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# Lamotrigine monotherapy for paroxysmal kinesigenic dyskinesia in children

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ABSTRACT

*Purpose:* To evaluate the efficacy and tolerability of lamotrigine monotherapy in children with paroxysmal kinesigenic dyskinesia.
*Method:* A sample of eighteen children aged between 2 years old and 13 years old who fulfilled the diagnostic criteria from January 2008 to December 2014 was enrolled, they received video electroencephalography, brain image scans and proline-rich transmembrane protein 2 genetic tests. Children with known or suspected diseases which would cause secondary paroxysmal kinesigenic dyskinesia were excluded. The initial dosage of lamotrigine was 6.25 mg, and it was gradually increased every week until attacks were controlled. Patients entered the maintenance dose phase upon reaching the effective dosage, and by being attack free at two consecutive outpatient visits. They were followed up for a couple of years until December 2014.
*Results:* By the end of the 4th week, the attack-free rate reached 100% among all the patients. During the maintenance dose phase, 16 patients remained attack free, 2 patients received additional drug due to attack relapses when they entered puberty. Three patients had relapses because of non-compliance to the therapy, but they became attack free as soon as they re-started the medicine. The mean daily dosage was 26.4 mg (range 6.25–50). Definite adverse effect related to the drug was not reported in follow up.
*Conclusion:* LTG monotherapy is effective and well tolerated for PKD in children.


## 1. Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is the most common paroxysmal movement disorder, characterized by recurrent attacks of dyskinesia which is triggered by sudden voluntary movement. These attacks are usually brief, and could last from a few seconds to one minute, and they occur multiple times per day [1,2].

The scanned brain image and electroencephalography (EEG) of such patients are usually normal [3], however, mutations of proline-rich transmembrane protein 2 (PRRT2) have recently been identified in PKD [4]. The most common drugs used for PKD treatment in the clinical at present are carbamazepine (CBZ) and oxcarbazepine (OXC) [5]. While lamotrigine (LTG) is also effective based on a few sporadic case reports [6], but clinical researches that proves LTG's effectiveness is very limited.

The study reported herein is designed as an evaluation of the possibility of LTG monotherapy for PKD in children. The goal is to seek how many children would become attack free, the amount of drug which is effective, and whether there is genetic or behavior predictors for response to LTG.

## 2. Methods

Written informed consent has been obtained from the parents prior to enrolment and this study was performed in Department of Pediatric Neurology, the Second Affiliated Hospital & Yuying Children's Hospital, Wenzhou Medical University. The research

*Abbreviations:* BFIE, benign familial infantile epilepsy; BFNE, benign familial neonatal epilepsy; CBZ, carbamazepine; CwG, convulsions with gastroenteritis; EEG, electroencephalography; HM, families with hemiplegic migraine; ICCA, infantile convulsions with choreoathetosis; LTG, lamotrigine; OXC, oxcarbazepine; PKD, paroxysmal kinesigenic dyskinesia; PRRT2, proline-rich transmembrane protein 2.

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was registered in Chinese Clinical Trial Registry (ChiCTR-OPC-15006294).

### 2.1. Patients

Eighteen non-blood related patients <16 years old were enrolled. All the patients were of Han Chinese descents and diagnosed with PKD according to the clinical diagnostic criteria of Bruno in 2004 [7].

- Identified kinesigenic trigger for the attacks.
- Short duration of attacks (<1 min).
- No loss of consciousness and no pain during attacks; Exclusion of other organic diseases and normal neurologic examination results.
- Control of attacks with an antiepileptic drug such as carbamazepine or phenytoin, if tried.
- Age at onset between 1 and 20 years if no family history of PKD. Age criteria might not be as important in the familial cases.

### 2.2. Procedures and assessments

Every patient enrolled received a video-EEG more than 4 h of duration during which each patient was allowed to fall asleep naturally. When awake the patient is asked to do his/her own trigger action such as sudden movement to induce the attack.

LTG was titrated and given in escalation dose. The dosage started from 6.25 mg per day, and gradually increased every week until attacks were controlled. Patients entered the maintenance dose phase upon reaching their effective dosage, by being attack free at two consecutive outpatient visits. They were followed up in the Child Neurology Department from January 2008 to December 2014. The data were collected and analyzed with simple correlation, *t*-test or *F* test in SPSS 17.0. Statistical significance was defined as $P < 0.05$.

## 3. Results

Eighteen patients were enrolled in this study, 13 males and 5 females; the mean age of onset was $7.89 \pm 3.03$ years (range 2–12). According to the parents, all attack-durations were less than 30 s, and the frequency ranged from less than 1 time per day to more than 10 times per day. In our research, top three triggers were sudden movement (18/18), intention to move (8/18) and stress (2/18). Three patients had failed trial of OXC, and the others had no past drug history. All the patients had normal video-EEGs and brain CT or MRI scans. Fourteen patients had a positive family history and 4 patients were apparently sporadic cases. Family history was considered positive if a patient had at least one affected relative within three generations. Mutations of PRRT2 gene were found in 15 patients (c.649dupC in 12 cases, c.291delC in 3 cases). Seven patients had experienced febrile convulsions, focal seizure or afebrile infantile seizure before. The mean period of following up was $39.2 \pm 16.9$ months (range 9–73). Demographics and clinical characteristics were presented in Table 1. The initial dosage of 6.25 mg was same for all participants (range 0.104–0.568 mg/kg), and gradually increased every week. By the end of the 4th week, all (18/18) patients were attack free. At maintenance dose phase, mean serum concentration was $0.87 \pm 0.33$ μg/ml (range 0.22–1.42), and mean daily dosage was $26.39 \pm 13.31$ mg (range 6.25–50), no statistical differences were found in our study between young children and older ones or their disparity in weights or ages of onset, see Tables 2 and 3.

During maintenance dose phase in follow up, 89% (16/18) patients remained attack free. Most patients did not require additional drug during follow up except two (case 8 and 17) whose attacks relapsed when they entered puberty at 10 and 9 years old respectively. Three patients (case 3, 13 and 15) had relapses because of non-compliance to the therapy, but they became attack free as soon as they re-started the medicine. These factors may affect the amount of effective dosage such as sex, family history, PRRT2 mutations, history of epileptic seizures, trigger causes, duration of attack and frequency of attack, but none had statistical significance, see Table 4. Rash and pruritus were seen on trunks of 2 patients, both temporary and mild, but it is not certain to be related to LTG. No patients withdrew at any point from the study, see Table 2.

## 4. Discussion

PKD is the most common form of paroxysmal dyskinesia, patients always can describe their feeling about the attacks. The

**Table 1**
Clinical data of enrolled patients.

| Number | Sex | Age of onset (*Y*) | Trigger causes | Duration of attack (s) | Frequency of attack | PRRT2 mutations | Medication before (WC) | Follow-up (Mon) | Familial/AS | History of epileptic seizures |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 8 | SM | <15 | >10 per day | c.649dupC | OXC (no effect) | 73 | Familial | FC |
| 2 | M | 10 | SM/IM | <20 | 5–10 per day | None | None | 65 | AS | None |
| 3 | M | 10 | SM | <10 | >10 per day | c.649dupC | None | 54 | AS | FS |
| 4 | M | 7 | SM/IM | <30 | 5–10 per day | c.649dupC | None | 51 | Familial | None |
| 5 | M | 6 | SM | <30 | 1–5 per day | c.649dupC | None | 50 | AS | AIS |
| 6 | M | 5 | SM/S | <20 | 1–5 per day | c.649dupC | None | 49 | Familial | None |
| 7 | F | 12 | SM | <10 | 5–10 per day | c.649dupC | OXC (rash) | 46 | Familial | FC |
| 8 | F | 8 | SM/IM | <5 | 1–5 per day | c.291delC | None | 45 | Familial | None |
| 9 | M | 10 | SM/IM | <20 | >10 per day | c.649dupC | OXC (rash) | 39 | Familial | AIS |
| 10 | F | 3 | SM | <30 | 1–10 per day | c.649dupC | None | 38 | Familial | None |
| 11 | F | 4 | SM/IM | <30 | <1 per day | none | None | 36 | Familial | None |
| 12 | F | 11 | SM | <10 | 1–10 per day | c.649dupC | None | 34 | Familial | FS |
| 13 | M | 2 | SM/IM | <20 | <1 per day | c.291delC | None | 30 | Familial | None |
| 14 | M | 12 | SM | <5 | 1–10 per day | c.291delC | None | 27 | Familial | None |
| 15 | M | 10 | SM | <5 | 1–10 per day | c.649dupC | None | 25 | Familial | None |
| 16 | M | 6 | SM | <20 | 1–10 per day | c.649dupC | None | 19 | Familial | AIS |
| 17 | M | 8 | SM/IM | <30 | 1–10 per day | c.649dupC | None | 15 | Familial | None |
| 18 | M | 10 | SM/IM/S | <5 | <1 per day | None | None | 9 | AS | None |

Y, years; Mon, months; M, male; F, female; WC, withdrew cause; FC, febrile convulsions; FS, focal seizure; AIS, afebrile infantile seizure; AS, apparently sporadic; SM, sudden movements; IM, intention to move; S, stress; OXC, oxcarbazepine.