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The study of exercise tests in paroxysmal kinesigenic dyskinesia

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HIGHLIGHTS

- Paroxysmal kinesigenic dyskinesia (PKD) had distinct patterns in the long exercise test (LET).
- The differentiated PKD patients presented with greater amplitude increment than area in the LET.
- Abnormal muscle membrane excitability might be involved in the mechanisms responsible for PKD.

ABSTRACT

Objective: To unravel if there was muscular ion channel dysfunction in paroxysmal kinesigenic dyskinesia (PKD) patients using the exercises tests (ET).
Methods: Sixty PKD patients including 28 *PRRT2* mutations carriers were enrolled in this study, as well as 19 hypokalaemic periodic paralysis (HypoPP) patients as the positive controls and 45 healthy subjects as the negative controls. ET including long exercise test (LET) and short exercise test (SET) was performed in the corresponding subjects.
Results: In the LET, both the overall PKD patients and HypoPP patients had greater CMAP amplitude and area increments during exercise than healthy controls. At most 25% of PKD patients were identified from the normality with greater amplitude increment than the area. On the contrary, 50% of HypoPP patients were differentiated with greater area increment than the amplitude. More percentage of *PRRT2*− patients than *PRRT2+* patients had abnormal average amplitude increment. Unexpectedly, five PKD patients had abnormal maximum CMAP amplitude decrements after exercise in the LET, and one had abnormal maximum immediate amplitude decrement in the SET.
Conclusions: Distinct ET manifestations were found in PKD patients compared to normal controls and HypoPP patients.
Significance: Abnormal muscle membrane excitability might be involved in the mechanisms responsible for PKD.

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1. Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is the most common type of the paroxysmal movement disorders, which is characterized by transient and recurrent dystonic or choreoathetoid attacks triggered by sudden voluntary movements (Bruno et al., 2004, Gardiner et al., 2015). The knowledge of PKD has been accumulating recently; however, the underlying mechanisms remain mysterious. One hypothesis about PKD is that it could be a central nervous system ionic channelpathy (Bhatia et al., 2000, Celesia, 2001, Chen et al., 2011), since the attacks are often responsive effectively to the ion channel blockers (Huang et al., 2015). Clinically it was ever easily misdiagnosed as epilepsy, but recently it was also found to be confused with myotonia congenita (MC) (Kim et al., 2018). Indeed, PKD and MC do share some clinical phenomena. For example, sudden movements often trigger the attacks, while keeping exercises or warm-up exercises often relieve the attacks. In addition, both of them respond favorably to sodium-channel blockers (Conravey and Santana-Gould, 2010, Li et al., 2013). There was also a report about coexistence of one

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proline-rich transmembrane protein 2 *(PRRT2)* mutation and two chloride channel gene (*CLCN1*) mutations detected in a patient diagnosed with PKD and suspected MC (Li et al., 2014), which suggesting that certain interaction might exist between those two genes. That the mRNA of *PRRT2* tends to express extensively including in the periphery nerves and skeleton muscles (http://www.genecards.org) also makes this hypothesis have certain rationality. Therefore, it is intriguing to explore whether the peripheral mechanisms involved in PKD. The exercise tests (ET) are often used to diagnose skeleton muscular ion channelopathies and could reflect the muscle membrane excitability (Cannon, 2015, Fournier et al., 2004, Kuntzer et al., 2000). Here, in order to explore if there were abnormal ET patterns in PKD, we designed a cohort study with 60 PKD patients involved, 19 hypokalaemic periodic paralysis (HypoPP) patients as positive controls and 45 healthy volunteers as negative controls.

2. Methods

2.1. Patients and controls

This exploratory single-center study recruited 60 PKD patients from the mainland of China, as well as 19 hypokalaemic periodic paralysis (HypoPP) as the positive control, and 45 healthy volunteers as the negative control. The study was approved by the ethics committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, and registered in the Chinese clinical trial website (ChiCTR-ROC-17013020). All participants or their guardians provided written informed consents.

The diagnosis of PKD was determined according to Bruno's criteria (Bruno et al., 2004). Among 60 PKD patients, 33 patients required medications (carbamazepine or oxcarbazepine). Those patients suspended medications for at least 2 days before ET studies, and other 27 patients were medication naïve. The diagnosis of HypoPP was determined based on clinical presentation (Sansone et al., 2008). All those HypoPP patients were in the interictal state. A total of 45 asymptomatic volunteers were recruited from the medical school. The genetic diagnosis was not known to the examiner or the patient at the time of the neurophysiological examination. The neurophysiologist was effectively blinded as to whether these subjects would eventually turn out to be patients or controls.

2.2. Exercise tests

Compound muscle action potentials (CMAPs) were recorded from right or left abductor digiti minimi (ADM) muscles with supramaximal ulnar nerve stimulation at the wrist. Recording skin electrodes consisted of a pair of small discs were carefully positioned to minimize the movement. Skin temperature was regularly measured and maintained between 32 °C and 34 °C throughout the whole electromyography session.

The long exercise test (LET) was performed as described by McManis et al. (1986) with a little modification. Before exercise, the CMAP recordings were evoked by supramaximal ulnar nerve stimulation for about 1–2 min to obtain a stable baseline amplitude. Next, the patients were asked to abduct the right ADM muscle as hard as possible for 5 min at 1 min interval with 15 s rest. Then, the CMAPs were recorded at 1 minute interval for the first 5 min of rest, and at 2 or 3 minute intervals for 55 min.

The short exercise test (SET) program was performed as described by Streib (1984, 1987) and Fournier et al. (2004). Briefly, before exercise, supramaximal ulnar nerve stimulation was applied to obtain a stable baseline amplitude. Next, the patients were asked to abduct the left ADM muscle as hard as possible for 10 s. Then CMAPs were recorded 2 s immediately after the end of exercise and every 10 s interval for 1 minute of rest. The process was repeated 3 times.

2.3. Statistical analysis

All statistical analyses were conducted using IBM SPSS software 22.0. CMAP amplitude (negative peak) and area (negative peak area) were expressed as a percentage change from the baseline values before exercise. The values were given as means ± standard errors (SE). The normal range was defined as mean ± 2 standard deviations (SD). Increments or decrements were expressed as increments or decrements of amplitude and area. Categorical variables were summarized by counts of patients and percentages. All variables were tested for normality by Kolmogorov-Smirnov. The differences among three independent groups were analyzed by one way analysis of variance (ANOVA) or Krustal-Wallis test followed by Bonferroni correction. The difference between two independent groups were analyzed by two-sample t-tests, Chi-square tests with Fisher's correction, or Mann-Whitney U tests. The difference between paired samples was evaluated by the paired T test or paired Wilcoxon test. A two-sided $p < 0.05$ was considered significant.

3. Results

3.1. Demographics

Table 1 presents the demographic data of the subjects. In the LET, 60 PKD patients were included, 52 were men and 8 were women (mean age 23 ± 6.8 years; range, 10–45 years). The mean age at onset was 11 ± 4 years (range, 3 months to 21 years). A total of 28 patients carried *PRRT2* mutations, including 13 familial cases (9 families) and 15 sporadic ones. The other 32 patients carried no *PRRT2* mutations, including 4 familial cases (4 families) and 28 sporadic ones. Eighteen HypoPP patients were included as the positive controls, 17 were men and 1 was a woman (mean age 27 ± 8.8 years; range, 14–43 years). Two patients had calcium voltage-gated channel subunit alpha1 S (*CACNA1S*) mutations and two had sodium voltage-gated channel alpha subunit 4 (*SCN4A*) mutations. Twenty-two healthy volunteers were also performed with the LET, including 20 men and 2 women (mean age 31 ± 9.4 years; range, 19–53 years).

In the SET, 53 PKD patients were tested, 45 were men and 8 were women (mean age 22 ± 6.5 years; range, 13–45 years). The mean age at onset was 11 ± 4 years (range, 3 months to 21 years). Thirteen patients (11 families) and 12 sporadic patients were *PRRT2* positive, while 5 patients (5 families) and 23 sporadic patients were *PRRT2* negative (Table 1). Seventeen HypoPP patients were included as the positive controls, 16 were men and 1 was a woman (mean age 28 ± 8.8 years; range, 14–43 years). Two patients had *CACNA1S* mutations and one had a *SCN4A* mutation (Table 1). Twenty-nine healthy volunteers were performed with the SET, including 25 men and 4 women (mean age 26 ± 4.8 years; range, 19–45 years).

3.2. Overall patients with PKD had greater CMAP amplitude and area increment during exercise in the LET

The baseline CMAP amplitude and area in PKD patients (n = 60) were similar with that in healthy controls (n = 45) (6.3 ± 0.1 vs. 6.7 ± 0.2, $p = 1$; 17.9 ± 0.3 vs. 19.1 ± 0.6, $p = 0.213$). In contrast, both the baseline CMAP amplitude and area in HypoPP patients (n = 19) were significantly lower than that in healthy controls (5.5 ± 0.2 vs. 6.7 ± 0.2, $p = 0.001$; 16.2 ± 0.6 vs. 19.1 ± 0.6, $p = 0.011$) (Table 2).

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