Quick Flicks: Association of Paroxysmal Kinesigenic Dyskinesia and Tics

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Abstract: Background: Paroxysmal kinesigenic dyskinesia (PKD) is a rare disorder characterised by brief attacks of chorea, dystonia, or mixed forms precipitated by sudden movement. Methods: Observational study with a cohort of 14 PKD patients and genetic testing for PRRT2 mutations. Results: In a series of 14 PKD patients seen in our clinic at the National Hospital of Neurology, Queen Square, from 2012–2017, we noted tics in 11 patients (79%), which stand in stark contrast to the estimated lifetime prevalence of tics estimated to reach 1%. Conclusions: The two reasons to point out this possible association are the clinical implications and the potential opportunity of a better understanding of shared pathophysiological mechanisms of neuronal hyperexcitability.

Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is a rare disorder, characterised by brief (seconds to minutes) attacks of chorea, dystonia, or mixed forms precipitated by sudden movement.1 Approximately half of the cases are due to autosomal-dominant PRRT2 mutations, the phenotypic spectrum of which has broadened to also associate with infantile convulsions with paroxysmal choreoathetosis (ICCA), benign familial infantile epilepsy, and (hemiplegic) migraine and episodic ataxia.2 Apart from rare case reports, an association with tics has not been noted so far.3–5

Tics are rapid, brief, stereotyped movements or vocalizations. They may manifest as eye blinking, shoulder shrugging, grimacing, sniffing, or grunting (simple motor or phonic tics), or as a combined sequence of stereotyped movements or saying words or phrases (complex tics). Typically, tics are (temporarily) suppressible, but patients will describe an inner rising tension or urge. Tics can be associated with different movement disorders, including dystonia.5 Here, we describe the association of tics with PKD as observed in a cohort of PKD patients.

Methods

This was an observational study with a cohort of 14 PKD patients. Genetic testing for PRRT2 mutations focused on the known mutational hotspot and included Sanger sequencing of all three coding exons and flanking introns of the PRRT2 gene (PRRT2-001: ENST00000358758).

Results

In a series of 14 PKD patients (17 to 52 years, median 24 years; 2 females; details in Table 1) seen in our clinic at the National...
**TABLE 1** Characteristics of PKD Patients Seen at Queen Square from 2012–2017

<table>
<thead>
<tr>
<th>#</th>
<th>Age, Sex</th>
<th>PRRT2 mutation</th>
<th>Epilepsy, migraine</th>
<th>Family history</th>
<th>Tics</th>
<th>Psychiatric comorbidities (OCD, ADHD, other)</th>
<th>Treatment for PKD</th>
<th>Tics present prior to treatment with AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, M</td>
<td>None detected</td>
<td>Epilepsy age 6m – 3y</td>
<td>-</td>
<td>+</td>
<td>Simple motor and phonic tics (affecting face, shoulders, hands; sniffing)</td>
<td>-</td>
<td>CBZ yes</td>
</tr>
<tr>
<td>2</td>
<td>30, M</td>
<td>n.d.</td>
<td>migraine</td>
<td>-</td>
<td>-</td>
<td>Simple motor tics</td>
<td>CBZ yes</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>22, M</td>
<td>c.649dupC</td>
<td>Paternal uncle OCD</td>
<td>-</td>
<td>-</td>
<td>Simple motor and phonics (facial tics, shoulder elevation, sniffing)</td>
<td>CBZ yes</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>27, M</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Simple motor tics</td>
<td>-</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>28, M</td>
<td>None detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
</tr>
<tr>
<td>6*</td>
<td>21, M</td>
<td>common C insertion at c.649/p.R217Pfs*8</td>
<td>Epilepsy until age 1.5y</td>
<td>Migraine: mother, maternal grand-mother, maternal aunt and brothers; Epilepsy: mother and father, young siblings, complex motor tics (twitching, shoulder shrugging, head tilting/turning, need to touch certain items), simple phonic tics (grunting, sniffing)</td>
<td>Simple and complex motor tics (excessive blinking, repetitive arm twitching, shoulder shrugging, head tilting/turning, need to touch certain items), simple phonic tics (grunting, sniffing)</td>
<td>OCD, ADHD, Autism spectrum disorder</td>
<td>CBZ yes</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>19, F</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Simple motor and vocal tics</td>
<td>-</td>
<td>CBZ yes</td>
</tr>
<tr>
<td>8</td>
<td>20, M</td>
<td>None detected</td>
<td>Migraine</td>
<td>History of migraine on the paternal side</td>
<td>Simple motor and phonics (eye blinking, eye rolling, pulling the side of the mouth; throat clearing)</td>
<td>-</td>
<td>CBZ yes</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>32, M</td>
<td>n.d.</td>
<td>-</td>
<td>Epilepsy and PKD</td>
<td>-</td>
<td>Simple and complex motor tics, simple phonic tics (facial tics, hitting head with hand; a right shoulder jerk; guttural sounds)</td>
<td>-</td>
<td>n.a.</td>
</tr>
<tr>
<td>10</td>
<td>41, M</td>
<td>None detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
</tr>
<tr>
<td>11</td>
<td>52, M</td>
<td>+ common C insertion at c.649/p.R217Pfs*8</td>
<td>Migraine</td>
<td>Possible family history of epilepsy on maternal side: brother possibly PKD</td>
<td>-</td>
<td>-</td>
<td>CBZ n.a.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>17, M</td>
<td>n.d.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Simple motor tics and few phonic tics such as sniffs</td>
<td>-</td>
<td>n.a.</td>
</tr>
<tr>
<td>13</td>
<td>24, F</td>
<td>n.d.</td>
<td>Possible infantile seizures</td>
<td>-</td>
<td>-</td>
<td>Simple motor tics and phonics tics such as eye blinking, perioral movements, shoulder shrugging, sniffs, throat clearing; complex motor tics such as clenching and unclenching the hands, pulling and tugging at clothes</td>
<td>OCD CBZ yes</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>24, F</td>
<td>n.d.</td>
<td>Migraine and tics in her mother</td>
<td>-</td>
<td>-</td>
<td>Simple motor tics such as eye blinking, shoulder shrugging; complex motor tics, history of phonics tics like sniffing</td>
<td>OCD CBZ yes</td>
<td></td>
</tr>
</tbody>
</table>

*previously reported*[^1]

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBZ, carbamazepine; n.a., not applicable; n.d., no data on genetic testing/no genetic testing performed; OCD, obsessive-compulsive disorder, PHT, phenytoin.
Hospital of Neurology, Queen Square, from 2012 to 2017, we noted tics in 11 patients (79%). All patients were unrelated and had classic PKD with regard age of onset, type, and frequency of attacks and had a good treatment response to antiepileptic drugs. The tics did not differ in their phenomenology from those seen in primary tic disorders, and comprised varying degrees of (mostly simple) motor and vocal tics.7 In general, tics were of mild-to-moderate severity and occurred a few to multiple times during the consultations. They were typically not, or only mildly, interfering. All patients could suppress their tics and described an urge while doing so. In all patients, tics were noted prior to treatment with antiepileptic drugs (Table 1). Other features, such as attention deficit hyperactivity disorder and obsessive-compulsive traits were present in some patients (Table 1). There was no correlation between tics and the PRRT2 mutational status. Of note, genetic testing for PRRT2 mutations in this series focused on the known mutational hotspot, which yielded positive results only in a quarter of cases. However, this approach would not exclude other, more rare mutations elsewhere in the gene, the presence of which is not unlikely, given that a classic PKD phenotype (as in our cases) is associated with PRRT2 gene mutations in up to 90%.8

Discussion

The estimated lifetime prevalence of tics has been estimated to reach 1%,9,9 which stands in stark contrast to the observation of tics in 79% of our PKD patients. However, this notion of a possible association is strengthened by previous single case reports,1-3 describing the occurrence of tics in PKD or PKD-like patients. The fact that in our cohort, tics were observed in treatment-naïve patients, argues against the possibility of them being a pharmacological side effect of antiepileptic drug treatment.

The two reasons to point out this possible association of PKD and tics are the clinical implications and the potential opportunity of a better understanding of shared pathophysiological mechanisms.

From a clinical perspective, cooccurring tics might confound the ascertainment of PKD disease burden, more so since both tics and PKD attacks are brief, hyperkinetic movement disorders that may be preceded by sensory symptoms (premonitory urge in tics, aura-like symptoms in PKD). Given that most of the patients seek medical attention, especially for PKD, the neurologists might overlook the tics. The recognition of cooccurring tics would also lead to different management approaches. Conversely, in patients diagnosed with a tic disorder, the unusual and sudden movements of PKD attacks have been misdiagnosed as complex tics.4 Interestingly, the vast majority of our patients was male, and there is a male preponderance in both PKD and tic disorders.1,7

To date, one can only speculate about any potential shared mechanisms, which may underlie tics and PKD. Support for the notion of some pathophysiological commonalities between tic disorders and other disorders of neuronal hyperexcitability (like epilepsy) comes from population-based case-control studies showing a higher incidence of tics amongst patients with epilepsy,10 and an increased risk of epilepsy in children with Tourette’s syndrome.11 Some authors consider PKD attacks as a form of subcortical epilepsy.12 Experimental work showed that intraputaminal or intracortical injections of the GABA-A antagonist bicuculline cause tics or epilepsy, respectively.13,14

PRRT2 mutations are known to cause epilepsy, and on a neuronal level, to interfere with glutamatergic signalling, thus resulting in neuronal hyperexcitability.15 Similarly, recent studies also substantiated evidence of pathological glutamatergic neurotransmission underlying Tourette’s syndrome.16 Furthermore, there is some evidence suggesting changes in connectivity of certain circuits (corticostriato-pallido-thalamo-cortical in tics; thalamomotor-cortical circuits in PKD with or without PRRT2 mutations) as shared pathophysiological mechanism.17,18

Of course, the small numbers caution to careful consideration of this observation. Larger studies would be needed to conclusively investigate this matter, and considering the relative rareness of PKD, this might require a multi-centre approach.

Author Roles


B.B.: 1C, 3A
S.W.: 1C, 3B
D.M.: 3B
C.D.G.: 1C, 3B
A.L.: 1C, 3B
C.G.: 3B
H.H.: 1C, 3B
K.B.: 1A, 1B, 1C, 3B

Disclosures

Ethical Compliance Statement: We hereby confirm that the present study conforms to the ethical standards and guidelines of the journal. The patients have given written and informed consent for online publication of their videos.

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References


Supporting Information

A video accompanying this article is available in the supporting information here.

Video S1. Patient 6, who has PKD and carries a mutation of the PRRT2 gene, shows various simple and complex motor tics such as shoulder shrugging, head tilting/turning, perioral movements, drumming the fingers, pulling and tugging at clothes as seen in the video. He can suppress them momentarily with a rising inner tension.

Video S2. The first segment shows footage of a PKD attack consisting of a mixture of dystonia and chorea, videoed by the patient herself with a smart phone. The second segment shows the patient in clinic, showing a number of tics, such as eye blinking, grimacing, sniffing, and the ability to supress tics. This video segment starts when she is asked to relax and let any movements occur (0:44). At 0:46 she makes a sniffing sound as a vocal tic, and at 0:46/0:47 she has an eye blinking tic and upper lip elevation. She is then asked to suppress the tics by the videographer (0:55). Between 0:57 and 1:03 she suppresses her tics. She is then asked to relax and let the tics happen at 1:03, and they reappear and you see eye blinking and hear sniffing. She has also these complex tics of wiping her nose with the back of her right hand, and repetitive movement of her hands.