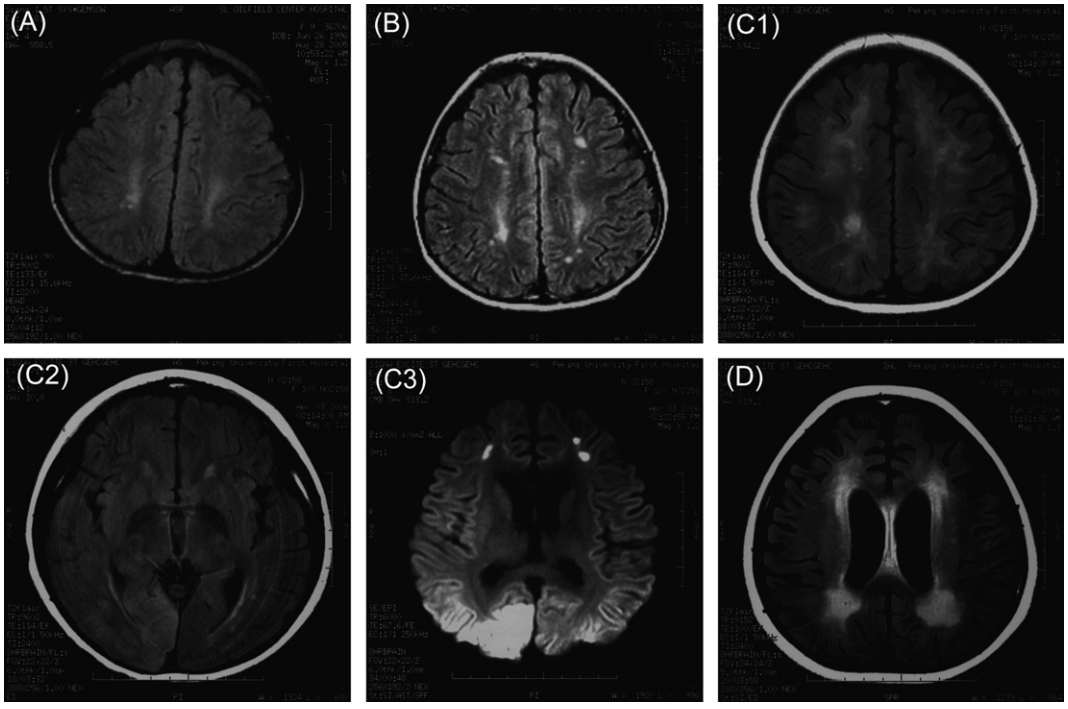

Fig. 1. Magnetic resonance image of the brain. (A and B) Flair image of brain MRIs in 2 days and in 3 months of the onset of the disease showing increased signaling in white matter. (C1) Flair image of brain MRI 7 months later showing the abnormal signal in white matter was more extensive. (C2) Flair image of brain MRI showing increased signaling in right occipital region. (C3) DWI of brain MRI showing increased signaling in both occipital regions. (D) Flair image of brain MRI 10 months later showing diffuse brain atrophy, and the abnormal signal in white matter was further extensive.

53.8 mg/24 h to 445 mg/24 h (normal value < 7 mg/24 h). IgG index increased from 0.53 to 1.62 (normal value < 0.7).

Brainstem auditory evoked potential showed increased I–III latency. Hearing threshold of left and right ear was 50 dB and 30 dB, respectively. Nerve conduct velocity studies showed decreased sensory and motor nerve conduct velocity. Sensory nerve conduct velocity of sural nerve and median nerve was 37 m/s and 39.3 m/s, respectively (normal value > 50 m/s). The motor nerve conduct velocity of common peroneal nerve was 40.3 m/s (normal value > 45 m/s).

Several brain MRIs were performed (Fig. 1). The brain MRIs showed increased T2 and flair signals in hemioval central white matter and cerebellar white matter at 2 days and 3 months after the onset of the disease (Fig. 1A and B), and 7 months later, brain MRI showed that the abnormal signal in white matter was more extensive (Fig. 1C1). Increased T2 and flair signals in the right occipital region (Fig. 1C2) and increased DWI signal in both occipital regions were observed (Fig. 1C3). No enhancement was found in the contrast-enhanced brain MRI at 9 months after disease onset. One month later, MRI revealed diffuse brain atrophy, and the increased T2 signal in the white matter was further extensive (Fig. 1D).

Pathology studies of muscle, peripheral nerve, and brain biopsy were performed. Gastrocnemius muscle biopsy was unremarkable, no ragged-red-fiber was found in the Gomori–Trichrome stain. Sural nerve biopsy showed damaged axon and myelin (Fig. 2). Left occipital lobe biopsy showed astrocytosis, neuronal loss and sponginess in the cortex and partial demyelination, gliosis, and vacuolization in white matter (Fig. 3).

Screening of mtDNA common mutations including 3243A > G, 3271T > C, 3460G > A, 8344A > G, 8356T > C, 8363G > A, 8993T > C, 8993T > G, 11778G > A, 14459G > A, and 14484T > C with the method previously described [13,14] was negative. Large mtDNA deletions and rearrangements were not detected by Southern blot analysis [13,14]. Because of the intractable seizures and liver failure that are consistent with hepatocerebral mtDNA depletion syndrome, sequencing of coding exons of deoxyguanosine kinase (*DGUOK*) and DNA polymerase γ1 (*POLG1*) was performed [15–17]. Deleterious mutations were not detected in *DGUOK*. However, two novel heterozygous missense variants, c.248T > C (p.L83P), c.2662G > A (p.G888S) were detected in *POLG1* gene. Sequence analysis of parental blood DNA revealed that her father carried L83P and her mother carried G888S (Fig. 4). These two novel missense variants occurred at highly conserved amino acid residues (Fig. 5). The mitochondrial DNA copy number in muscle was examined by real time quantitative PCR [18], and was found to be about 70% of age-matched mean.

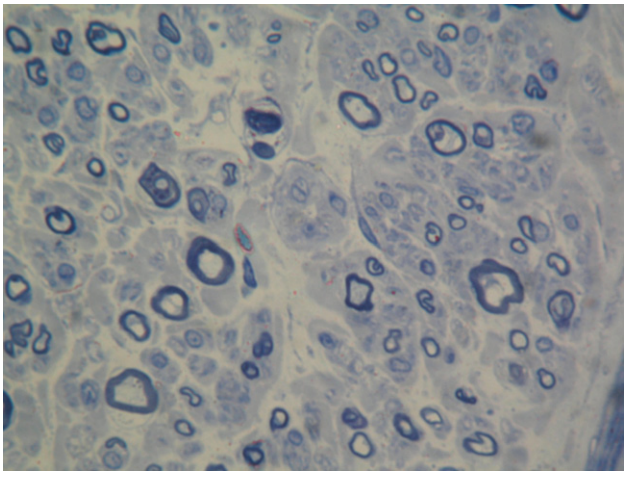

Fig. 2. Microscopic section of the sural nerve showing axon degeneration.

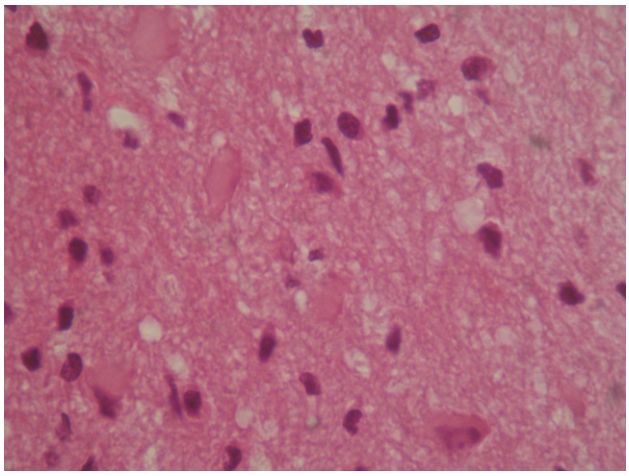

Fig. 3. Microscopic section of the left occipital lobe showing astrocytosis, neuronal loss and sponginess. Haematoxylin–eosin originally 40×.

3. Discussion

This 10-year-old girl presented with focal, multifocal, and generalized seizures, which were uncontrollable by various antiepileptic medicines. After the administration of VPA, the patient developed acute liver failure. The clinical course was likely to be the Alpers syndrome. The axonopathy in peripheral sensory nerve biopsy and the pathology of brain occipital lobe including the neuronal loss, spongiform degeneration, astrocytosis were similar to those described in Alpers syndrome [6,19,20]. Hearing loss is a common clinical feature reported to be associated with mitochondrial DNA disorders, but it is less frequent in patients with Alpers syndrome.

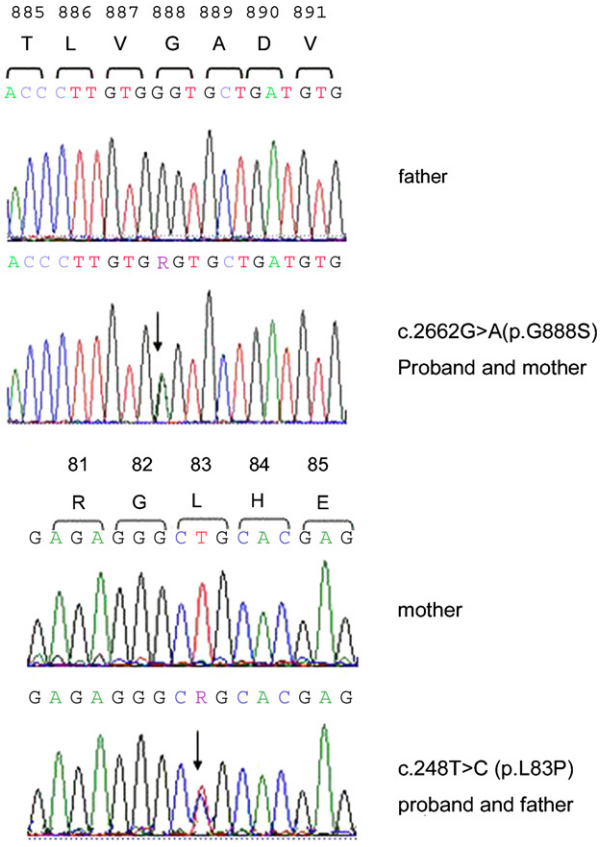

Fig. 4. Two novel heterozygous missense variants. c.248T > C (p.L83P), c.2662G > A (p.G888S) were detected in DNA polymerase gamma1 (*POLG1*). These two missense variants inherited from her father and mother, respectively.

The mitochondrial DNA polymerase γ is required for the replication and repair of the 16,569-bp of human mitochondrial genome. It has been reported that the mutant catalytic subunit POLG1 containing the most common mutation, A467T, possesses only 4% of the wild-type DNA polymerase activity due to its failure to interact with the accessory subunit, POLG2, which stimulates the polymerase activity [21]. MtDNA depletion and multiple deletions have been found in muscle or liver tissues from patients with Alpers syndrome [6,11]. In our case, the mitochondrial DNA content in muscle was found to be about 70% of age-matched mean. This is not a dramatic reduction. Unfortunately, liver specimen was not available for analysis. Reduction in mtDNA content causes reduced synthesis of all respiratory chain complexes containing mtDNA-encode subunits leading to generalized deficiency in mitochondrial respiratory chain function. Nevertheless, the blood and CSF lactate levels, the pathology and histochemistry of muscle, and the mtDNA copy number in muscle could be normal in some patients, especially in the early stage of the disease [6,7,11,20].

More than 83 *POLG1* mutations have been recorded in the Human DNA Polymerase Gamma Mutation Database (http://dir-apps.niehs.nih.gov/polg/). Most of them are missense mutations. The most common A467T mutation accounts for approximately 40% of the *POLG1* mutant alleles described in Alpers syndrome [22–25]. Other recurrent mutations include W748S, G848S, and T914P. Most of the remaining mutations occur only once [6,7,11,22]. Two novel mutations c.248T > C (p.L83P) and c.2662G > A (p.G888S) were identified in our patient. The L83 is located in between the polyQ stretch and the beginning of the exonuclease domain, an area of no known function, but appears to be very well conserved from yeast to man (http://dir-apps.niehs.nih.gov/polg/) [21]. The G888 is an absolutely conserved amino acid found in motif A of the polymerase domain. It is two residues away from a critical Asp (D890) residue which makes up one of three carboxylic amino acids (triad) to chelate the two magnesium ions at the active site. Mutation at the neighboring residue, A889T, is found in autosomal dominant progressive external ophthalmoplegia with an early age of presentation. These patients also appear to have ataxia. On the other side, the T885S is associated with Alpers

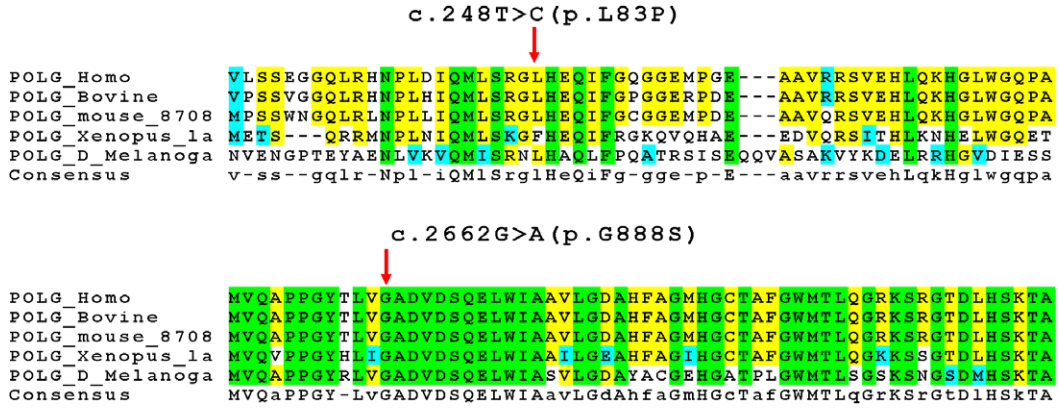

Fig. 5. Alignment showing the Polγ regions in which the two novel amino acid substitutions were detected. The two novel amino acid substitutions are highly conserved among different species.

syndrome (http://dir-apps.niehs.nih.gov/polg/). Thus, although the pathogenicity of these two novel missense variants has not been directly proven, it is most likely that they are responsible for the clinical course of this patient. In addition, the asymptomatic parents were confirmed to be carriers of each of the mutations.

Alpers syndrome is known as a neurodegenerative disease affecting mainly the gray matter. However in this case, MRI showed symmetric abnormal signals in bilateral cerebral and cerebellar white matter during the course of the disease. Demyelination and gliosis were also found in the biopsy of white matter. Although MRI and pathological changes in the white matter have been reported in Alpers syndrome [6,20,26], such remarkable white matter changes were unprecedented. Whether this phenotype correlated with the genotype in the Chinese ethnic background is not clear.

Immunological studies in Alpers syndrome have never been reported. In our patient, the CSF showed positive oligo-clone bands, very high IgG synthesis rate, and IgG index throughout the entire course of the disease. These laboratory findings made the diagnosis of inflammatory demyelinative disease initially considered. However, the patient did not respond to the treatment with 2 g/kg IVIG, and 20 mg/kg methylprednisolone daily for 3 days with oral prednisone taper. Thus, the diagnosis of inflammatory demyelinative disease was unlikely. The immunological abnormality may be secondary to the brain damage. Whether it plays a role in the disease progression does need further investigation.

Mutations in *POLG1* can cause a broad spectrum of clinical disease [12,27]. Even among the patients of Alpers syndrome, the clinical manifestations may be variable. This Chinese case demonstrated that the white matter may also be severely involved in Alpers syndrome. In addition, the immunological reactions may play a role in the disease progression.

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