Epileptic-dyskinetic encephalopathies are rare epilepsies characterized by early-onset epileptic encephalopathies (EOEEs) with involuntary movement. Herein, we investigated the impact of gene variants in epileptic-dyskinetic encephalopathies. Four independent patients from four families who exhibited involuntary movements were recruited from Tokyo Metropolitan Neurological Hospital. The inclusion criteria were as follows: onset within 1 year after birth, frequent seizures, severe developmental delay and accompanying involuntary movements.

We detected four genetic mutations, including STXBP1, GNAO1, CYFIP2, and SCN8A variants. The involuntary movements were drug-resistant. However, pallidal electrocoagulation followed by gabapentin were partially effective in treating chorea and ballismus of the extremities in patients with GNAO1 variants, and perampanel partially suppressed seizures and involuntary movements in one patient with a SCN8A variant. Movement disorders are common to many neurodevelopmental disorders, including a variety of EOEEs. Although we could not establish a definitive correlation using genetic variants in patients with EOEE and movement disorders, involuntary movements in patients with EOEEs may be a key diagnostic finding. The usage of genetic variants could prove beneficial in the future as more patients are investigated with epileptic-dyskinetic encephalopathies.

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1. Introduction

Early-onset epileptic encephalopathies (EOEEs) are characterized by severe developmental impairment and intractable seizures starting from the infantile period; increasing evidence indicates that various EOEEs are caused by genetic variants [1]. Achieving a genetic diagnosis is important for understanding the biological basis of the disease and has implications for appropriate treatments and family planning. However, pediatric movement disorders encompass a heterogeneous group of neurodevelopmental and neurodegenerative disorders affecting movement and limiting activities of daily living. The etiology of many pediatric movement disorders currently remains uncharacterized.

Recent studies reported that hyperkinetic movements are sometimes observed in EOEEs caused by gene variants, which are known as epileptic-dyskinetic encephalopathies [2–12]. Herein, we describe four patients with epileptic-dyskinetic encephalopathy caused by genetic factors.

We review the clinical features of these and previously reported patients with genetic variants to verify the association between
their phenotypic spectrum and genetic backgrounds. We also discuss the biological impact of genetic variants on involuntary movements and the possibility for the application to therapy.

2. Patient description

Four independent patients from four families who exhibited involuntary movements were recruited from Tokyo Metropolitan Neurological Hospital between 2008 and 2018. The inclusion criteria were as follows: onset within 1 year after birth, frequent seizures, severe developmental delay and accompanying involuntary movements.

Polygraphic recording was performed with electromyography (EMG) and video-electroencephalography (EEG), though the information gained from EMG was inadequate during clinical events and less useful than clinical observation. Therefore, EMG findings were not detailed in this report. Each patient’s involuntary movements were evaluated by three independent specialists in pediatric neurology (A.A., S.K., and M.F.). Underlying genetic causes were investigated using microarray genetic testing and whole-exome sequencing in Showa University School of Medicine, Hamamatsu University School of Medicine and Yokohama City University Graduate School of Medicine. Patient 1 has been reported by Saito et al. [13], and patient 3 has been reported by Nakashima et al. [14] separately. However, the two previously published reports of the patients did not include clinical videos, and one did not include detailed clinical descriptions supplemented in this report.

2.1. Patient 1 (STXBP1 variant)

Patient 1 was a 20-year-old man. At 2 months of age, he exhibited tonic seizures and suppression-burst on EEG and was diagnosed with EOEE. At 3 months, seizures developed into epileptic spasms with hypsarrhythmia on EEG, which developed into West syndrome. Spasms were accompanied by a generalized electrodecremental pattern on EEG.

Adrenocorticotropic hormone (ACTH) injection was transiently effective. The seizures were resistant to multiple antiseizure medications. At 5 years of age, chorea and ballismus appeared. All laboratory data and brain magnetic resonance imaging (MRI) showed no abnormality. He showed constant violent choreo-ballistic movements, including oromandibular movements while awake (Supplementary video). Her EEG showed interictal multifocal spikes, spike-and-waves, and generalized polyspike-and-waves (Fig. 1. A-1, 2). During involuntary movements, the record showed no electrographic seizures. He showed irregular, violent movements while awake and during sleep (Fig. 1. C-1, 2) but did not indicate electrographic seizures during involuntary movements. At 12 years of age, a CYFIP2 gene variant (c.259C > T, p. Arg87Cys) was identified. Antiseizure medications were ineffective in treating involuntary movements.

2.2. Patient 2 (GNAO1 variant)

Patient 2 was a 17-year-old woman. At 2 months of age, she exhibited drug-resistant tonic seizures. At 16 months, chorea and ballismus were observed. At 2 years of age, her involuntary movements worsened and induced hyperthermia and resulted in injury. Only high-dose phenobarbital was partially effective, resulting in a transient mild elevation of aspartate transaminase and alanine transaminase. Except for her liver function, all laboratory data and brain MRI results were normal. She also showed irregular, violent, choreo-ballistic movements, including oromandibular movements, while awake (Supplementary video). Her EEG showed interictal multifocal spikes, spike-and-waves, and generalized polyspike-and-waves (Fig. 1. B-1, 2), but no electrographic seizures were observed during involuntary movements. At 14 years of age, palilial electrocoagulation, which was partially effective for treating involuntary movement, was performed. After the operation, a GNAO1 gene variant (c.607G > A, p.Gly203Arg) was identified. The involuntary movements were partially ameliorated by adding gabapentin to phenobarbital and clonazepam.

2.3. Patient 3 (CYFIP2 variant)

Patient 3 was a 12-year-old boy. He began to exhibit tonic seizures at 2 months of age. At 3 months, he was diagnosed with EOEE. At 6 months, the seizures and hypsarrhythmia led to West syndrome. ACTH injection and multiple antiseizure medications were ineffective. A corpus callosotomy was performed at 22 months of age, which was partially effective in reducing the seizure frequency. Choreiform movements were observed in early childhood, mainly while awake, sometimes involving oromandibular movements (Supplementary video). His interictal EEG showed multifocal spikes as well as spike-and-waves (Fig. 1. C-1, 2) but did not indicate electrographic seizures during involuntary movements. At 12 years of age, a CYFIP2 gene variant (c.259C > T, p. Arg87Cys) was identified. Antiseizure medications were ineffective in treating involuntary movements.

2.4. Patient 4 (SCN8A variant)

Patient 4 was a 4-year-old girl. Her mother reported rapid, fine fetal movements during pregnancy, and the patient suffered from continuous myoclonus at birth. She showed fine myoclonus induced by sleep and stimulation at 1 month of age, and drug-resistant generalized tonic-clonic seizures developed at 1 year (Supplementary video). All laboratory data and brain MRI findings were normal. Her EEG showed a posterior dominant theta rhythm while awake and bilateral independent focal spikes while sleeping (Fig. 1. D-1, 2), but no electrographic seizures were observed during involuntary movements. Although sodium valproate, levetiracetam, and clonazepam were ineffective, perampanel partially suppressed her seizures and involuntary movements. At 4 years of age, an SCN8A gene variant (c.632T > G, p. Val211Gly) was identified.

3. Discussion

Achieving a genetic diagnosis is important for understanding the biological basis of a disease and has implications for appropriate treatment and family planning. In this study, we described four patients with epileptic-dyskinetic encephalopathies caused by a genetic variant identified using whole-exome sequencing.

In recent years, the co-occurrence of hyperkinetic movement disorders in EOEE has been increasingly recognized and detailed, to the point that movement disorders are now considered a feature of several EOEEs [3]. The clinical phenotypes and genetic variants found in patients with epileptic-dyskinetic encephalopathies are summarized in Table 1.

Although they were originally described in association with ARX variants, STXBP1 and FOXG1 variants have also been found to cause a similar phenotype characterized by dystonia or choreoathetosis and epilepsy [3-5,8-9]. Epileptic-dyskinetic encephalopathies have also been associated with GNAO1 [6-7], GRIN1 [10], GABRA2 [11], HECW2 [12], and an increasing number of other genes. EOEEs caused by SCN8A variants result in dystonia, dyskinesia, and myoclonus, but tremulous movements are relatively rare [15,16]. Recently, an EOEE caused by a PIGF variant resulted in dyskinesia [17], and an EOEE associated with a GRIN2B variant also resulted in dystonia and dyskinesia [18] (Table 1). Movement disorders are common to many neurodevelopmental disorders including a variety of EOEEs. EOEE is a genetically heterogeneous disorder, with more than 100 possible causative genes [19], and many
Fig. 1. Interictal electroencephalography (EEG) findings. Patient 1 (STXBP1 variant); interictal EEG showed continuous, generalized irregular spike-and-wave complexes while awake (A-1) and during sleep (A-2). Patient 2 (GNAO1 variant); multifocal spikes, spikes and waves during waking (B-1), and generalized polyspikes and waves during sleep (B-2). Patient 3 (CYFIP2 variant); multifocal spikes and spike-and-waves during waking (C-1) and bilateral independent focal spikes and spike-and-waves during sleep (C-2). Patient 4 (SCN8A variant); posterior dominant theta rhythm while awake (D-1) and bilateral independent focal spikes during sleep (D-2).
unknown pathogenic consequences of the gene markers have been identified.

The detection rate of gene variants has gradually increased, and disease-causing variants were reported in 81.8% (9/11 cases) of EOEE patients with involuntary movements using whole-exome sequencing [2]. In the future, improved accuracy of genetic testing will increase the detection rate of pathological gene variants. Although the exact prevalence and mechanisms of involuntary movements in EOEE are unknown, involuntary movements may be important symptoms for identifying causative genetic abnormalities.

Several pathological mechanisms have been proposed for the wide-ranging involuntary movements associated with various gene variants that cause EOEE, such as impaired fusion of membranes allowing the exocytosis of synaptic vesicles in STXBP1 variants, voltage-dependent calcium current dysfunction in GNAO1 variants, aberrant actin polymerization caused by CYFIP2 variants, and abnormal function of the α8-subunit of the neuronal voltage-gated sodium channel Nav1.6 in SCN8A variants. However, a clear relationship among genetic variants, pathological mechanisms, and involuntary movements remains unproven. Furthermore, the origin of involuntary movements in EOEE is unknown, as is whether secondary activation of the basal ganglia by electrical activity in the cortex or primary activation of the basal ganglia by genetic variants occurs in EOEE.

Although there was no obvious correlation between the clinical features of previously reported cases or our cases and genetic findings, and only a few patients were reported for each genetic variant

| Genes | Mutation | Involuntary movement | Number of cases | Reference |
|-------|----------|----------------------|-----------------|-----------|
| ARX   | c.333_334ins [GGG] | Dystonia | 6 | [38] |
|       | c.989C>A | Dystonia | 1 | |
| STXBP1| c.1434G>A (p.Trp478X) | Dyskinetic movement | 5 | [49] |
|       | c.1209+1G>T | Dyskinetic movement | 7 | |
|       | c.956+7G>T (p.Thr322_Glu603 del) | Dyskinetic movement | 7 | |
|       | c.7_120+7del (No protein) | Dyskinetic movement | 3 | |
|       | c.1217G>A (p.Arg406His) | Generalized tremor | 3 | |
|       | c.1061T>G (p.Val353Asn) | Erratic myoclonus | 6 | |
| GNAO1 | c.572_592del (pThr191_phe197del) | Dystonia, chorea, athetosis | 5 | [5] |
|       | c.607G>A (p.Gly203Arg) | Dystonia, chorea, athetosis | 3 | |
| FOXG1 | c.1059G>A (p.Glu353Lys) | Dystonia, chorea, athetosis | 1 | |
| GRIN1 | c.1656G>A (p.Asp552Glu) | Myoclonus, chorea, dyskinesia | 4 | [10] |
|       | c.1950G>A (p.Asn650Lys) | | |
|       | c.2443G>C (p.Gly815Arg) | | |
|       | c.1923G>A (p.Glu641Val) | | |
| GRIN2B| c.1623G>C (pSer541Arg) | Dystonia, HS, chorea | 1 | [18] |
|       | c.1853G>T (p.Val618Gly) | Dystonia, myoclonus | 1 | |
|       | c.2065G>A (p.Gly689Ser) | Dystonia | 1 | |
|       | c.2452G>C (p.Glu820Lys) | Dystonia | 1 | |
| CDKL5 | c.533G>A (p.Arg178Gln) | Dystonia, dyskinesia | 1 | |
|       | c.1589_1602del (pThr513Glnfs*2) | Dystonia, dyskinesia, myoclonus | 1 | |
|       | c.65-3A>G | | |
| SCN2A | c.1264G>T (p.Val422Leu) | Dystonia, dyskinesia | 1 | |
| SCN2B | c.2588G>A (p.Arg853Gln) | Dystonia, dyskinesia | 1 | |
| SETD5 | c.2347-7A>G (p.Ala783Leufs*2) | Dystonia, dyskinesia | 1 | |
| ALG13 | c.320A>G (p.Asn107Ser) | HS | 1 | |
| TBL1XR1| c.209G>A (p.Cys70Ala) | HS | 1 | |
| HECW2 | c.3988G>A (p.Arg1333Trp) | Rett-like symptoms (hand tapping, flapping) | 1 | [12] |
| GABRA2| c.1736C>T (p.Asn580Lys) | Dystonia, dyskinesia | 1 | |
| SCN8A | p.Gly1475Arg | Dystonia, dyskinesia | 1 | |
|       | p.Arg1617Gln | Dystonia, dyskinesia | 1 | |
|       | p.Ala1650Val | Dystonia | 1 | |
| CYFIP2| c.259G>T (p.Arg87Cys) | Dystonia | 1 | |
| PI3P | c.384del (p.Glu129Asnfs*34) | Dystonia | 4 | [17] |

HS: hand stereotypes.
(Table 1), genetic diagnosis might be useful and provide a reference for treatment selection. For example, GNAO1 encodes the Gao subunit of heterotrimeric G proteins, which mediates inhibition of calcium currents elicited by norepinephrine. Thus, abnormal neuronal firing associated with GNAO1 variants may be improved by calcium channel blockers such as gabapentin [6]. Indeed, in our GNAO1 variant case, gabapentin was partially effective for intractable involuntary movements. Although carbamazepine was not effective in our variant case, gabapentin was partially effective for intractable involuntary movements. Although carbamazepine was not effective in our variant case, gabapentin was partially effective for intractable involuntary movements.

SCN1A has been reported that a ketogenic diet is effective in patients with intractable epilepsy [15]. It was reported that patients with SCN1A variants may be improved by calcium channel blockers such as gabapentin [13]. It has been reported that a ketogenic diet is effective in patients with developmental and epileptic encephalopathy with genetic etiology, especially in patients with SCN1A, KCNQ2, STXBP1, and SCN2A mutations [20]. However, there were very limited data about the treatment of involuntary movements in these disorders, and reports of drug treatments were personalized.

In summary, we reported genetic mutations identified in four EOEE patients having involuntary movements, which may be a key diagnostic finding. Although we could not establish a definitive correlation using genetic variants in a small number of patients with EOEE and movement disorders, the usage of genetic variants could prove beneficial in the future as more patients are investigated. Further studies are required to clarify the mechanisms of involuntary movements and develop an appropriate personalized treatment for EOEE.

Ethical statement

Informed consent for publication was obtained from the patients’ parents. The institutional review board of Tokyo Metropolitan Neurological Hospital and the review boards of each institution approved this study.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2020.100417.

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