Characteristics of infantile convulsions and choreoathetosis syndrome caused by PRRT2 mutation

Yaxian Deng1 | Juanyu Xu1 | Chunmei Yao1 | Lei Wang1 | Xiaohuan Dong1 | Chengsong Zhao2

1Department of Pediatrics, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
2Department of Outpatient, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China

Correspondence
Yaxian Deng, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China.
Email: dengyx77@163.com
Chengsong Zhao, Department of Outpatient, Beijing Children’s Hospital, Capital Medical University, Beijing 100045, China.
Email: zhaochensong@bch.com.cn

Received: 25 May 2021
Accepted: 25 August 2021

INTRODUCTION
Paroxysmal kinesigenic dyskinesia (PKD) (OMIM 128200) was first reported by Kertesz1 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

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

DOI: 10.1002/ped4.12308

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 Chinese Medical Association. Pediatric Investigation published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.
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\(_1\) 1.2 and Na\(_1\) 1.6 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 · kg\(^{-1}\) · 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 | 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                                   | Choreoathetosis       | SM Excitement Stirke | 5–30            | 4–10                        | c.649_650insC     | Father source      | 5                 | 3 ICCA          |
|                |                         |                                     | Dystonia              | SM Excitement Stirke |                |                             | p.R217Pfs<8       |                   |                    | 12 BFIE         |
|                |                         |                                     |                       | SM Excitement Stirke |                |                             |                 |                    |                   | 3 PKD           |
| 2              | M                       | 9.7                                 | Dystonia              | SM Excitement Stirke | 10             | >10                         | c.649_650insC     | Father source      | 5                 | 1 ICCA          |
|                |                         |                                     |                       | SM Excitement Stirke |                |                             | p.R217Pfs<8       |                   |                    | 2 BFIE          |
|                |                         |                                     |                       | SM Excitement Stirke |                |                             |                 |                    |                   | 1 PKD           |
| 3              | F                       | 3                                   | Dystonia              | SM Excitement Stirke | 10–40          | 4–5                         | c.649_650insC     | Mother source      | 5                 | No              |
| 4              | M                       | 8                                   | Dystonia              | SM Excitement Stirke | 5–20            | 4–12                        | c.649_650insC     | de novo           | 9                 | No              |
| 5              | M                       | 12                                  | Dystonia              | SM Excitement Stirke | <10            | 5–12                        | c.649_650insC     | de novo           | 17                | No              |
| 6              | M                       | 12                                  | Dystonia              | SM Excitement Stirke | 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, 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 · kg⁻¹ · 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 · kg⁻¹ · 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 ± 5.9 months (range, 5–17 months).

DISCUSSION

Paroxysmal dyskinesias comprises a group of episodic movement disorders, was first described in 1967. Additionally, Demirkiran and Jankovic divided paroxysmal
dyskinesias into four main types according to the inducing factor: PKD, paroxysmal non-kinetic dyskinesia, paroxysmal hypnogenic dyskinesia, and paroxysmal exercise-induced dyskinesia. These disorders were further subdivided into idiopathic and secondary, according to their etiologies. PKD is the most common form of paroxysmal dyskinesia. In 2011, Chen et al. identified PRRT2 as the causative gene of PKD. Wang et al. 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). Among all patients with PRRT2 sequence variants, ICCA is present in approximately 14.1%–16.7%. 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. Recently, Fruscione et al. reported that PRRT2 controls neuronal excitability by interacting with Na\textsubscript{v}1.2 and Na\textsubscript{v}1.6 channels, which negatively modulates their membrane expression levels. Valente et al. reported that PRRT2 is an important component of the Ca\textsuperscript{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. 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.

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. 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. Treatment is theoretically not indicated in patients with BFIE; watchful waiting is appropriate after the first afebrile seizure in patients with the familial disease. However, if seizures reoccur frequently, anticonvulsant therapy should be considered. Currently, therapy is indicated in patients with cluster seizures, and an early genetic diagnosis can enable targeted therapy. For patients with PRRT2 variants, carbamazepine is the drug of choice for the cessation of clustered seizures in infants. 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. 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 kg\textsuperscript{-1} day\textsuperscript{-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.

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.

REFERENCES
1. Kertesz A. Paroxysmal kinesigenic choreoathetosis. An entity within the paroxysmal choreoathetosis syndrome. Description of 10 cases, including 1 autopsied. Neurology. 1967;17:680-690. DOI: 10.1212/wnl.17.7.680
2. Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology. 2004;63:2280-2287. DOI: 10.1212/01.wnl.0000147298.05983.50
3. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512-521. DOI: 10.1111/epi.13709
4. Szepetowski P, Rochette J, Berquin P, Piussan C, Lathrop GM, Monaco AP. Familial infantile convulsions and paroxysmal choreoathetosis: a new neurological syndrome linked to the pericentromeric region of human chromosome 16. Am J Hum Genet. 1997;61:889-898. DOI: 10.1086/514877
5. Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet. 2011;43:1252-1255. DOI: 10.1038/ng.1008
6. Valente P, Castellofiorio E, Rossi P, Fadda M, Sterlini B, Cervigni R, et al. PRRT2 is a key component of the Ca2+-dependent neurotransmitter release machinery. Cell Rep. 2016;15:117-131. DOI: 10.1016/j.celrep.2016.03.005
7. Fruscione F, Valente P, Sterlini B, Romei A, Baldassari S, Fadda M, et al. PRRT2 controls neuronal excitability by negatively modulating Na+ channel 1.2/1.6 activity. Brain. 2018;141:1000-1016. DOI: 10.1093/brain/awy051
8. Lee HY, Huang Y, Bruneau N, Roll P, Roberson ED, Hermann M, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep. 2012;1:1-2. DOI: 10.1016/j.celrep.2011.11.001
9. Wang JL, Mao X, Hu ZM, Li JD, Li N, Guo JF, et al. Mutation analysis of PRRT2 in two Chinese BFIS families and nomenclature of PRRT2 related paroxysmal diseases. Neurosci Lett. 2013;552:40-45. DOI: 10.1016/j.neulet.2013.07.020
10. Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. Ann Neurol. 1995;38:571-579. DOI: 10.1002/ana.410380405
11. Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain. 2015;138:3476-3495. DOI: 10.1093/brain/awv317
12. van Vliet R, Breedveld G, de Rijk-van Andel J, Brilstra E, Verbeek N, Verschuren-Bemelmans C, et al. PRRT2 phenotypes and penetrance of paroxysmal kinesigenic dyskinesia and infantile convulsions. Neurology. 2012;79:777-784. DOI: 10.1212/WNL.0b013e318266fe3
13. Vlaskamp D, Callenbach P, Rump P, Giannini L, Brilstra EH, Dijkhuizen T, et al. PRRT2-related phenotypes in patients with a 16p11.2 deletion. Eur J Med Genet. 2019;62:265-269. DOI: 10.1016/j.ejmg.2018.08.002
14. Li M, Niu F, Zhu X, Wu X, Shen N, Peng X, et al. PRRT2 mutant leads to dysfunction of glutamate signaling. Int J Mol Sci. 2015;16:9134-9151. DOI: 10.3390/ijms16059134
15. Vazquez B. Monotherapy in epilepsy: role of the newer antiepileptic drugs. Arch Neurol. 2004;61:1361-1365. DOI: 10.1001/archneur.61.9.1361
16. van Roest A, Van de Vel A, Lederer D, Ceulemans B. The clinical and genetic spectrum in infants with (an) unprovoked cluster(s) of focal seizures. Eur J Paediatr Neurol. 2020;24:148-153. DOI: 10.1016/j.ejpn.2019.12.003
17. Okumura A, Shimojiima K, Kuraishi H, Numoto S, Shimada S, Ishii A, et al. PRRT2 mutations in Japanese patients with benign infantile epilepsy and paroxysmal kinesigenic dyskinesia. Seizure. 2019;71:1-5. DOI: 10.1016/j.seizure.2019.05.017
18. Vigevano F. Benign familial infantile seizures. Brain Dev. 2005;27:172-177. DOI: 10.1016/j.braindev.2003.12.012
19. Wilsnashurst JM, Gaillard WD, Vinayan KP, Tsuchida TN, Plouin P, Van Bogaert P, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56:1185-1197. DOI: 10.1111/epi.13057
20. Lee EH. Epilepsy syndromes during the first year of life and the usefulness of an epilepsy gene panel. Korean J Pediatr. 2018;61:101-107. DOI: 10.3345/kjp.2018.61.4.101
21. Djordjevic N, Jankovic SM, Milovanovic JR. Pharmacokinetics and pharmacogenetics of carbamazepine in children. Eur J Drug Metab Pharmacokinet. 2017;42:729-744. DOI: 10.1007/s13318-016-0397-3
22. Zhao G, Liu X, Zhang Q, Wang K. PRRT2 mutations in a cohort of Chinese families with paroxysmal kinesigenic dyskinesia and genotype-phenotype correlation reanalysis in literatures. Int J Neurosci. 2018;128:751-760. DOI: 10.1080/00207454.2017.1418345
23. Li F, Lin ZD, Hu Y, Li W, Xue CC, Poonit ND. Lamotrigine monotherapy for paroxysmal kinesigenic dyskinesia in children. Seizure. 2016;37:41-44. DOI: 10.1016/j.seizure.2016.02.009

How to cite this article: Deng Y, Xu J, Yao C, Wang, L, Dong X, Zhao C. Characteristics of infantile convulsions and choreoathetosis syndrome caused by PRRT2 mutation. Pediatr Investig. 2022;6:11-15. https://doi.org/10.1002/ped4.12308