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Case report

Compound heterozygosity in *GPR56* with bilateral frontoparietal polymicrogyria

Yuji Fujii [a,*], Nobutsune Ishikawa [a], Yoshiyuki Kobayashi [a], Masao Kobayashi [a], Mitsuhiro Kato [b]

[a] *Department of Pediatrics, Hiroshima University Hospital, Hiroshima, Japan*
[b] *Department of Pediatrics, Yamagata University, Faculty of Medicine, Yamagata, Japan*

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Abstract

Polymicrogyria is caused by a diverse etiology, one of which is gene mutation. At present, only one gene (*GPR56*) is known to cause polymicrogyria, which leads to a distinctive phenotype termed bilateral frontoparietal polymicrogyria (BFPP). BFPP is an autosomal recessive inherited human brain malformation with abnormal cortical lamination. Here, we identified compound heterozygous *GPR56* mutations in a patient with BFPP. The proband was a Japanese female born from non-consanguineous parents. She presented with mental retardation, developmental motor delay, epilepsy exhibiting the feature of Lennox–Gastaut syndrome, exotropia, bilateral polymicrogyria with a relatively spared perisylvian region, bilateral patchy-white-matter MRI signal changes, and hypoplastic pontine basis. *GPR56* sequence analysis revealed a c.107G>A substitution leading to a p.S36N, and a c.113G>A leading to a p.R38Q. Although affected individuals with compound heterozygosity in *GPR56* have not been previously described, we presume that compound heterozygosity of these two mutations in a ligand binding domain within the extracellular N-terminus of protein could result in BFPP. In addition, we observed unusually less involvement of perisylvian cortex for polymicrogyria, and Lennox–Gastaut syndrome for epilepsy, which are likely common features in patients with BFPP caused by *GPR56* mutations.

Keywords: Polymicrogyria; Lennox–Gastaut; GPR56; Heterozygous mutation

1. Introduction

The autosomal recessive bilateral frontoparietal polymicrogyria (BFPP) is a well-characterized neuronal migration defect that shows bilateral polymicrogyria with an anterior to posterior gradient, bilateral patchy-white-matter MRI signal changes (without specific patterns), and brainstem or cerebellar hypoplasia. Patients with BFPP present with mental retardation, developmental motor delay, seizures, ataxia, and dysconjugate gaze [1]. The causative gene for BFPP is the G protein-coupled receptor 56 gene (*GPR56*) [2]. GPR56 is one of the adhesion G protein-coupled receptors (GPCRs). Like other members of the adhesion GPCRs, GPR56 has an unusually long N-terminal extracellular domain that contains a high percentage of serine and threonine residues and a GPCR proteolytic site domain just before the first transmembrane spanning domain [3,4]. The serine and threonine-rich region can serve as an O- and/or N-glycosylation site [3,4].

So far, multiple independent mutations have been identified in *GPR56*, all of which are homozygous germline mutations. To date, 25 mutations in *GPR56*, including nine N-terminal extracellular domain mutations, are

* Corresponding author. Address: Department of Pediatrics, Hiroshima University Hospital, Faculty of Medicine, Hiroshima University, 1-2-3 Kasumi-cho, Hiroshima 734-8551, Japan. Tel.: +81 82 257 5212; fax: +81 82 257 5214.
E-mail address: yujinn0728@ybb.ne.jp (Y. Fujii).

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reported in humans [1,2,5–8]. Here we report a BFPP patient carrying compound heterozygous mutations with a novel *GPR56* mutation, p.S36Q, and a previously reported mutation, p.R38Q. Additionally, we review previous reports and discuss the radiological and clinical features of BFPP patients.

2. Case report

The proband was a Japanese female born from non-consanguineous parents. She had normal prenatal and perinatal histories and normal head growth, but showed developmental delay within the first year of life. Complex partial seizures occurred at 2 months; carbamazepine was effective for the seizures. Since the age of two years, epileptic spasms in clusters have appeared and have been refractory to medications. Around the age of four years, she developed tonic seizures causing drop attacks, in addition to epileptic spasms.

The seizures persisted despite treatment with multiple antiepileptic drugs. Interictal electroencephalogram (EEG) showed generalized bursts of sharp waves and slow spike-wave discharges with anterior predominance (Fig. 1). Video-EEG monitoring (Grass Technology, West Warwick, RI, USA) at 6 years old revealed that she suffered from frequent atypical absence seizures and tonic seizures. She was diagnosed with Lennox–Gastaut syndrome by specific EEG features and seizures. At this age, she had moderate to severe developmental delay (developmental quotient = DQ: 33). She was unable to walk without help, and her speech was limited to a few isolated words. Neurologic examination revealed mild spasticity, hyperactive deep-tendon reflexes, poor coordination, and exotropia. She showed neither dysmorphic features nor other congenital anomalies.

Brain MRI at 6 years of age revealed bilateral polymicrogyria with an anterior to posterior gradient, in contrast to the relatively spared perisylvian regions, patchy signal change in the bilateral white matter, hypoplastic pons, and multiple small cysts in the corpus callosum (Fig. 2).

2.1. Mutation analysis

DNA was extracted from peripheral blood leukocytes obtained from the patient and her parents using standard methods, and after obtaining informed consent from the parents. We performed a mutation screening of for all coding exons and flanking introns of *GPR56* using the high-resolution melt analysis (HRM) or capillary sequencing. PCR samples showing an aberrant melting curve pattern were sequenced. PCR primers and conditions are available on request.

Mutation analysis revealed a compound heterozygous mutation in exon 2 of*GPR56,* (c.107G>A and c.113G>A), (which presumably leads to amino acid changes), (p.S36N and p.R38Q, respectively) in the extracellular N-terminus of the protein. Her father was heterozygous for the p.S36N mutation, and her mother carried the p.R38Q mutation, which indicates an autosomal recessive inheritance (Fig. 3). Both changes were not found in one individual among 80 Japanese controls.

3. Discussion

BFPP is an autosomal recessive polymicrogyria syndrome, which was frequently underdiagnosed before genetic testing and high-resolution neuroimaging were available.

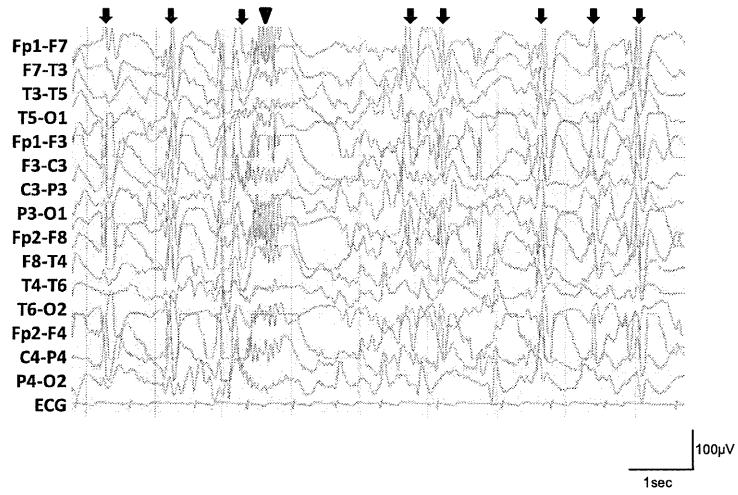

Fig. 1. Electroencephalography (EEG) finding. Generalized bursts of sharp waves (arrow head) and slow spike–wave discharges (arrows) with anterior predominance were seen during sleep.

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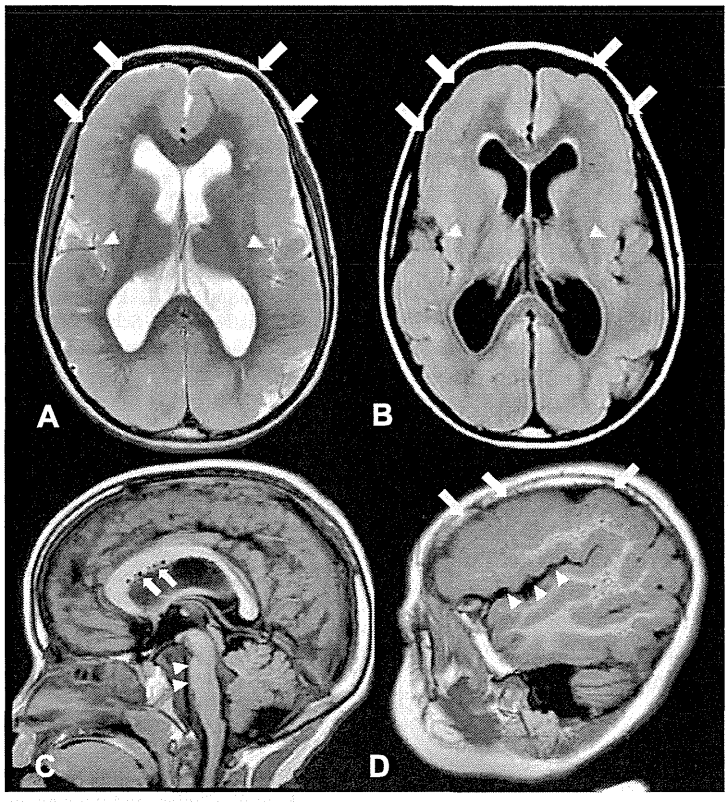

Fig. 2. Neuroimaging. Axial T2WI (A) and FLAIR (B) images demonstrate bilaterally symmetric thick cortex and irregular gyri compatible to polymicrogyria with anterior to posterior gradient (arrows) and, patchy high signals on both T2WI and FLAIR in the frontal subcortical white matter. Note the less involved insular cortex (arrow heads). Sagittal T1WI (C) shows flat pontine basis (arrow heads) and small cystic lesions in the corpus callosum (arrows). Sagittal T1WI (D) shows bilateral polymicrogyria with anterior to posterior gradient (arrows), in contrast with relatively spared perisylvian region (arrow heads).

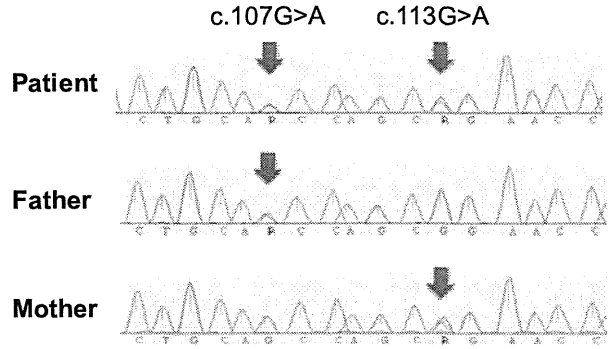

Fig. 3. Mutation analysis. Sequence chromatograms showing segregation of the compound heterozygous c.107G>A and c. 113G>A mutations in *GPR56* in the patient and her parents.

Piao, et al. [2] reported that the clinical phenotype of BFPP patients harboring *GPR56* mutations show considerable clinical homogeneity. This included five common clinical features and three typical MRI findings: (1) mental retardation of moderate to severe degree; (2) motor development delay; (3) seizures, most commonly symptomatic generalized epilepsy; (4) cerebellar signs, consisting of ataxia; (5) dysconjugate gaze, presenting variably as esotropia, nystagmus, exotropia, or strabismus; (6) bilateral polymicrogyria with anterior to posterior gradient; (7) bilateral patchy-white-matter signal changes without specific pattern; and (8) brain stem and cerebellar hypoplasia [1]. Thus, according to this description, our patient demonstrates the cardinal features of BFPP. Polymicrogyria typically has a predilection for the perisylvian cortex [9]. Our patient, however, shows less involvement of the perisylvian cortex, compared to the other regions where lesions were observed. Frontoparietal distribution of polymicrogyria is the most common feature of BFPP, but some patients show extensive distribution throughout the entire brain, as was observed with our patient [5,10]. Although other previous reports do not describe perisylvian cortex findings in detail, less involvement of perisylvian cortex might be a feature of BFPP caused by a GPR56 mutation.

Epilepsy is a common clinical problem in patients with BFPP caused by *GPR56* mutations [1,5–8,10]. Similar to our patient, four affected individuals from three families with BFPP caused by *GPR56* mutations had

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Lennox–Gastaut syndrome [6]. Lennox–Gastaut syndrome manifestations can occur among patients with BFPP caused by GPR56 mutations.

Our patient had a compound heterozygous mutation of*GPR56* (p.S36N and p.R38Q), whereas other patients with BFPP have homozygous mutations of *GPR56* [1,2,5–8]. Both mutations are located in the ligand binding domain within the extracellular N-terminus of the protein, as was observed in the nine previously reported ligand binding domain mutations [1,2,5,6,8]. A homozygous p.R38Q mutation never has been reported with BFPP [1]. Moreover, a detailed analysis of the biochemical modifications by *GPR56* revealed that the disease-associated *GPR56* missense mutations in the tip of the N-terminal domain (p.R38Q) produced proteins with reduced intracellular trafficking and poor cell surface expression [11]. Similar to p.R38Q, p.S36N is another substitution and a novel mutation that locates a ligand binding domain within the extracellular N-terminus of the protein. Compound heterozygosity of these two mutations in the ligand binding domain could impair the subcellular trafficking of the GPR56 receptor, and reduce its cell surface expression, leading to BFPP.

Acknowledgments

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Original article

Epidemiological study of Landau–Kleffner syndrome (LKS) in Japan

Makiko Kaga*, Masumi Inagaki, Reiko Ohta

National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan

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Abstract

Objective: We aimed to determine the incidence and prevalence of LKS in Japanese children. *Methods:* A questionnaire was sent to all 3004 Japanese hospitals that have a department of pediatrics. The questionnaire asked for the number of first-visit LKS patients and LKS patients who were followed up at or visited their clinic during the past one year Vital statistics of the same year (2008) published by Ministry of Health, Labor and Welfare, Japan were referenced to calculate the estimated incidence and prevalence of LKS among Japanese children. *Results:* Chiefs of 1562 pediatric departments answered our inquiry (51.9% of returns). Six chiefs had one new LKS patient, aged 6–14 years. Thirty two patients with LKS were followed in the same period. The number of children with LKS less than 20 years of age who needed medical care was at least 23 and at most 31. Vital statistics of Japan 2009 revealed that the population of children aged 5–14 years was 11,861,464 and that aged 5–19 years was 18,007,968. *Discussion:* The number of the first-visit LKS patients was 6 in a year. We estimated the incidence of LKS in the 5- to 14-years-old Japanese population as about 1 in 978,000. The number of LKS patients aged 5–19 was estimated to range from 44.2 to 59.6 among a population of 18,007,968. This means the prevalence of LKS under medical care is roughly one in 302,147–407,420 children aged 5–19. This study is the first epidemiological estimation of the incidence and prevalence of children with LKS in Japan or, for that matter, in any other area. *Conclusion:* (1) Incidence of children with LKS aged 5–14 years was about 1 in a million in Japan. (2) Prevalence of children with LKS aged 5–19 and under medical care was one in about 300,000–410,000 in Japan. (3) This study constitutes the first epidemiological estimation of LKS in Japan.

Keywords: Landau–Kleffner syndrome (LKS); Japanese children; Incidence; Prevalence; Epidemiology

1. Introduction

Landau–Kleffner syndrome (LKS) was first reported as acquired aphasia with convulsive disorder in children in 1957 [1]. LKS is a rare neurological disease which emerges in patients around 6 years of age. The main symptom of LKS is auditory agnosia with apparent hearing impairment, regression of speech, and diffuse spike and wave complexes especially in sleep EEG. Those signs and symptoms usually continue for several years [1,2], and a limited number of patients have some auditory verbal sequelae after they reach adulthood [2].

Historically, more than four hundred English studies on LKS have been published as review articles or case reports, although one original paper described the characteristic symptoms of 5 children [1]. However, there has been no systematic epidemiological study in the literature.

The objective of the present research was to elucidate the incidence and prevalence of LKS in Japanese children by sending a questionnaire by mail to the hospitals where certified pediatrician(s and or) child neurologist(s) are employed.

* Corresponding author. Address: Tokyo Metropolitan Tobu Ryoiku Center, 3-3-25 Shinsuna, Koto-ku, Tokyo 136-0075, Japan.
E-mail address: kaga@ncnp.go.jp (M. Kaga).

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2. Methods

A questionnaire package was sent to all Japanese hospitals (3004 hospitals as of March 2009), which have a department of pediatrics. These hospitals are officially registered by Japanese law and are listed for the public at an Internet site managed by the Welfare and Medical Service Agency (http://www.wam.go.jp). The questionnaire asked for the number of first-visit LKS patients the hospital had diagnosed during the past one year (from August 1, 2008 to July 31, 2009). When the hospital had records of the relevant patient visits, we also asked for these patients' age and sex. We also asked for the number of patients who were followed up at their clinic during the same period. In the package, a document explaining our purpose and the definition of LKS (see Table 1) was enclosed to ensure the exact number of patients was obtained.

We analyzed the answers sent back to us during the next 3-month period in 2009. The vital statistics of the same year (2008) published by the Ministry of Health, Labor and Welfare, Japan [3] were referenced in calculating the incidence and prevalence of LKS among all children in Japan.

3. Results

The chiefs of 1562 pediatric departments answered our inquiry (51.9% of returns). Six patients (5 boys and 1 girl) newly diagnosed with LKS aged 6–14 years were reported to have visited the out-patient clinics.

Among 1562 pediatric departments, 26 chief pediatricians replied that they followed-up and saw 32 patients with LKS in the same period. Twenty-two (69%) of these were male. The eldest was 41 years old, and the ages of 8 patients were not described. The ages of the rest of the patients ($n = 23$) were distributed from 6 to 19 years of age. Thus, the number of children with LKS less than 20 years of age who needed medical care in one year was at least 23 (16 males and 7 females) and no more than 31.

Table 1
Explanation and definition of LKS. LKS is a rare neurological disease which begins around age 6 (mainly 2–10).

Signs and symptoms of LKS
(1) Apparent hearing impairment due to abnormal auditory perception (auditory agnosia or word deafness)
(2) Regression of speech, sometimes to sensory aphasia, then to total aphasia
(3) Above symptoms are sometimes associated with behavioral or character change
(4) Diffuse spike and wave complexes especially in sleep EEG
(5) Above signs and symptoms usually continue or show repeated exacerbation/remission in several years with complete recovery
(6) A limited number of patients have some auditory verbal sequelae after they reach adulthood

The vital statistics of Japan 2009 revealed that the population of children aged 5–14 years was 11,861,464 (5–9 years was 5,864,879 and 10–14 years was 5,996,585) [3]. The number of children aged 5–19 years was 18,007,968 (15–19 years was 6,146,504) [3].

4. Discussion

LKS is mainly a childhood disease, with onset in early childhood. Generally, patients' behavior such as their daily conversation grows more and more abnormal, and parents believe that their children have some extraordinary disease for which doctors should be consulted. If these doctors are family physicians, they are sure to recommend further evaluation at the local hospital, which has more facilities for a full work-up.

Thus, we assumed that every LKS patient visited a department of pediatrics at some point in their disease course.

Among the respondents to our questionnaire, the number of the first-visit LKS patients in Japan was 6 in one year. Their age range was 5–14 years. It is reasonable to speculate that if the 1442 (3004 minus 1562) nonanswerers experienced LKS, the number would not exceed the ratio of 6 among 1562 departments. Therefore, 11.5 (6 plus 5.5) should be the maximum data of our survey of children from 5 to 14 years of age. Thus, the incidence of LKS in 5- to 14-years-olds was about 1 in 978,000 in Japan.

As above mentioned, the number of children (<20 years) with LKS who needed medical care in the year of study was at least 23 (16 males and 7 females) and no more than 31. Therefore, the number of LKS patients aged 5–19 can be assumed to have ranged from 44.2 (23 plus 21.2) to 59.6 (31 plus 28.6) among the total population of 18,007,968 children age 5–19. This means the prevalence of LKS patients under medical care was one in 302,147–407,420 children of this age group.

There have been no epidemiological reports of LKS in previous studies. The reason may stem from two aspects of LKS: epilepsy and childhood language disorder. From the epileptic point of view, their seizure types and characteristics are not specific to LKS. From the point of view of language disorders, clinical signs and symptoms are not well known even to pediatricians. Thus, our estimated incidence may be low. In this study, we were able to show the clinical features of LKS and obtain data from pediatricians who worked at hospitals and treated this disease.

This study is the first epidemiological estimation of the incidence and prevalence of children with LKS in Japan, or in any other area.

5. Conclusions

(1) The incidence of children with LKS aged 5–14 years was about 1 in a million (978,000) in Japan.

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(2) The prevalence of children with LKS aged 5–19 and under medical care was one in 302,147–407,420 in Japan.
(3) This constitutes the first epidemiological estimation of LKS in Japan.

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Case report

Girl with a *PRRT2* mutation and infantile focal epilepsy with bilateral spikes

Hiroyuki Torisu [a,b,*], Kyoko Watanabe [c], Keiko Shimojima [d], Midori Sugawara [d], Masafumi Sanefuji [a], Yoshito Ishizaki [a], Yasunari Sakai [a], Hironori Yamashita [c], Toshiyuki Yamamoto [d], Toshiro Hara [a]

[a] *Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[b] *Department of Pediatrics, Fukuoka Dental College Medical and Dental Hospital, Fukuoka, Japan*
[c] *Department of Pediatrics, Kokura Medical Center, Kitakyushu, Japan*
[d] *Tokyo Women's Medical University Institute for Integrated Medical Sciences, Tokyo, Japan*

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Abstract

This paper documents the case of a female Japanese patient with infantile focal epilepsy, which was different from benign infantile seizures, and a family history of infantile convulsion and paroxysmal choreoathetosis. The patient developed partial seizures (e.g., psychomotor arrest) at age 14 months. At the time of onset, interictal electroencephalography (EEG) showed bilateral parietotemporal spikes, but the results of neurologic examination and brain magnetic resonance imaging were normal. Her seizures were well controlled with carbamazepine, and she had a normal developmental outcome. EEG abnormalities, however, persisted for more than 6 years, and the spikes moved transiently to the occipital area and began to resemble the rolandic spikes recognized in benign childhood epilepsy. Her father had paroxysmal kinesigenic dyskinesia, with an onset age of 6 years, and her youngest sister had typical benign infantile seizures. Genetic analysis demonstrated that all affected members had a heterozygous mutation of c.649_650insC in the proline-rich transmembrane protein-2 (*PRRT2*) gene. This case indicates that the phenotypic spectrum of infantile seizures or epilepsy with *PRRT2*-related pathology may be larger than previously expected, and that genetic investigation of the effect of *PRRT2* mutations on idiopathic seizures or epilepsy in childhood may help elucidate the pathological backgrounds of benign childhood epilepsy.

Keywords: Infantile focal epilepsy; Paroxysmal kinesigenic dyskinesia; Infantile convulsion and paroxysmal choreoathetosis (ICCA); PRRT2; Mutation; c.649_650insC

1. Introduction

Close observation and examination of patients with infantile seizures has established the existence of a clinically benign type of infantile seizure [1–3]. Further investigations discovered several subtypes of benign infantile seizures (BIS), including 4 genetically different types of benign familial infantile seizures (BFIS1-4), benign non-familial infantile seizures, benign infantile seizures associated with mild gastroenteritis, and benign infantile focal epilepsy with midline spikes and waves during sleep (BIMSE) [4]. In 2011–2012, mutations in the proline-rich transmembrane protein-2 (*PRRT2*) gene were found to be responsible for paroxysmal kinesigenic dyskinesia (PKD; OMIM: 128200), BFIS2, and infantile convulsion

* Corresponding author. Address: Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel.: +81 92 642 5421; fax: +81 92 642 5435.
E-mail address: htorys@pediatr.med.kyushu-u.ac.jp (H. Torisu).

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and paroxysmal choreoathetosis (ICCA; OMIM: 602066) [5–10]. Despite these advances in the identification of related genetic mutations, the entire clinical spectrum of *PRRT2*-related diseases has not been fully elucidated.

This report presents the case of a female Japanese patient with infantile focal epilepsy with parietotemporal spikes and a significant family history of ICCA. Her father and youngest sister had PKD and typical BIS, respectively (Fig. 1). All affected members had the *PRRT2* mutation c.649_650insC, frequently found in patients with BFIS2 and ICCA [6]. This case suggests underlying contribution of *PRRT2* to the development of paroxysmal diseases with stronger effects than previously expected.

2. Case report

The female patient (identified as II-1 in Fig. 1) was the first child of non-consanguineous Japanese parents. She was born via spontaneous vaginal delivery at 41 weeks gestation, without asphyxia. At birth, she weighed 2876 g and her head circumference was 33.0 cm. She developed normally, could control her head at 3 months, sit alone at 7 months, walk at 13 months, and speak a word at 12 months. At 14 months, she developed sudden-onset eye rolling and cyanosis that lasted for 1 min. This episode was thought to represent a seizure, and she had a similar episode 11 days later. Neurologic examination and brain magnetic resonance imaging results were normal. Interictal electroencephalography (EEG) during sleep revealed multifocal spikes in the bilateral centrotemporal areas (Fig. 2A). At 15 months, she developed sudden-onset staring associated with turning her head to the left, which progressed to a generalized tonic seizure that lasted for 3 min. Treatment with carbamazepine was initiated at that time. Seizures were well controlled by the medication, but the EEG abnormalities continued over 6 years and gradually changed to bilateral spikes similar to the rolandic spikes recognized in benign childhood epilepsy (Fig. 2B–D). At age 7 years and 10 months, the patient went off the medication and subsequently had a generalized seizure.

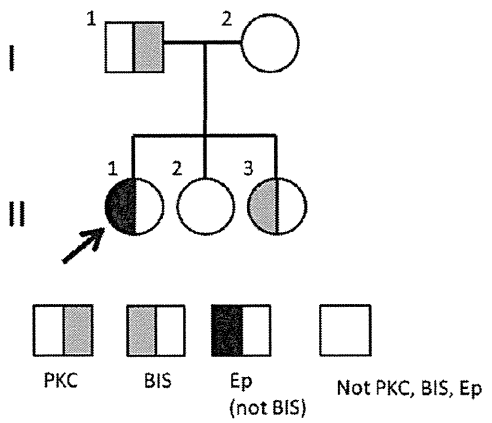

Fig. 1. Family pedigree. The proband (II-1) with epilepsy was the first child of I-1 with PKD. His third child (II-3) had BIS. PKD: paroxysmal kinesigenic dyskinesia, BIS: benign infantile seizure, Ep: epilepsy.

The father of the present patient (identified as I-1 in Fig. 1) had PKD. His dyskinetic movements began at age 6 years, but EEG at that time revealed no paroxysmal discharges. His development was normal with no developmental or neurologic problems and no febrile seizures since birth. His paroxysmal movements were well controlled with carbamazepine.

The youngest sister of the patient (identified as II-3 in Fig. 1) had 2 focal seizures at age 6 months. Again, her sister developed normally, without developmental or neurologic problems, and EEG did not show apparent epileptic discharges. After the focal seizures, carbamazepine therapy was initiated. She continued carbamazepine thereafter and continued to develop normally, with no further seizures.

After obtaining informed consent, the *PRRT2* gene was sequenced using DNA extracted from the peripheral blood of affected family members. A heterozygous frameshift mutation, c.649_650insC, was detected, resulting in p.Arg217Profs*8 (Fig. 3).

3. Discussion

The findings in this case indicate that epilepsy or seizures other than BIS could be associated with a *PRRT2* mutation. This association is supported by a few previous reports describing patients having a *PRRT2* mutation with epilepsy, including absence epilepsy [6,7]. The molecular function of the encoded protein PRRT2 has not been fully defined. PRRT2 is likely expressed in the brain and spinal cord in the embryonic and postnatal stages of development [5,6,8]. PRRT2 is thought to interact with a 25-kDa synaptosomal-associated protein (SNAP25) [8]. SNAP25 is a part of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, which fuse synaptic vesicles to the presynaptic plasma membrane and release neurotransmitters. Defects in synaptic functions are predicted to be associated with brain disorders, including epilepsy, and PRRT2 dysfunction may disturb nerve conduction in the central nervous system and cause various types of paroxysmal diseases. The current case indicates that there may be a larger phenotypic spectrum of infantile seizures or epilepsy, with PRRT2-related molecular pathology, than previously expected. Future investigations should explore the involvement of PRRT2 in the pathology of paroxysmal disorders.

However, the current case may be a rare case with a *PRRT2* mutation incidentally occurring with other epileptic backgrounds. Despite considerable phenotypic

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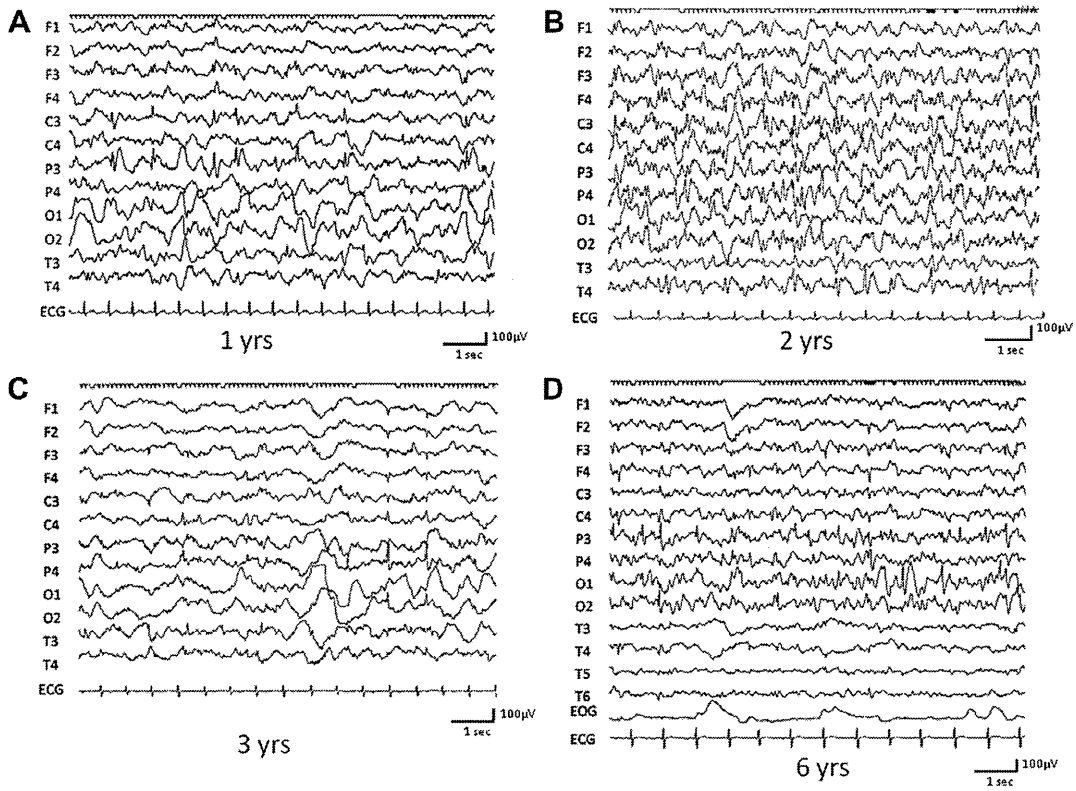

Fig. 2. Interictal EEG recordings of the patient. Interictal EEG data revealed multifocal spikes at the P3 and T4 areas at age 1 year (A), at C3–T3 and P4–T4 at age 2 years (B), at T3 and P4 at age 3 years, and at P3–O1 and O2 at age 6 years (D). The multiple spikes were tri-phasic in shape, similar to rolandic spikes.

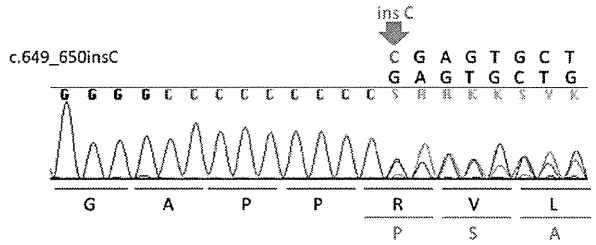

Fig. 3. Direct sequencing analysis of the proband (II-1) reveals a heterozygous mutation of *PRRT2*: c.649_650insC. The insertion of C at position 649 changed the reading frame, resulting in the production of an altered protein.

similarity between the current patient's epilepsy and BIS (i.e., family history of seizures, normal development prior to onset, no underlying disorders or neurologic abnormalities, partial seizures [e.g., psychomotor arrest], and a normal developmental outcome), she presented with some features that differ from most patients with BIS. Most notably, the patient had persistent spikes on interictal EEG, which differs with respect to the location and chronologic course of spike discharges, from both patients with BIS and those with BIMSE. In particular, in the current patient, the spikes moved transiently to the occipital area and began to resemble the rolandic spikes recognized in benign childhood epilepsy with centrotemporal spikes and Panayiotopoulos syndrome. Hence, it is possible that the current patient incidentally has the pathological background of benign childhood epilepsy. However, this background remains to be fully understood. Genetic investigations of the effects of *PRRT2* mutation on idiopathic childhood-onset seizures or epilepsy may help elucidate the association between PRRT2-related pathology and the epileptic background of benign childhood epilepsy.

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Letter to the Editor

AKT3 and *PIK3R2* mutations in two patients with megalencephaly-related syndromes: MCAP and MPPH

To the Editor:

Megalencephaly-capillary malformation syndrome (MCAP) and megalencephaly-polymicrogyria-polyd actyly-hydrocephalus syndrome (MPPH) belong to a spectrum of megalencephaly-related syndromes. The diagnostic criteria for MCAP include megalencephaly plus capillary malformations or syndactyly, and those for MPPH include megalencephaly and polymicrogyria, an absence of vascular anomalies, syndactyly, and brain heterotopia (1). Recently, *AKT3*, *PIK3R2*, and *PIK3CA* mutations have been identified in MCAP and MPPH (2). The proteins encoded by these genes are core components of the phosphatidylinositol 3-kinase (PI3K)-AKT pathway (3). Here, we report two patients with an *AKT3* and *PIK3R2* mutation. The study protocol was approved by the Institutional Review Boards for Ethical Issues at Yokohama City University and Yamagata University.

Patient 1 is an 8-year-old girl who has been previously reported as having MPPH (4). Brain magnetic resonance imaging (MRI) at 6 years showed asymmetry of the gyral pattern, dilated lateral ventricles, polymicrogyria, and abnormal signals in the occipital lobes, suggesting dysmyelination (Fig. 1a–c). Patient 2 is a 2-month-old boy who showed macrocephaly, cutis marmorata of the distal extremities, and hyperextensibility

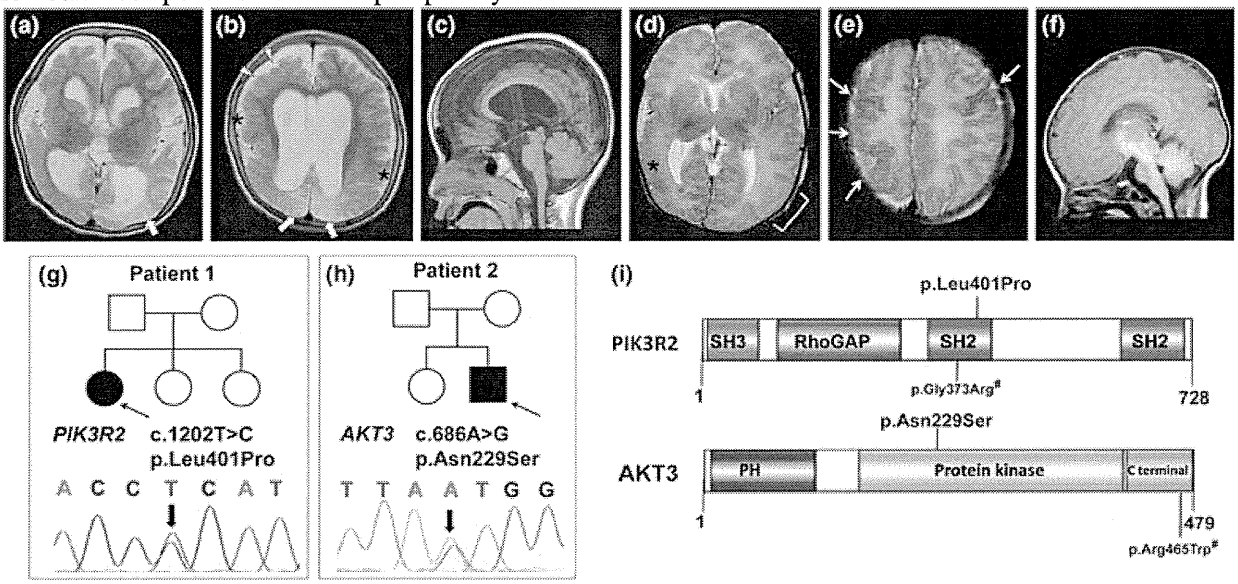

Fig. 1. Magnetic resonance imaging of patient 1 at 6 years of age (**a–c**). (**a**, **b**) Axial T2-weighted imaging showing enlarged lateral and third ventricles, enlarged extra-axial space, and decreased white matter volume with occipital lobe predominance. Irregular small gyri with areas of cortical thickening compatible with polymicrogyria are observed prominently in the bilateral perisylvian regions (asterisks) and the right frontal lobes (white arrowheads). Abnormal high-intensity signals are seen in the bilateral occipital lobes (thick white arrows). (c) Sagittal T1-weighted imaging showing normal brainstem and cerebellum. Magnetic resonance imaging of patient 2 at 7 days of age (**d–f**). (**d**) Axial T2-weighted imaging at the level of the basal ganglia showing enlargement of the left hemisphere. Polymicrogyria is seen in the perisylvian fissures with right-side dominance, which extends to the right temporal lobe (asterisk). The left parietal cortex shows a blurred border between the gray matter and the white matter (bracket), suggesting dysplasia of cortical development. (**e**) Axial T2-weighted imaging showing polymicrogyria in the right parietal lobe adjacent to the central sulcus (white arrows). (**f**) Sagittal T1-weighted imaging showing a relatively small pontine base. Family pedigrees and causative mutations (**g–i**). (**g**) Patient 1 with MPPH showing a *de novo* heterozygous missense mutation in *PIK3R2* (c.1202T>C, p.Leu401Pro). (h) Patient 2 with MCAP showing a *de novo* missense heterozygous mutation in *AKT3* (c.686A>G, p.Asn229Ser). (i) Distribution of mutations in *PIK3R2* and *AKT3*. SH2, Src homology 2 domain; SH3, Src homology 3 domain; RhoGAP, Rho GTPase-activating protein domain; PH, pleckstrin homology domain. #Reported by Riviere et al. (2).

of the skin. Brain MRI at 7 days showed an asymmetric cerebral hemisphere with right-dominant perisylvian polymicrogyria (Fig. 1d–f), and at 2 months showed a thin corpus callosum and progressive hydrocephalus. These findings were compatible with MCAP.

Whole exome sequencing using DNA extracted from blood leukocytes revealed a *de novo* missense mutation in each patient: p.Leu401Pro in *PIK3R2* (patient 1) and p.Asn229Ser in *AKT3* (patient 2) (Fig. 1g–i). Both mutations were absent from the 6500 eomes sequenced by the National Heart, Lung, and Blood Institute exome project and our 144 in-house control exomes. The read count for mutant alleles possessing p.Leu401Pro in *PIK3R2* was 47.7% (84/176 reads), and that for p.Asn229Ser in *AKT3* was 52.2% (128/245 reads). Therefore, these mutations are likely germline rather than mosaic mutations.

The novel *PIK3R2* mutation (p.Leu401Pro) in patient 1 is within the first Src homology 2 (SH2) domain of the PIK3R2 protein; this domain binds to phosphotyrosine-containing motifs and regulates many aspects of cellular communication (5). Eleven MPPH families have been reported to have a recurrent *PIK3R2* mutation (p.Gly373Arg), which is also located in the first SH2 domain (2). The phenotypes of all 13 cases with the p.Gly373Arg mutation were similar to that of patient 1 (Table 1) (1, 2), implying that impaired function of the SH2 domain is important in the pathogenesis of MPPH. The *AKT3* mutation (p.Asn229Ser) detected in patient 2 with MCAP has been reported in a case of MPPH (2). Furthermore, another case with a different *AKT3* mutation (p.Arg465Trp) was diagnosed with overlapping features of MCAP and MPPH (Table 1). These findings support the notion that the two syndromes have a common genetic basis. Interestingly, somatic mosaicism of an *AKT3* mutation causes hemimegalencephaly, which is similar to MPPH or MCAP (6, 7). Mutation screening of *AKT3* should be considered for patients with MPPH or MCAP as well as those with hemimegalencephaly, for whom pathological tissue is available.

MCAP and MPPH are categorized as overgrowth syndromes, as are Cowden disease and Proteus syndrome that are caused by abnormal activation of the PI3K–AKT pathway, which participates in diverse cellular processes (3, 8). The PI3K–AKT pathway is linked to mammalian target of rapamycin (mTOR) (6), which is a specific molecule for targeted therapeutics (sirolimus or everolimus). Further investigation into potential treatments for overgrowth syndromes is essential.

In summary, we have described two patients with either an *AKT3* or a *PIK3R2* mutation. Our data highlight the importance of the SH2 domain of PIK3R2 in MPPH, and support that MPPH and MCAP have the same genetic origin.

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Table 1. Phenotypes associated with *PIK3R2* and *AKT3* mutations

Patient (diagnosis) Mutation	Patient 1 (MPPH) *PIK3R2* (p.Leu401Pro)	13 patients[a] (MPPH) *PIK3R2* (p.Gly373Arg)	Patient 2 (MCAP) *AKT3* (p.Asn229Ser)	LR11-354[a] (MPPH) *AKT3* (p.Asn229Ser)	LR08-018[a] (overlapping MCAP and MPPH) *AKT3* (p.Arg465Trp)
Features					
HC SD (age)	+2.6 (1 y 9 m)	+2–8 (8 m–13 y)	+3.0 (2 m)	+6.0 (2 y 5 m)	+5.5 (7.5 m)
Overgrowth	–	2/13	–	–	–
Vascular abnormalities	–	0/13	Skin capillary malformation	–	umbilical hemangioma
Connective tissue dysplasia	–	0/13	+	+	+
Syndactyly	–	0/13	–	–	–
Polydactyly	+	2/13	–	–	–
Epileptic seizures	+	6/9	+	ND	+
Visual impairment	+	ND	–	ND	ND
Neuroimaging features					
Polymicrogyria	+	13/13	+	+	+
Hydrocephalus or ventriculomegaly	+	13/13	+	+	+
CBTE	–	8/13	–	–	+

MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; MCAP, megalencephaly-capillary malformation syndrome; HC, head circumference; SD, standard deviation; y, years; m, months; ND, no data; CBTE, cerebellar tonsillar ectopia.

[a] Riviere et al. (2) and Mirzaa et al. (1).

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K. Nakamura[a,b]
M. Kato[b]
J. Tohyama[c]
T. Shiohama[d]
K. Hayasaka[b]
K. Nishiyama[a]
H. Kodera[a]
M. Nakashima[a]
Y. Tsurusaki[a]
N. Miyake[a]
N. Matsumoto[a]
H. Saitsu[a]
[a]Department of Human Genetics
Yokohama City University Graduate School of Medicine
Yokohama, Japan
[b]Department of Pediatrics
Yamagata University Faculty of Medicine
Yamagata, Japan
[c]Department of Pediatrics
Epilepsy Center, Nishi-Niigata Chuo National Hospital
Niigata, Japan
[d]Department of Pediatrics
Kimitsu Chuo Hospital
Chiba, Japan

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Correspondence:
Dr Kazuyuki Nakamura, MD
Department of Pediatrics
Yamagata University Faculty of Medicine
2-2-2 Iida-nishi
Yamagata 990-9585
Japan
Tel: +81-23-628-5329
Fax: +81-23-628-5331
e-mail: kazun-yamagata@umin.ac.jp

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Original article

Magnetoencephalography localizing spike sources of atypical benign partial epilepsy

Hideaki Shiraishi [a], Kazuhiro Haginoya [b], Eiji Nakagawa [c], Shinji Saitoh [a], Yutaka Kaneko [d], Nobukazu Nakasato [e], Derrick Chan [f,g], Hiroshi Otsubo [f,*]

[a] *Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan*
[b] *Department of Pediatrics, Tohoku University School of Medicine, Sendai, Miyagi, Japan*
[c] *Department of Neurology, National Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan*
[d] *Department of Neurosurgery, National Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan*
[e] *Department of Epileptology, Tohoku University School of Medicine, Sendai, Miyagi, Japan*
[f] *Division of Neurology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*
[g] *Neurology Service, Department of Pediatric Medicine, KK Women's and Children's Hospital, Singapore*

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Abstract

Rationale: Atypical benign partial epilepsy (ABPE) is characterized by centro-temporal electroencephalography (EEG) spikes, continuous spike and waves during sleep (CSWS), and multiple seizure types including epileptic negative myoclonus (ENM), but not tonic seizures. This study evaluated the localization of magnetoencephalography (MEG) spike sources (MEGSSs) to investigate the clinical features and mechanism underlying ABPE. *Methods:* We retrospectively analyzed seizure profiles, scalp video EEG (VEEG) and MEG in ABPE patients. *Results:* Eighteen ABPE patients were identified (nine girls and nine boys). Seizure onset ranged from 1.3 to 8.8 years (median, 2.9 years). Initial seizures consisted of focal motor seizures (15 patients) and absences/atypical absences (3). Seventeen patients had multiple seizure types including drop attacks (16), focal motor seizures (16), ENM (14), absences/atypical absences (11) and focal myoclonic seizures (10). VEEG showed centro-temporal spikes and CSWS in all patients. Magnetic resonance imaging (MRI) was reported as normal in all patients. MEGSSs were localized over the following regions: both Rolandic and sylvian (8), peri-sylvian (5), peri-Rolandic (4), parieto-occipital (1), bilateral (10) and unilateral (8). All patients were on more than two antiepileptic medications. ENM and absences/atypical absences were controlled in 14 patients treated with adjunctive ethosuximide. *Conclusion:* MEG localized the source of centro-temporal spikes and CSWS in the Rolandic-sylvian regions. Centro-temporal spikes, Rolandic-sylvian spike sources and focal motor seizures are evidence that ABPE presents with Rolandic-sylvian onset seizures. ABPE is therefore a unique, age-related and localization-related epilepsy with a Rolandic-sylvian epileptic focus plus possible thalamo-cortical epileptic networks in the developing brain of children.

Keywords: Epileptic negative myoclonus; Focal seizure; Atypical absence; Centro-temporal spike; Continuous spike and waves during sleep; Secondary bilateral synchrony

* Corresponding author. Address: Division of Neurology, The Hospital for Sick Children, 555 University Avenue, University of Toronto, Toronto, ON, Canada M5G 1X8. Tel.: +1 416 813 6660; fax: +1 416 813 6334.
E-mail addresses: hiotsubo@rogers.com, hiroshi.otsubo@sickkids.ca (H. Otsubo).

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1. Introduction

Atypical benign partial epilepsy in childhood (ABPE) initially presents with the following signs and symptoms: (i) onset age of 2.5–6 years; (ii) multiple seizure types including focal motor, atypical absences and myoclonic-atonic seizures; (iii) electroencephalography (EEG) showing central and mid-temporal spikes and diffuse slow spike-wave activities during drowsiness or sleep; and (iv) normal development or mild mental retardation [1]. Despite multiple seizure types and slow spike and waves on EEG, ABPE is distinguished from Lennox–Gastaut syndrome by its characteristic spontaneous remission, lack of tonic seizures or developmental delay, and normal awake EEG background activity. Since hemi-convulsive seizures during sleep and contralateral/bilateral centro-temporal epileptiform discharges are present at the beginning, the electro-clinical findings of ABPE are indistinguishable from those of benign epilepsy with centro-temporal spikes (BECTS) [2–5]. BECTS is the most well-recognized, age-related idiopathic focal epilepsy with occasional epileptic seizures despite frequent centro-temporal spikes on EEG. In contrast, ABPE patients tend to develop atypical absences or myoclonic-atonic seizures during the course of their condition. Tovia et al. [6] showed that 0.5% of patients with BECTS were categorized as atypical variants, while Doose et al. [7] found that 29% of the relatives of ABPE patients had some abnormal activities on EEG. Finally, Gobbi et al. [8] reviewed several subtypes of idiopathic focal epilepsies to categorize ABPE as a "Rolandic epilepsy-related disorder"; these age-related epilepsies including ABPE and BECTS were attributed to a maturational continuum with different manifestations.

Epileptic negative myoclonus (ENM) is one of the characteristic seizure patterns in ABPE. Oguni et al. [6] analyzed the ictal EEG findings of ENM and demonstrated generalized, bilateral synchronous discharges, while ictal magnetoencephalography (MEG) of an ABPE patient showed that the spike sources of ENM were localized at the peri-sylvian region [7].

MEG is a relatively new clinical technique that uses superconducting quantum interference devices (SQUIDs) to measure and localize sources of extracranial magnetic fields generated by intraneuronal electric currents. Current MEG machines have a whole-head array of more than 100 sensors contained within a helmet-shaped Dewar, which effectively covers most of the brain surface. MEG has been increasingly used for localization of the epileptic zone and functional mapping in epilepsy patients. MEG in BECTS patients showed spike sources with an anterior–posterior oriented perpendicular to the Rolandic fissure [8,9]. No case series of ABPE have thus far used MEG to localize epileptic spike sources.

We conducted a multi-center study to collect clinical, EEG and MEG findings in ABPE patients, with MEG used to characterize the spike sources (MEGSSs) in ABPE. We hypothesize that the epileptic network in ABPE is localized in both the Rolandic-sylvian cortex and thalamo-cortical networks, based on their unique clinical and electrophysiological features.

2. Patients and methods

We collaborated with four institutions on this study: the Department of Pediatrics, Hokkaido University School of Medicine (HU); Department of Pediatrics, Tohoku University School of Medicine (TU); Department of Pediatrics, National Center of Neurology and Psychiatry (NCNP), Japan; and the Division of Neurology, The Hospital for Sick Children (HSC), Toronto, Ontario, Canada.

2.1. Patients

We studied 18 patients with ABPE (nine females and nine males). We diagnosed ABPE according to the triad of diagnostic criteria as follows: (1) focal motor seizures, absences/atypical absences, atonic seizures including ENM, myoclonic seizures and drop attacks described by parents; (2) EEG findings of central and middle temporal spikes and generalized slow spike-wave activity during drowsiness or sleep similar to continuous spike and slow waves during sleep (CSWS); (3) normal development or mild mental retardation during the clinical course.

2.2. EEG

Scalp video EEGs were recorded using the international 10-20 electrode placement system and electromyography (EMG) electrodes for bilateral deltoid muscles to capture ENM. Awake and sleep EEGs were recorded in all patients.

2.3. MEG and magnetic resonance imaging

Initial MEG studies were conducted at the onset of ENM. Seven patients had multiple MEG studies up to six times. Parents or guardians of all patients provided written informed consent for the MEG studies. MEG and EEG were done in a magnetically shielded room. MEG was recorded using a system with 306 SQUIDs (Vectorview; Elekta-Neuromag Ltd., Helsinki, Finland) at HU, NCNP and TU, and with an Omega system (151 channels, VSM MedTech Ltd., Port Coquitlam, BC, Canada) at HSC. MEG data were recorded with a band pass filter of 0.03–133 Hz at HU, NCNP and TU, and of 1–208 Hz at HSC. Sampling frequency was 400 Hz at HU, 600 Hz at NCNP and TU, and 625 Hz at HSC. EEGs were recorded using the international 10-20 system, with additional electrocardiogram (ECG)

electrodes. MEG data were recorded for >1 h per patient, collecting data in 4-min blocks at HU, NCNP and TU. At HSC, MEG was recorded in 15 two-minute blocks for a total of 30 min [10]. Patients were lying in the supine position. Sedative agents were used for uncooperative patients. The relative position of the head and the MEG sensors were determined by attaching three small head-position indicator coils to the head. The positions of the coils were digitized and subsequently recorded by the MEG sensors for co-registration with 1.5 T (tesla)/3 T magnetic resonance image (MRI) with high-resolution sequences.

2.4. MEG source analysis

MEG data were digitally filtered using a band filter of 3–30 Hz at HU, NCNP and TU, or at 3–70 Hz at HSC for offline analysis. Segments containing abnormal paroxysms were selected manually. Individual spikes were analyzed to localize the spike source per spike using an equivalent current dipole (ECD) model or dynamic statistical parametric mapping (dSPM) [11,12].

3. Results

3.1. Seizure profiles (Table 1)

Seizure onsets ranged from 1.3 to 8.8 years with a median age of 2.9 years. The seizures started as focal motor seizures in 15 patients (83%) and absences/atypical absences in three patients (17%).

All patients except one patient had multiple types of seizures in their seizure histories. Drop attacks, in which the precise seizure type remains unknown, were most common (16 patients, 89%). One patient (Patient 17) presented with a history of only drop attack seizures. Focal motor seizures (16 patients, 89%), ENM (14 patients, 78%), absences/atypical absences (11 patients, 61%), myoclonic seizures (10 patients, 56%) and secondarily generalized tonic-clonic seizures (nine patients, 50%) were seen in more than half of the patients (Supplementary videos 1 and 2). Focal sensory seizures (six patients, 33%) and epileptic spasms (two patients, 11%) were also reported.

Table 1
Seizure profiles.

Seizure onset	1.3–8.8 years (median, 2.9 years)	
Initial seizures	Focal motor seizures	15 (83%)
	Absences/atypical absences	3 (17%)
Type of seizures in patient history	Drop attacks	16 (89%)
	Focal motor seizures	16 (89%)
	Epileptic negative myoclonus	14 (78%)
	Absences/atypical absences	11 (61%)
	Myoclonic seizures	10 (56%)
	Secondarily generalized tonic-clonic seizures	9 (50%)
	Focal sensory seizures	6 (33%)
	Epileptic spasms	2 (11%)

3.2. Past and family history

There was no past history of epilepsy before the seizure onset in any of the 18 patients, while three patients (17%) had a positive family history of febrile seizures.

3.3. Cognitive functions

Cognitive function was evaluated in 15 patients. All 15 patients had the evaluations while they presented with ENM. A developmental quotient results ranged from 54 to 85 in five patients. The full-scale intelligence quotient test (Wechsler Intelligence Scale for Children) results ranged from 53 to 103 in 10 patients.

3.4. MRI

No patient showed an abnormality on MRI.

3.5. EEG (Fig. 1)

EEG showed interictal centro-temporal spikes in all 18 patients. Continuous generalized and/or centro-temporal spike and waves during sleep were also noticed in all patients. When video EEG captured ENM, generalized high-amplitude spike or polyspikes, and waves were associated with a brief attenuation of EMG activities corresponding to muscle atonia in 12 patients (Supplementary video 1). Absences/atypical absences showed generalized and irregular spike and slow waves around 3 Hz on EEG in 16 patients (Supplementary video 2).

3.6. MEG (Fig. 2 and Table 2)

MEG localized MEGSSs over both Rolandic and sylvian fissures in eight patients, the peri-sylvian region alone in five patients, and the peri-Rolandic region alone in four patients. One patient had MEGSSs in the left parieto-occipital region, even though EEG showed left centro-temporal spikes (Patient 6). Most spike sources were oriented perpendicularly to either the Rolandic or sylvian fissure. The spike sources demonstrated identical orientations in 11 patients (61%). MEGSSs were located in bilateral hemispheres in 10 patients (56%) and in a

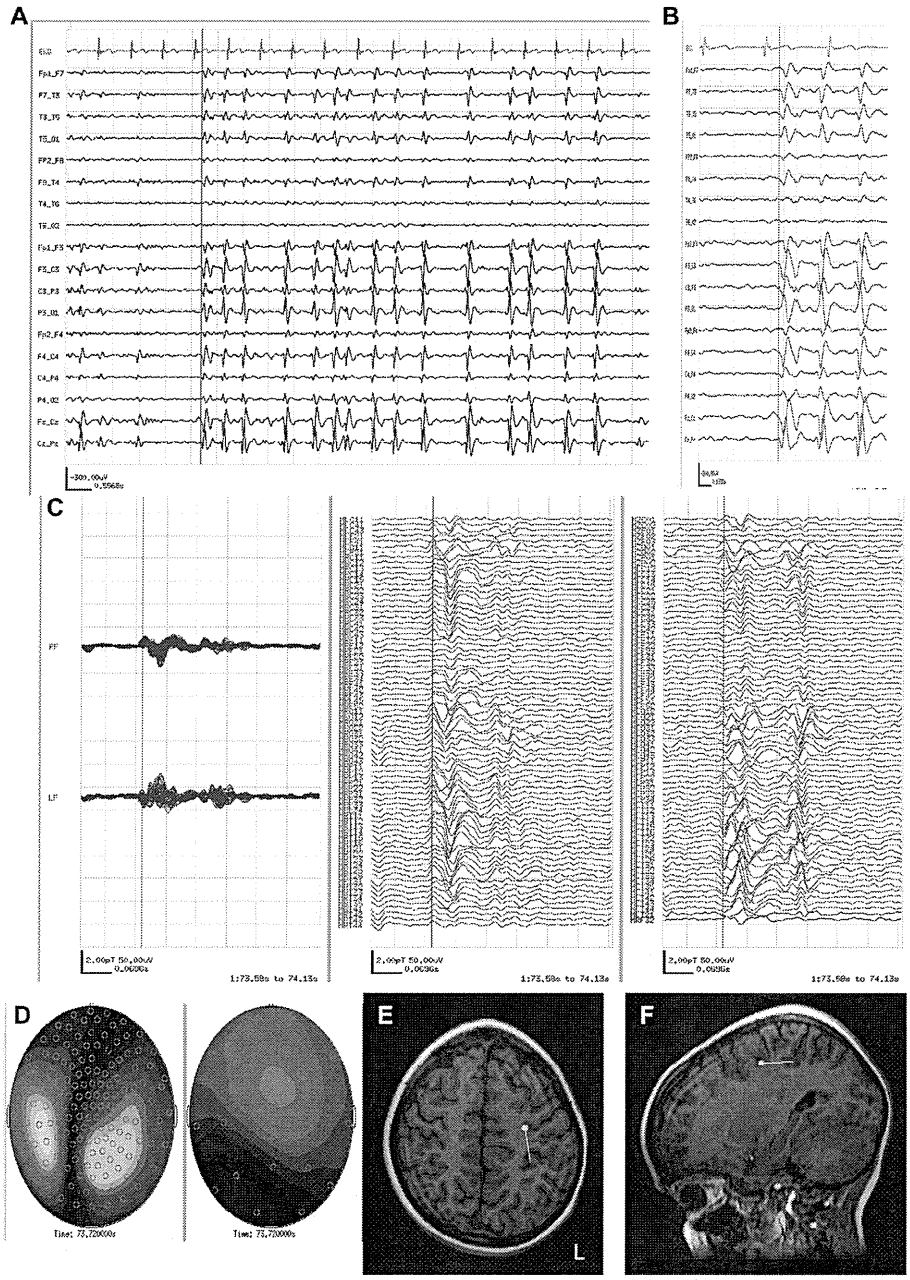

Fig. 1. MEG and EEG in case 18. (A) A–P bipolar EEG shows continuous spike and waves during sleep at the time of MEG study (low frequency filter, 3 Hz; high frequency filter, 70 Hz). (B) The same EEG of A is expanded to demonstrate left centro-temporal spikes preceding to the right central spikes after the red cursor. (C) 151 MEG channels are labeled by two colors (red for right hemisphere and blue for left hemisphere), and show the view of overlay (left), right channels (middle), and left channels (right). MEG shows more complex polyspikes than EEG on the overlay left channels. Note the MEG spikes (red cursor) leading to EEG spikes (behind the red cursor) on B. (D) MEG topography (left) and EEG topography (right). Note that magnetic and electric topographies are perpendicular to each other. (E) Axial MRI shows MEG spike source at the time of red cursor at the left Rolandic region (circle, position; tail, orientation, and moment). (F) Sagittal MRI shows the same MEG spike source of (E) at the left Rolandic region. The equivalent current dipole (spike source) is oriented horizontally, projecting negativity towards the frontal region and positivity towards the parietal region, corresponding to the EEG topography (D, right). (For interpretation of color in Fig. 1, the reader is referred to the web version of this article)

unilateral hemisphere in eight patients (44%). In all 10 patients with bilateral MEGSS, the MEGSS showed identical patterns and locations in the both hemispheres. ECD could not be estimated in one patient due to diffuse right hemispheric discharges without leading spikes. Therefore, we applied dSPM and localized the MEGSSs in the right sylvian fissure (Patient 7). Seven patients underwent multiple MEG studies. Six patients with

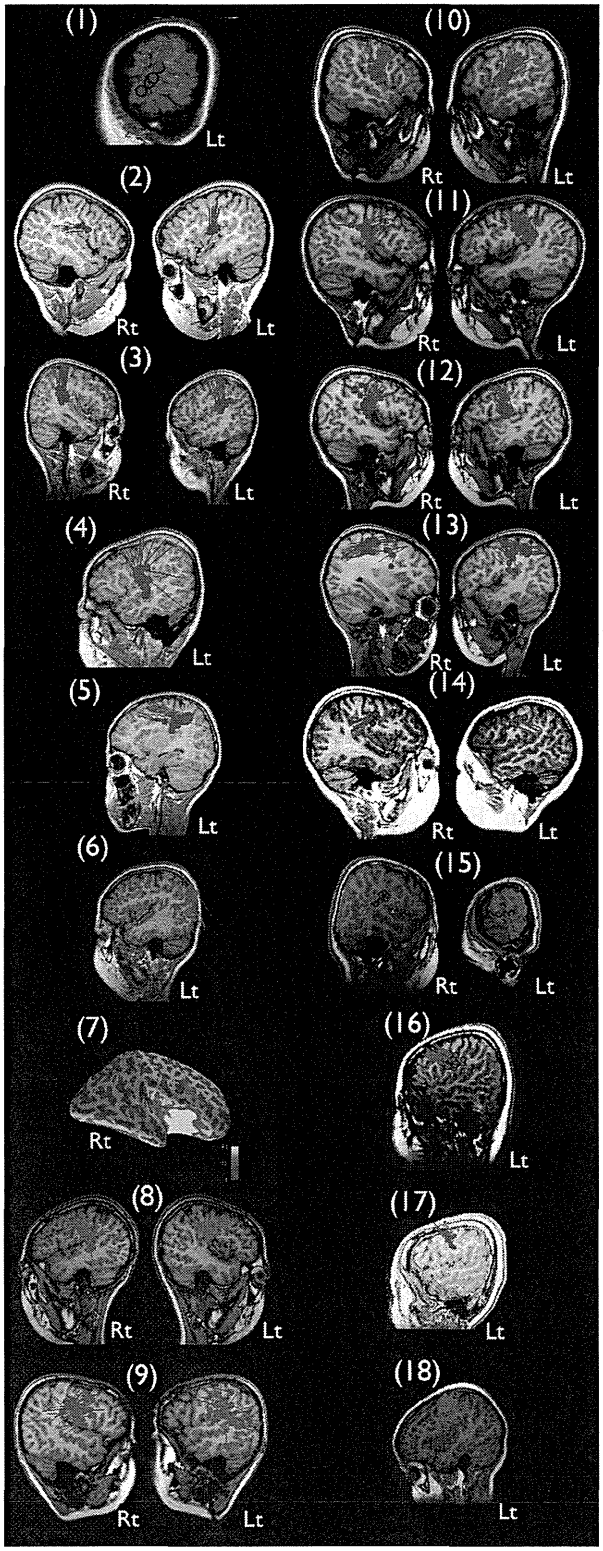

Fig. 2. MRI with MEG spike sources in 18 cases. Red circles demonstrate the source of MEG spikes. Tails indicate orientations and moments of the MEG spike sources. Case 7 shows dynamic statistical parametric mapping. The color bar indicates the P value, ranging from gray, 1×10^{-1} to yellow, $1 \times 10^{-4.3}$. (For interpretation of color in Fig. 1, the reader is referred to the web version of this article)

bilateral MEGSS became unilateral MEGSS. One patient showed consistent unilateral MEGSS. Six patients showed no MEGSS at the last MEG study when they were seizure free.

3.7. Treatments

All 18 patients were administered multiple antiepileptic medications ranging from 2 to 12 medications (mean 5.8) during their courses. Ethosuximide (ESM) succeeded in controlling various seizure types of ABPE, especially ENM and absences/atypical absences in 14 patients (78%); of these, all achieved seizure freedom after ESM was started, and 11 (89%) of the 14 were still on ESM at the last follow-up. Two of three patients in whom ESM was discontinued were no longer on any antiepileptic medication. CBZ was initially started in 16 patients (89%), but 14 (88%) experienced worsening of seizures after CBZ was initiated, and the treatment was discontinued. Two patients were seizure free on a combination of CBZ and ESM (Patient 6) or CBZ, ZNS and CLB (Patient 8). Valproic acid (VPA) was tried in 16 (89%) patients, and six of these (38%) were still on VPA at the last follow-up. Other medications tried included zonisamide (10 patients, 56%), clobazam (10 patients, 56%), clonazepam (eight patients, 44%) acetazolamide (five patients, 28%), phenytoin (five patients, 28%) and diazepam (four patients, 22%). The medications still being used at the last follow-up consisted of zonisamide in 3/10 patients (30%), clobazam in 4/10 patients (40%), clonazepam in 3/8 patients (38%), acetazolamide in 2/5 patients (40%) and diazepam in 2/4 patients (50%).

Two patients underwent epilepsy surgery. Patient 8 underwent cortical excision over the left supra-marginal gyrus at the age of 12 years. Surgical pathology revealed microdysgenesis with increased ganglion cells. She achieved 75–90% seizure reduction after the surgery, and was seizure free on three medications at 17.5 years old. Anterior two-thirds corpus callosotomy was performed at the age of 6 years for drop attacks in Patient 9. The patient was seizure free on two medications at 10 years old.

3.8. Seizure outcome

The age at last follow-up of the 18 patients ranged from 5.4 to 17.5 years (median 11.8 years). All were seizure free, two patients (11%) without any medication. Five patients (28%) were only on one medication, including four patients with ESM. The remaining 11 patients had multiple medications; six were on two medications, four were on three medications, and one patient was on four medications. Among seven patients with multiple MEG studies, medication changes, cognitive results effected less prominent for MEGSS than seizure improvements.

4. Discussion

MEG localized a Rolandic-sylvian epileptic focus of ABPE.

In ABPE, interictal MEG revealed localized clusters of spike sources around the Rolandic-sylvian fissures corresponding to both centro-temporal spikes and CSWS on EEG. The identically clustered Rolandic-sylvian MEGSSs of interictal epileptic discharges in patients with ABPE suggested that the epileptic focus was located around the Rolandic-sylvian regions involving the motor cortex in most cases. In our series, the peri-sylvian region MEGSSs were also recorded in 13 of 18 ABPE patients. In contrast, MEGSSs in BECTS were specifically localized along the Rolandic region with definite identical orientations vertical to the central sulcus [8,9]. In the older children with BECTS, MEGSSs shifted to the lower part of the Rolandic region close to the operculum.

Kubota et al. [10] reported an ictal MEG study localizing the spike source of ENM with generalized EEG spikes at the sylvian fissure in one ABPE patient [7]. ENM was characterized by spike or polyspikes on EEG time-locked to attenuation of EMG activity, which corresponded to muscle atonia [6]. Series of ENM often caused atonic seizures. Both interictal and ictal MEGSSs indicate that a subset of the epileptogenic zones responsible for focal seizures and ENM in ABPE patients is localized around the Rolandic-sylvian regions. In contrast, MEGSSs in three patients with Lennox–Gastaut syndrome with ENM were localized over inconsistent and various brain regions that did not include the Rolandic-sylvian regions [13].

Table 2
MEG spike source localization.

Patients	Regions			Hemispheres	
	Rolandic	Sylvian	Other lobe	Bilateral	Unilateral
1		1			1
2	1	1		1	
3		1		1	
4		1			1
5	1				1
6			Occipital		1
7		1			1
8	1	1		1	
9	1	1		1	
10		1		1	
11	1	1		1	
12	1	1		1	
13	1	1		1	
14	1			1	
15	1	1		1	
16	1				1
17	1				1
18	1	1			1
Total	12	13		10	8

Fifteen of eighteen patients in this series presented with focal motor seizures at the onset, and these persisted in addition to multiple other seizure types developing in 16 patients. ABPE might also be confused diagnostically with BECTS as ABPE appears superficially similar on scalp EEG and also presents with focal motor seizures. In ABPE patients, MEGSS extended to peri-sylvian region in addition to Rolandic region or localized even peri-sylvian region alone.

4.1. MEG localized spike dipoles in CSWS of ABPE

Sleep EEG often shows almost-continuous generalized or centro-temporal spike and waves during sleep in ABPE patients, resembling CSWS. Another differential diagnosis of ABPE is epileptic encephalopathy with CSWS (ECSWS), and there are no reports of source localizations using MEG in patients with ECSWS. The role of MEG remains to be explored in this entity. Kelemen et al. [17] reported three patients with CSWS secondary to destructive lesions in the thalamus [14], and CSWS development was often observed in patients with a thalamic lesion, indicative of thalamo-cortical dysfunction with an epileptic network [15,16]. ESM can be efficacious for seizures in ABPE patients, especially for ENM [6]. In 13 (72%) of the 18 ABPE patients studied herein, ESM completely suppressed their ENM. In other studies, systemic administration of ESM significantly reduced spike and wave discharges in genetic absence epilepsy models [17–19]. Continuous and generalized slow spike and waves during sleep in patients with ECSWS have been associated with secondary bilateral synchrony with leading foci [20,21]. The CSWS in ABPE could also be due to secondary bilateral synchrony, but originating specifically from the Rolandic-sylvian regions. The effect of ESM on the clinical seizures and CSWS indicates that the epileptic substitute of thalamic and Rolandic-sylvian networks produce ABPE.

Patry et al. [22] reported six patients with ECSWS, and heterogeneous seizure types of ECSWS that comprise focal motor seizures, absences, and epileptic falls while awake [21] resemble those of ABPE. Consequently, it can be difficult to distinguish ABPE from ECSWS clinically not analyzing the localization of epileptic foci. Further investigation of MEG in ECSWS may therefore serve to differentiate epileptic sources in these patients and improve our understanding of the epileptic networks and mechanisms leading to the observed cognitive disabilities.

5. Conclusions

MEG localized spike dipoles of centro-temporal spikes and CSWS over the Rolandic-sylvian regions in ABPE, indicating that ABPE is the localization-related