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PRELIMINARY REPORT

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Preliminary report for Epilepsia Open A case of West syndrome with severe global developmental delay and confirmed KIF5A gene variant

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Abstract

Objective: Kinesin family member 5A (KIF5A) is a molecular motor protein responsible for intracellular transport, specifically in neurons. While abnormalities in the *KIF5A* gene have been reported in the onset of various neurological diseases, there are no studies demonstrating an association between this gene and West syndrome.

Methods: In the case presented here, epileptic spasms appeared at 7 months; electroencephalogram (EEG) investigation confirmed hypsarrhythmia, resulting in a diagnosis of West syndrome. The patient exhibited peculiar facies, hypotonia, failure to thrive, and severe global developmental delay.

Results: Cranial magnetic resonance imaging (MRI) revealed severe delayed myelination. ^{123}I-iomazenil SPECT image at 7 months demonstrated decreased accumulation in bilateral areas, including the primary somatosensory and motor cortices, and the primary and association visual areas compared to an age-matched control. Whole exome sequencing analysis demonstrated a novel de novo heterozygous missense variant in *KIF5A*, (NM_004984.4:c.710A>T: p. Glu237Val).

Significance: It was concluded that the *KIF5A* variant impaired the transport of $GABA_A$ receptors to the cell membrane surface, thus leading to an imbalance of these receptors between regions of the cerebrum and resulting in the onset of epilepsy.

KEYWORDS
epileptic encephalopathy, epileptic spasm, hypomyelination

1 | INTRODUCTION

Kinesin family member 5A (KIF5A) is a molecular motor protein responsible for intracellular transport specifically in neurons.[1] While abnormalities in the *KIF5A* gene have been reported in diseases such as hereditary spastic paraplesia (HSP), Charcot-Marie-Tooth disease type 2 (CMT2), familial amyotrophic lateral sclerosis (ALS), cerebral white matter lesions, myoclonus, hypotonia of the trunk, optic nerve anomalies, dysphagia, apnea, bradyacusia, and neonatal intractable myoclonus (NEIMY) with severe developmental delay,[2–6] there are no reports that demonstrate an association

of connecting this gene with West syndrome. Here, we present the case of a patient with West syndrome with *KIF5A* gene variant. The aim of this case report was to elucidate the pathogenesis of West syndrome by evaluating further genetic aspects of the *KIF5A* gene and by functional neuroimaging.

2 | CASE REPORT

The patient was admitted to our hospital at 7 months for a detailed investigation when short episodes of limb extension appeared and gradually became repetitive, increasing in frequency until occurrences became daily. She was born at 37 weeks 0 days weighing 2272 g as the second child of a 2 chorion 2 amnion twin pregnancy with no particular abnormalities in her family history. Prior to visiting our hospital, she had been examined by a local doctor due to nystagmus, strabismus, and a lack of head control at 3 months of age.

Upon admission, failure to thrive was observed as she weighed 5.1 kg (−3.3 SD) at a height of 62.7 cm (−2.1 SD). Head circumference was 40.5 cm (−1.6 SD). The patient was not capable of gaze fixation or visual tracking and exhibited bilateral esotropia, horizontal nystagmus, poor visual response in the right eye, and mild pallor of the right optic nerve head in fundus examination, in addition to a lack of head control and global hypotonia. The deep tendon reflex was normal in both upper and lower limbs with no lateral difference. Peculiar facies was observed with upward slanted eyes and a flat nose. General blood and cerebrospinal fluid findings were unremarkable chromosome analysis (G-band method) revealed a 46,XX normal karyotype.

A cranial magnetic resonance imaging (MRI) performed at 7 months revealed severe delayed myelination (Figure 1). Interictal study of ^{99m}Tc-ECD single-photon emission computerized tomography (SPECT) indicated no localized reduction in blood flow. The ^{123}I-iomazenil SPECT delayed image did not indicate localized decrease in accumulation upon visual inspection, but compared to an age-matched control, decreased accumulation in the bilateral areas including the primary somatosensory and motor cortices, and the primary and association visual areas were observed (Figure 1). Ictal electroencephalogram (EEG) findings coincided with rigid movement of the limbs and demonstrated low amplitude fast waves superimposed over diffused slow wave activity (Figure 2A,B). The seizure type was determined to be epileptic spasm (ES). Background activity demonstrated hypsarrhythmia (Figure 2C), and the patient was diagnosed with West syndrome. Valproate sodium administration was initiated, and a partial response was observed. Adrenocorticotropic hormone (ACTH) therapy was implemented, which resulted in cessation of seizures on day 3. Slow wave activity persisted in the bilateral occipital areas on EEG, but clinical improvement was observed. After the disappearance of seizures, the patient acquired head control, gaze fixation,

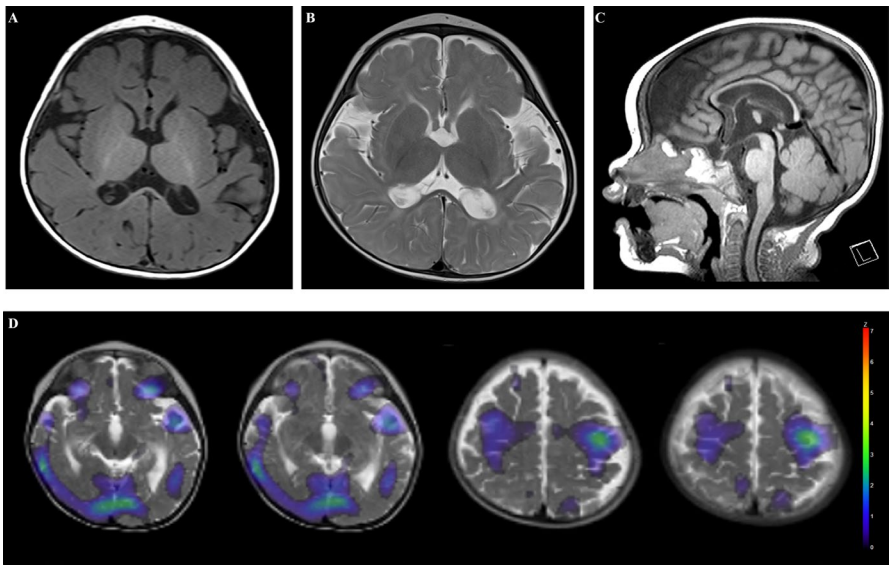

FIGURE 1 Brain magnetic resonance imaging (MRI) and ^{123}I iomazenil single-photon emission computerized tomography (SPECT) (For 123I-iomazenil SPECT, a delayed image reflecting benzodiazepine receptor distribution obtained three hours after injection. The appropriate radioisotope dose was determined by body weight and injected intravenously. The scan was initiated 180 min after injection for delayed BZR images.). Brain MRI showed severe delayed myelination 7 months after birth. (A, axial sequence of T1 weighted image, B, axial sequence of T2 weighted image, C, sagittal sequences of T1 weighted image) D, shows the images combining the ^{123}I iomazenil SPECT delayed image and MRI. These images indicate decreased lesions compared to an age-matched control, and reveal less accumulation in the green area than in the blue area. The images demonstrated decreased accumulation in the bilateral areas including the primary somatosensory and motor cortices, and the primary and association visual areas compared to an age-matched control on the ^{123}I-iomazenil SPECT delayed image

and visual tracking. An EEG conducted at 10 months revealed the appearance of bilateral frontal spike and wave activity (Figure 2D), and lamotrigine (LTG) administration was initiated. At 1 year 0 months, background activity demonstrated hypsarrhythmia and ES recurred. A second round of ACTH therapy was implemented, resulting again in the cessation of seizures on day 3 and improvement in the EEG findings (Figure 2) but no appreciable developmental improvement was observed. Topiramate (TPM) was administered to prevent recurrence, but at 1 year 5 months a single ES second did occur. Interictal EEG revealed diffuse spike and wave activity predominantly in the bilateral frontal areas. Clobazam (CLB) was administered but was ineffective. A third round of ACTH therapy was initiated, and again, seizures ceased after one week. The patient is presently 2 years, 6 months old and has been progressing with no seizure recurrence or neurological regression, but remains nonverbal, is unable to sit unassisted, and exhibits severe psychomotor developmental delay.

Trio-based exome sequencing was performed as described previously[7] and demonstrated a novel de novo heterozygous variant in *KIF5A*, (NM_004984.4:c.710A > T: p. Glu237Val). This variant was classified as likely pathogenic based on the American College of Medical Genetics variant classification guideline.[8]

3 | DISCUSSION

This is the first reported case of West syndrome with a confirmed pathogenic *KIF5A* variant. ACTH therapy was effective in suppressing seizures for short periods, but repeated recurrences persisted. It is notable that cranial MRI revealed severe delayed myelination and the ^{123}I-iomazenil SPECT image demonstrated abnormal distribution of $GABA_A$ receptors.

The molecular motor protein KIF5A, classified as a kinesin superfamily protein, is expressed specifically in neurons

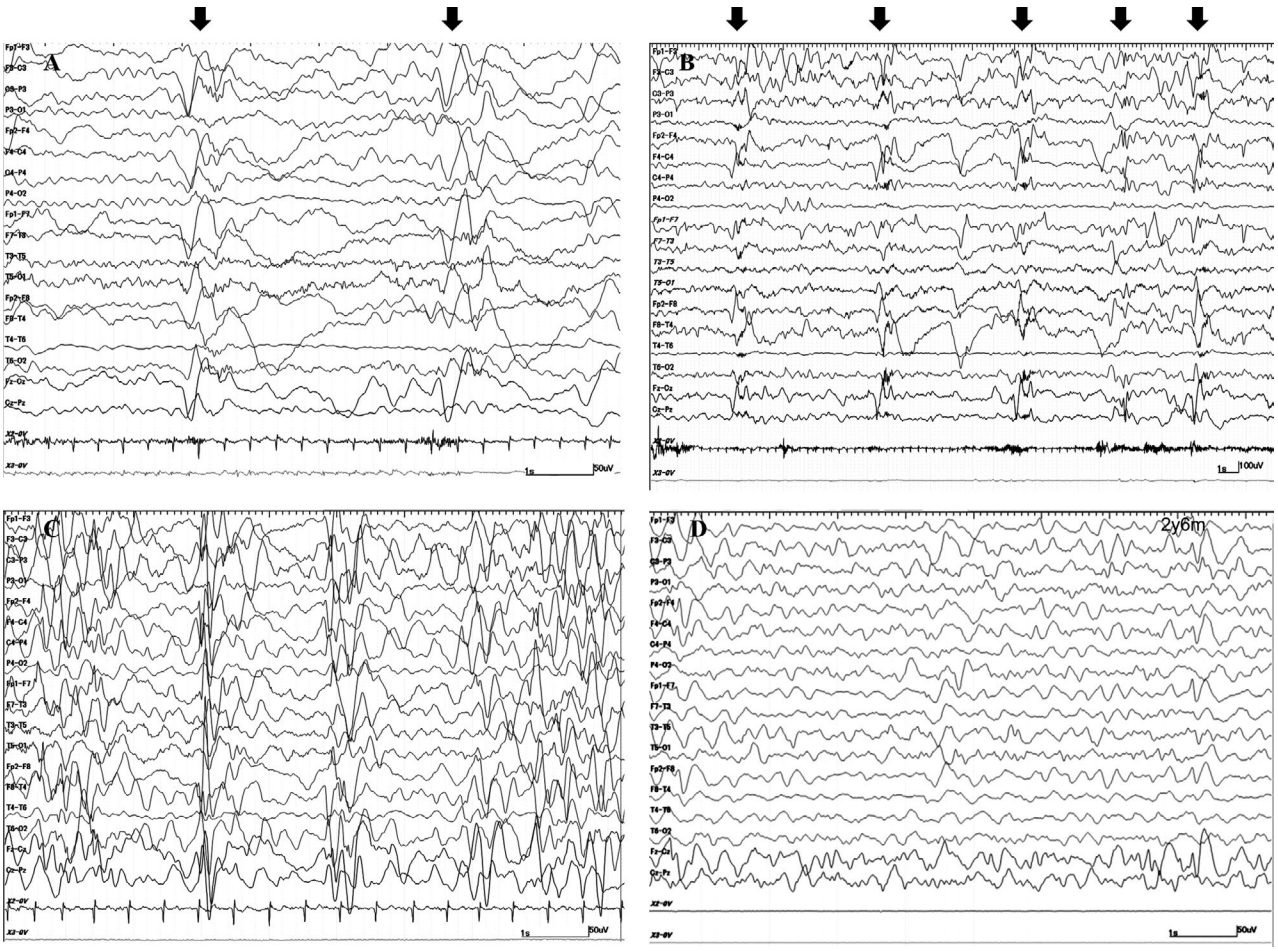

FIGURE 2 Electroencephalogram findings. Digital electroencephalogram was performed using 21 scalp electrodes, which were placed according to the International 10-20 system. Ictal electroencephalogram (EEG) findings and findings of EEG with video monitoring and electromyogram with electrodes attached around the bilateral deltoid muscles were evaluated. A and B, show the ictal electroencephalogram (EEG) findings which demonstrated low amplitude fast waves superimposed over diffused slow wave activity (arrows). C, shows hypsarrhythmia. EEG findings improved dramatically, but sharp waves appeared in the bilateral frontal areas after adrenocorticotropic hormone therapy (D).

and is responsible for transport along the microtubules, which compose the cytoskeleton of an axon.[1] Aberrations in the *KIF5A* gene have been reported in various diseases including heterozygous missense variants of the N-terminal motor domain and coiled-coil domain in HSP and CMT2,[2] and heterozygous frameshift variants of the C-terminal domain in NEIMY.[3,4] A mutation hot spot in the C-terminal domain has been reported in familial amyotrophic lateral sclerosis (ALS).[5,6] In this case, a novel variant was detected in the N-terminal motor domain. Based on in silico analysis, this missense variant was considered extremely likely to be disease-causing (SIFT = 0.000, PolyPhen-2 = 1.000, CADD_PHRED = 27.6, M-CAP = 0.737, PhastCons = 1.000, GERP = 4.170).

The mechanism of epileptogenesis due to a *KIF5A* abnormality is unclear. In a study by Nakajima et al on *KIF5A* knockout mice,[9] impaired transport of the $GABA_A$ receptors resulted in a reduced number of inhibitory postsynaptic $GABA_A$ receptors, which further caused a decrease in inhibitory neurotransmission and lead to the onset of epilepsy. In general terms, the GABAergic interneurons control the neural circuitry and network activity in the brain.[10] Recent advances in genetics have identified genes that control the development, maturation, and integration of GABAergic interneurons and implicate them in the pathogenesis of epileptic encephalopathies or neurodevelopmental disorders. ^{123}I-iomazenil SPECT functional brain imaging assesses the intracerebral distribution of central benzodiazepine $GABA_A$ receptors. Benzodiazepine receptor binding in the primary sensorimotor cortex, primary visual cortex, cerebellar vermis, and striatum declines more rapidly than in the cerebellar hemispheres and the frontal cortex.[11] In the present case, ^{123}I-iomazenil SPECT imaging was performed at 7 months of age and revealed decreased accumulation in the bilateral areas including the primary somatosensory and motor cortices, and the primary and association visual areas. In the cases of *KIF5A* abnormalities, it is expected that decreased accumulation will occur due to the impaired transport of $GABA_A$ receptors. Furthermore, ACTH therapy was characteristically effective in this case. ACTH is known to stimulate the synthesis of two allosteric modulators of $GABA_A$ receptors including deoxycorticosterone and tetrahydroxy-corticosterone, which are strong anticonvulsants.[12,13] Therefore, ACTH therapy may play an important role as a therapy in future cases involving *KIF5A* abnormalities.

In addition to West syndrome, severe delayed myelination was another important characteristic of this case. There are three previously reported cases of NEIMY. The two cases reported by Duis J et al exhibited involuntary movement in the form of myoclonus and chorea. One of the two cases resulted in mortality at three months, while the other displayed delayed myelination in MRI.[3] The single case reported by Rydzanicz, M. et al exhibited myoclonic seizures and progressive leukoencephalopathy and was characterized by changes in imaging related to myelination.[4] The pathogenesis of HSP is thought to be axonal degeneration due to synaptic dysfunction, which could be associated with the presence of both mutant and wild-type *KIF5A* genes resulting in perturbation of axonal transport, or a dysfunctional mutant KIF5A blocking the microtubule track and interfering with normal function.[14] The severe delayed myelination observed in this case is hypothesized to be due to axonal impairment similar to that of HPS and beginning in the early stages of infancy when there is active myelination.

This study, however, had several limitations that require further investigation. Functional analysis was not possible, and we were unable to assess the effect of this genetic variant on protein function. As this was a single case, we cannot confirm whether the ^{123}I-iomazenil SPECT findings are disease-specific. However, our findings aid in the diagnosis of West syndrome and delayed myelination associated with the *KIF5A* gene and indicate the utility of ACTH therapy.

In conclusion, a pathogenic *KIF5A* variant in this case resulted in severe delayed myelination as well as onset of West syndrome thought to be caused by an abnormal distribution of the $GABA_A$ receptors. These characteristic findings may have implications for the diagnostic approach and clinical management of cases of *KIF5A* abnormalities, including ACTH treatment. Future investigation including similar cases are warranted to understand the pathology and to examine the epilepsy prognosis and neurological outcome.

- This is the first reported case of West syndrome with a confirmed pathogenic *KIF5A* variant. ACTH therapy was characteristically effective.
- It is notable that cranial MRI revealed severe delayed myelination and the ^{123}I-iomazenil SPECT image demonstrated abnormal distribution of $GABA_A$ receptors.
- It is assumed an imbalance of $GABA_A$ receptors between regions of the cerebrum resulted the onset of epilepsy.
- These characteristic findings may have implications for the diagnostic approach and clinical management of cases of *KIF5A* abnormalities.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR'S CONTRIBUTION

Masataka Fukuoka, Shin Okazaki, and Hisashi Kawawaki conceptualized and designed the report, wrote the manuscript, and were responsible for all stages of the report. Kiyohiro Kim, Megumi Nukui, and Takeshi Inoue were the attending doctors for the patient and were responsible for data collection. Ichiro Kuki provided critical revision of the manuscript for important intellectual content and helped draft the manuscript. Mitsuko Nakashima and Naomichi Matsumoto performed whole exome sequencing and interpreted the result. All authors read and approved the final manuscript.

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