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Seronegative neuromyelitis optica spectrum disorder in primary familial brain calcification with *PDGFB* variant

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Dear Editor,

Primary familial brain calcification (PFBC) was previously known as idiopathic basal ganglia calcification or Fahr's disease. This disorder is characterized by calcification of the basal ganglia, thalamus, and the dentate nucleus of the cerebellum. The symptoms include parkinsonism, cerebellar ataxia, psychiatric symptoms, and cognitive impairment. *SLC20A2*, *PDGFRB*, *PDGFB*, *XPR1*, *MYORG*, and *JAM2* have been reported as causative genes, and PFBC phenotype and genotype show correlation [1]. Here, we report a rare case of PFBC with a *PDGFB* variant, with optic neuritis and myelitis. It has been known that platelet-derived growth factor subunit B (PDGFB) is involved in the maintenance of the blood-brain-barrier (BBB) and astrocyte function and has also been implicated in altered aquaporin-4 (AQP4) function. This case suggests that the *PDGFB* variant may be associated with neuromyelitis optica spectrum disorder (NMOSD).

A 43-year-old Japanese man with a family history of brain calcification was diagnosed with PFBC (Fig. 1A) at age 14. At 31 years old, he developed left retrobulbar optic neuritis, which was resolved with methylprednisolone pulse therapy (1000 mg/day for three days). Subsequently, he developed right retrobulbar optic neuritis at 36 years of age, for which he underwent methylprednisolone pulse therapy. A head magnetic resonance imaging (MRI) showed a high-intensity lesion in the area postrema (Fig. 1B). Serum anti-AQP4 antibody (CBA: cell-based assays), anti-myelin oligodendrocyte glycoprotein (MOG) antibody (CBA), oligoclonal bands in the cerebrospinal fluid, and m.3243 A > G mitochondrial DNA mutation, a cause of mitochondrial disease that can lead to brain calcification and optic neuropathy were all negative. The patient was clinically diagnosed with seronegative NMOSD based on Wingerchuck 2015 criteria. He was started on oral prednisolone (PSL); however, the patient had recurrent episodes of optic neuritis due to poor medication compliance. At the age of 40, he developed hyperalgesia in the right lower abdomen, and an MRI of the cervical spinal cord showed a high-intensity lesion at C3 level (Fig. 1C). He continued treatment with PSL; however, myelitis at T5 and T8 level (Fig. 1D) and relapse at C3 level were observed. He was treated with plasma exchange (PE); sensory impairment and muscle weakness improved partially.

In terms of PFBC-related symptoms, he presented with mild cognitive impairment, attention disorder, and frontal lobe dysfunction but no headache or parkinsonism. Genetic testing by the Sanger method, performed at 42 years of age, revealed a point mutation in exon 5 of *PDGFB* (c.356C > T, p.Leu119Pro). The same variant was found in his mother and brother, and we diagnosed them with PFBC associated with a *PDGFB* variant.

In this case, the *PDGFB* variant may be associated with NMOSD development.

PDGFB is a member of the *PDGF* gene family of mitogenic factors in mesenchymal cells. In the CNS, PDGFB is secreted from endothelial cells undergoing vasculogenesis, which mobilizes PDGF-receptor β (PDGFRB)-expressing pericytes surrounding the lumen. The pericytes contribute to BBB, stimulating endothelial cells to form tight junctions [2]. The cause of brain calcification in PFBC with *PDGFB* variants is possibly the BBB disruption due to PDGFB dysfunction, resulting in the influx of plasma proteins and mineralization [3]. In addition, it has been reported that PDGFB increases the activity of PiT-1, a phosphate transporter [4] and that the *PDGFB* variant inhibits the intracellular shift of phosphorus, resulting in mineralization. It has been reported that *PDGFB*-knockout mice show reduced pericyte coverage and abnormal permeability, while *SLC20A2*-knockout mice, which are affected by the genetic correlates of PFBC, do not [5]. Therefore, the mineralization mechanism in PFBC with *PDGFB* variants may be explained by PiT-1 dysfunction rather than a lack of pericytes.

The patient was diagnosed with NMOSD, which is typically anti-AQP4 antibody-associated astrocytopathy. In pericyte-knockout mice, re-distribution of AQP4 expressed in astrocytes has been observed [6], suggesting that the *PDGFB* variant may be involved in the development of both PFBC and NMOSD. Similarly, a case of brain calcification with NMOSD was reported in Germany [7]; however, it was published in 1960 and did not include the genetic mutation research. This report describes the second case of PFBC with NMOSD. A common mechanism may be involved in the pathogenesis of both conditions.

In conclusion, we report a case of seronegative NMOSD in a patient with PFBC and a *PDGFB* variant. This finding suggests a novel approach to NMOSD. It means that in cases of double seronegative (anti-AQP4 antibody seronegative and anti-MOG antibody seronegative) NMOSD, *PDGFB* variant may affect AQP4 without antibody-mediated effects and

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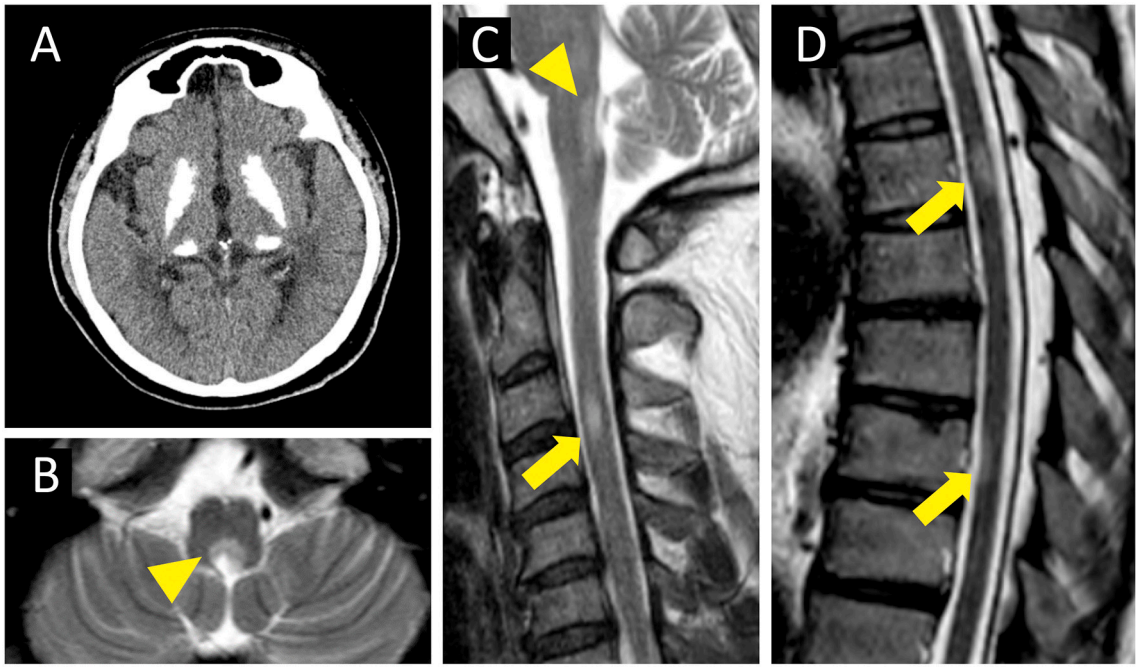

Fig. 1. Findings of head CT and MRI and spinal cord MRI.
(A) The CT shows bilateral symmetrical calcification of the basal ganglia and thalamus. (B) T2-weighted image shows a high-intensity lesion in the area postrema (arrowhead).
(C) T2-weighted image shows high-intensity lesions in the area postrema (arrowhead) and at the level of C3 (arrow).
(D) T2-weighted image shows high-intensity lesions at the level of T5 and T8 (arrows).

may be involved in pathogenesis. However, there are some limitations. The other two cases in the same family of our proband did not develop optic neuritis or myelitis; the mother had parkinsonism, and the brother presented schizophrenia-like symptoms and parkinsonism. In addition, the fact that steroid therapy and PE were each partially effective suggests the involvement of both an inflammatory mechanism and some immune mechanism, but the details are unknown. The clinical spectrum of double seronegative NMOSD remains poorly understood [8]. PDGFB may be the key in double seronegative NMOSD, especially in terms of BBB and pericyte dysfunction. It is necessary to consider interplay with other factors, and more cases are needed to clarify the relationship between NMOSD and PDGFB.

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