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Characteristics of infantile convulsions and choreoathetosis syndrome caused by *PRRT2* mutation

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ABSTRACT

Importance: Infantile convulsions and choreoathetosis (ICCA) is a rare neurological disorder. Many affected patients are either misdiagnosed or prescribed multiple antiepileptic drugs.

Objective: To explore therapeutic drug treatments and dosages for ICCA in children.

Methods: Detailed clinical features (e.g., past medical history and family history), genetic features, and treatment outcomes were collected from the records of six patients with ICCA.

Results: Mean age at paroxysmal kinesigenic dyskinesia (PKD) onset was 8 years 8 months (range, 3–12 years); the clinical presentation was characterized by daily short paroxysmal episodes of dystonia/dyskinesia. All patients had infantile convulsions at less than 1 year of age, and the mean onset age was 5.5 months (range, 4–7 months). Two patients had a family history of ICCA, PKD, or benign familial infantile epilepsy. Whole exome sequencing identified the c.649–650insC mutation in *PRRT2* in six patients; three mutations were inherited and three were *de novo*. All patients were prescribed low-dose carbamazepine and showed dramatic improvement with the complete disappearance of dyskinetic episodes after 3 days. They attended follow-up for 5–17 months and were attack-free until the final follow-up.

Interpretation: *PRRT2* mutations are the primary cause of ICCA. Low-dose carbamazepine monotherapy is effective and well-tolerated in children.

KEYWORDS

ICCA, Paroxysmal kinesigenic dyskinesia, *PRRT2*, Treatment

INTRODUCTION

Paroxysmal kinesigenic dyskinesia (PKD) (OMIM 128200) was first reported by Kertesz[1] and is the most common paroxysmal movement disorder, characterized by recurrent attacks of involuntary movements. PKD incidence is approximately 1: 150 000.[2] Usually, attacks occur after a trigger such as sudden movement or startle response. PKD

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can present in sporadic or familial form; in familial cases, the transmission is compatible with an autosomal dominant mode of inheritance. The co-occurrence of benign infantile epilepsy (BIE) or benign familial infantile epilepsy (BFIE) and PKD is known as infantile convulsion and choreoathetosis (ICCA) syndrome.[3,4]

Although instances of the proline-rich transmembrane protein-2 (PRRT2)-related BFIE, PKD, and ICCA have been reported since 2012,[5] many patients are either diagnosed incorrectly or cannot receive precise therapy because the mechanism underlying the effects of PRRT2 remains unclear. Recently, PRRT2 has been linked to the functions of $Na_v1.2$ and $Na_v1.6$ channels, as well as Ca^{2+}-dependent neurotransmitter release.[6,7] Considering the characteristics of PRRT2, it is advisable to treat these patients exhibiting *PRRT2* mutations with anticonvulsants that can target ion channels. This study was designed to evaluate the possibility of low-dose carbamazepine monotherapy for PKD in children.

METHODS

Ethical approval

This study was approved by the Research Ethics Board of Tiantan Hospital (KY 2020-145-02). Informed consent was obtained from the guardians of the patients.

Diagnosis and recruitment of patients

This study retrospectively collected patients who were clinically diagnosed with ICCA in Tiantan Hospital from January 2018 to December 2018. In this study, BIE was defined as epilepsy with onset during infancy, which met all of the following conditions: focal seizures, normal psychomotor development and neurological findings before onset, normal interictal electroencephalograms (EEGs), normal cranial CT, and MRI findings, and seizure freedom within 2 years of age. PKD was defined in accordance with the clinical diagnostic criteria established by Bruno et al.[2] in 2004: age at onset between 1 and 20 years, identified kinesigenic trigger for the attacks, short duration of attacks (<1 min), no pain or loss of consciousness during attacks, normal neurological examination results and no other organic diseases, and (if attempted) control of attacks with an antiepileptic drug (e.g., carbamazepine or phenytoin).

Six non-blood-related patients were enrolled; all patients were of Han Chinese descent. We recorded the following information for each patient: PKD status, history of convulsion, and family history of convulsion and/or PKD.

Each patient underwent a 24-h ambulatory EEG examination following an attack induced by sudden movement. All patients underwent blood examination, urine metabolic screening, and head MRI to exclude secondary PKD. *PRRT2* mutation analysis was performed by whole-exome sequencing in children; the selected sites were verified by Sanger sequencing.

Carbamazepine was prescribed for all patients. The initial dosage was 50 mg per dose, twice daily ($2–5\ mg \cdot kg^{-1} \cdot day^{-1}$). If attacks were not controlled, the dosage could be gradually increased at 3-day intervals. Patients were followed up by telephone or during a clinic visit.

RESULTS

Clinical characteristics of patients

Overall summaries of clinical features are presented in Tables 1 and 2. Six patients were enrolled in this study (four boys and two girls); the median age at PKD onset was 8 years 8 months (range, 3–12 years). The median duration of movement disorder before presentation to our outpatient clinic for diagnosis was 28.5 months (range, 2–48 months). The duration of each attack was < 40 s (range, 5–40 s), and the frequency ranged from four attacks daily to > 10 attacks daily. Triggers resulting in movement disorder included sudden movement ($n = 6$) (e.g., sudden standing, running, or jumping), stress or emotional excitement ($n = 2$), and sudden acceleration while running ($n = 2$). The characteristics of the attacks were variable, but most patients had episodic dystonia (e.g., twisting movement or choreoathetosis). Furthermore, most patients could not move during the first few seconds after suddenly standing. No altered consciousness was reported during any attacks. In two patients, attacks began with a brief sensory aura (i.e., "numbness" within the involved body parts). Occasionally, patients could terminate movement when they felt the aura; this required initiation of specific movement with the affected limb before attack onset. Medical history review indicated that all six patients had an infantile convulsion. The mean age at convulsion onset was 5.5 ± 1.1 months (range, 4–7 months). Two patients had ≤5 seizures, whereas four patients had >10 seizures and reported clusters of seizures. No patients exhibited status epilepticus. One patient had been administered carbamazepine and two patients had been administered valproate as antiepileptic therapy. Seizures ceased after 20 days to 2 months in all six patients. The duration of drug therapy was 2 years.

Detailed neurological examination revealed that birth and development were unremarkable in all patients. Two patients had positive family histories: in the family of patient 1, 18 members had a history of PKD, BFIE, or

TABLE 1 Summary of clinical features and family histories of patients with infantile convulsions and choreoathetosis (ICCA)

Patient number	Sex	Age at PKD onset (year)	Time from onset to diagnosis (month)	Description of attack	Trigger causes	Duration of attack (second)	Frequency of attack (per day)	*PRRT2* mutations	Response to treatment	Follow-up (month)	Family history
1	F	8	48	Choreoathetosis Dystonia	SM Excitement Startle	5–30	4–10	c.649_650insC Father source	+	5	3 ICCA 12 BFIE 3 PKD
2	M	9.7	2	Dystonia	SM	10	>10	c.649_650insC Father source	+	5	1 ICCA 2 BFIE 1 PKD
3	F	3	25	Dystonia	SM Startle	10–40	4–5	c.649_650insC Mother source	+	5	No
4	M	8	48	Dystonia	SM Excitement	5–20	4–12	c.649_650insC *de novo*	+	9	No
5	M	12	24	Choreoathetosis Dystonia	SM	<10	5–12	c.649_650insC *de novo*	+	17	No
6	M	12	24	Dystonia	SM	10–30	3–5	c.649_650insC *de novo*	+	17	No

Abbreviations: BFIE, benign familial infantile epilepsy; F, female; ICCA, infantile convulsions and choreoathetosis; M, male; PKD, paroxysmal kinesigenic dyskinesia; SM, sudden movement; "+", effective.

TABLE 2 Summary of clinical features of seizures among patients with infantile convulsions and choreoathetosis (ICCA)

Patient number	Age at seizure onset (month)	Seizure type	Duration of seizure (min)	Times of seizure	Cluster seizure/SE	Treatment (drug) and response	Duration of taking drug	Family history of seizure
1	7	Focal	<1	5	No/No	None	None	Yes
2	5	Focal	<1	>10	Yes/No	VPA, effective	2 years	Yes
3	6	Focal	<1	>10	Yes/No	CBZ, effective	2 years	No
4	5	Focal	<1	>10	Yes/No	VPA, effective	2 years	No
5	4	Focal, GTC	1	>10	Yes/No	None	None	No
6	6	Focal, GTC	<1	2	No/No	None	None	No

Abbreviations: CBZ, carbamazepine; GTC, generalized tonic-clonic seizure; SE, status epilepticus; VPA, valproic acid.

ICCA; in the family of patient 2, four members had a history of PKD, BFIE, or ICCA.

Auxiliary test findings

All patients' physical and neurological examinations produced unremarkable results. MRI of the brain, 24-h EEG, and laboratory analyses (complete blood count, plasma lactate, T3, T4, TSH, erythrocyte sedimentation rate, anti-streptolysin antibody, anti-nuclear antibodies, anti-phospholipid antibodies, and urine organic acids) produced normal results. A *PRRT2* gene variant was detected in all patients; the mutation site (c.649_650insC/p.R217Pfs*8) is consistent with previous reports,[8,9] and the prevalence in the general population is <1 in 1000 (0.00026). Overall, one patient inherited the mutation from her asymptomatic mother, two patients inherited the mutation from their symptomatic fathers (ICCA), and three patients had *de novo* mutations.

Treatment and outcome

No patients had received any medicine after PKD onset. The initial dosage of carbamazepine was 50 mg, twice daily, for all participants (range, 2–5 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}). All patients showed a dramatic improvement with complete resolution of episodes after 3 days of carbamazepine intake. During the follow-up maintenance dose phase, all patients remained attack-free. No side effects were reported. Patient 5 decreased carbamazepine to 50 mg daily (1 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) 4 months later and did not report recurrence until the final follow-up (6 months after initiation of carbamazepine treatment). The mean duration of follow-up was 9.7 $\pm$ 5.9 months (range, 5–17 months).

DISCUSSION

Paroxysmal dyskinesias comprises a group of episodic movement disorders, was first described in 1967.[1] Additionally, Demirkiran and Jankovic divided paroxysmal

dyskinesias into four main types according to the inducing factor: PKD, paroxysmal non-kinesigenic dyskinesia, paroxysmal hypnogenic dyskinesia, and paroxysmal exercise-induced dyskinesia. These disorders were further subdivided into idiopathic and secondary, according to their etiologies.[10] PKD is the most common form of paroxysmal dyskinesia. In 2011, Chen et al.[5] identified *PRRT2* as the causative gene of PKD. Wang et al.[9] identified the same *PRRT2* mutation as the causative gene of PKD and BFIE which is characterized by clusters of epileptic seizures in infancy. In some patients, infantile seizures and PKD occur concurrently; this is known as ICCA syndrome.

PRRT2 gene mutations are associated with various benign paroxysmal diseases, recently referred to as *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMD).[11,12] Among all patients with *PRRT2* sequence variants, ICCA is present in approximately 14.1%–16.7%.[13] The same mutation site in *PRRT2* can cause distinct clinical manifestations in different patients in a single-family. Multiple genes are presumed to have slightly different effects on *PRRT2* gene expression. In our cohort, patients presented with convulsion in infancy, followed by PKD in childhood and adolescence. Within the same family, the presentation can differ; patients may present with PKD, BFIE, or ICCA.

Diseases with *PRRT2* mutations have some common characteristics. First, the presentations are paroxysmal. Second, some aspects of treatment are similar. Patients with PKD, BFIE, or ICCA generally respond well to anticonvulsants.[12] Recently, Fruscione et al.[7] reported that *PRRT2* controls neuronal excitability by interacting with $Na_v1.2$ and $Na_v1.6$ channels, which negatively modulates their membrane expression levels. Valente et al.[6] reported that *PRRT2* is an important component of the Ca^{2+}-dependent neurotransmitter release machinery. *PRRT2* sequence variants have been shown to cause PRRT2 loss-of-function, impaired SNAP25 interaction, enhanced intracellular glutamate levels, and increased neuronal hyperexcitability.[8,14] Considering the characteristics of *PRRT2*, it is advisable to treat these patients exhibiting *PRRT2* mutations patients with anticonvulsants that can target ion channels. These findings also proved that PKD, BFIE, and ICCA function as channelopathies because transmitter release is triggered by the influx of some ions resulting from an action potential. This may also explain why two patients with homozygous *PRRT2* mutations exhibited a poor BFIE/PKD phenotype but responded well to carbamazepine.[15]

Among our patients, 24-h EEG findings were normal, regardless of dyskinesia onset. Interictal EEG examinations performed in infants with infant convulsion revealed multifocal spikes or spike waves from various locations in two patients who were diagnosed with BFIE. This is consistent with the findings described by van Roest et al.[16] in 2019. In our study, the median age at BFIE onset was 5 months; seizures ceased after 1–2 months. This is consistent with the report from Okumura et al.[17] Treatment is theoretically not indicated in patients with BFIE; watchful waiting is appropriate after the first afebrile seizure in patients with the familial disease.[18] However, if seizures reoccur frequently, anticonvulsant therapy should be considered.[19] Currently, therapy is indicated in patients with cluster seizures, and an early genetic diagnosis can enable targeted therapy.[20] For patients with *PRRT2* variants, carbamazepine is the drug of choice for the cessation of clustered seizures in infants.[21] Among our patients, three had been prescribed carbamazepine or valproate and then experienced cessation of seizures; two patients did not receive any anticonvulsant drugs and had experienced cessation of seizures after 1 year, consistent with previous findings.[17,22] Withdrawal of antiepileptic drugs was based on clinical evolution and genetic analysis results. However, before 2012, rapid genetic testing was not available and therefore patients received extended courses of treatment. The current recommendation involves treatment cessation after 2 years of seizure freedom.

In clinical practice, antiepileptic drugs such as carbamazepine and oxcarbazepine are the first choice for PKD treatment; other sodium ion channel blockers have been suggested. However, no studies have proposed a specific dosage; in most reports, the dosages of carbamazepine and oxcarbazepine have been higher. In our study, all patients exhibited idiopathic disease and had a history of infantile convulsion. Each patient attained complete resolution of clinical signs with low-dose carbamazepine treatment ($1–5\ mg \cdot kg^{-1} \cdot day^{-1}$); no patients reported any side effects of the medication. The excellent therapeutic outcomes may be related to the carbamazepine mechanism of action. Several other anticonvulsants, including lamotrigine, are also effective in treating PKD.[23]

We observed an extensive history of disease in the family of one patient (18 members with PKD, BFIE, or ICCA); another patient had a smaller number of family members with ICCA, and another patient's family carried an asymptomatic *PRRT2* variant. In all patients, symptoms largely disappeared in adulthood. However, because this study was retrospective, the data concerning family history may have been insufficient or inaccurate. Other limitations in this study included the small number of patients and the short follow-up duration. Prospective, multicenter studies are required to determine the efficacy and safety of carbamazepine.

Our report illustrates the efficacy of low-dose carbamazepine in the treatment of PKD. With its generally mild side-effect profile, compared with many of the older

anticonvulsants (e.g., phenytoin and anticonvulsants that influence the development of intelligence and speech), low-dose carbamazepine may be a superior treatment for PKD. The results of this study will provide useful basic information for genetic counseling regarding clinical symptoms, time course, and prognosis for patients with *PRRT2* mutations.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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