Non-motor symptoms and quality of life in patients with PRRT2-related paroxysmal kinesigenic dyskinesia

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Title: Non-motor symptoms and quality of life in patients with PRRT2-related paroxysmal kinesigenic dyskinesia

Authors: Asya Ekmen1,2 MD, PhD, Mohamed Doulazmi3 PhD, Aurélie Méneret1,2 MD, PhD, Prasanthi Jegatheesan1,2 PhD, Anais Hervé1 RN, Philippe Damier4 MD, PhD, Domitille Gras1 MD, PhD, Agathe Roubertie5 MD, PhD, Juliette Piard6 MD, PhD, Eugenie Mutez7 MD, PhD, Clément Tarrano1,2 MD, Quentin Welnialarz1,2 PhD, Marie Vidailhet1,2 MD, Yulia Worbe1,2 MD, PhD*, Cécile Gallea1* PhD, Emmanuel Roze1,2 MD, PhD*†.

† Corresponding author
* Equal contribution as senior authors

Affiliations:
1 Sorbonne Université, INSERM, CNRS, Paris Brain Institute;
2 APHP Hôpital de La Pitié Salpetrière et Saint-Antoine
3 Sorbonne University, Adaptation Biologique et Vieillissement (UMR8256), Institut de Biologie Paris Seine, CNRS, Paris France
4 University of Nantes, CHU Nantes, CIC 1314;
5 INM, Université de Montpellier, INSERM, CHU Montpellier, Département Neuropédriatrie
6 Centre de Génétique Humaine, CHU, Besançon, France; INSERM UMR1231, Génétique des Anomalies du Développement, Université de Bourgogne, Dijon, France
7 Univ. Lille, Inserm, CHU Lille, U1172 – LilNCog - Lille Neuroscience and Cognition.

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Corresponding authors contact information:
Address: ICM, 47-83 boulevard de l'hôpital, 75651 Paris Cedex 13, France;
Phone: +33 (0)157 27 46 27; Email: flamand.roze.75012@gmail.com

Running title: PRRT2 mutations and non-motor manifestations

Key words: PRRT2, paroxysmal disorders, non-motor symptoms, quality of life, stigma
ABSTRACT

Background: Monoallelic pathogenic variants of PRRT2 often result in paroxysmal kinesigenic dyskinesia (PKD). Little is known about health-related quality of life (HrQoL), non-motor manifestations, self-esteem, and stigma in patients with PKD.

Objectives: We investigated non-motor symptoms and how they related to HrQoL in a genetically homogeneous group of PRRT2-PKD patients. We paid special attention to perceived stigmatisation and self-esteem.

Methods: We prospectively enrolled 21 consecutive PKD patients with a pathogenic variant of PRRT2, and 21 healthy controls matched for age and sex. They were evaluated with dedicated standardized tests for non-motor symptoms, HrQoL, anxiety, depression, stigma, self-esteem, sleep, fatigue, pain, and psychological well-being.

Results: Patients reported an alteration of the physical aspects of HrQoL, regardless of the presence of residual paroxysmal episodes. Non-motor manifestations were frequent, and were an important determinant of the alteration of HrQoL. In addition, patients perceived a higher level of stigmatization which positively correlated with a delay in diagnosis ($\rho=0.615, p=0.003$) and the fear of being judged ($\rho=0.452, p=0.04$), but not with the presence of paroxysmal episodes ($\rho=0.203, p=0.379$).

Conclusions: Our findings have important implications for care givers concerning patient management and medical education about paroxysmal dyskinesia. PRRT2-PKD patients should be screened for non-motor disorders in routine care. A long history of misdiagnosis may play a role in the high level of perceived stigmatization. Improving knowledge about diagnostic clues suggestive of PKD is mandatory.
Monoallelic pathogenic variants of the Proline-rich transmembrane protein 2 (PRRT2) gene cause synaptopathy and can result in a large variety of paroxysmal neurological disorders (1–3). The most frequent disorder is Paroxysmal Kinesigenic Dyskinesia (PKD) which can be the sole manifestation of the disease in a large number of patients. PKD is characterized by attacks of dystonia and/or chorea, typically triggered by the sudden initiation of movements or brisk modification of an ongoing movement, that lasts less than a minute (4). They usually start in childhood or adolescence and peak during puberty, often with a high frequency of abnormal movement episodes – up to 100 per day – and complete remission between episodes. PRRT2-PKD can be treated with low doses of anti-epileptic drugs that modulate the activity of neuronal sodium channels and usually suppress the attacks (5).

PRRT2 is the main culprit gene for PKD (6,7) and PRRT2-PKD likely reflects a primary dysfunction of the cerebellum (8,9). The cerebellum has been involved in the pathogenesis of several dystonic syndromes (10). It also plays a role in non-motor processes such as cognition, sleep, and emotional regulation (11,12). Growing evidence indicates that non-motor manifestations are part of the clinical spectrum in various dystonic disorders, including idiopathic adult-onset focal dystonia and genetic forms of dystonia (13–18). Non-motor manifestations can be an important determinant of health-related quality of life (HrQoL), beyond the motor symptoms (15,16,19–23). Perceived stigmatization and diminished self-esteem can also influence quality of life in dystonic disorders (24–26). However, HrQoL, non-motor manifestations, self-esteem, and stigma have been poorly studied to date in patients with paroxysmal dystonic disorders, with only a few pilot findings (27).

Here, we investigated non-motor symptoms and how they relate to quality of life in a genetically homogeneous group of consecutive PRRT2-PKD patients and their age- and sex-matched controls. We paid special attention to perceived stigmatization and self-esteem.
METHODS

Study Population

In this exploratory study, we enrolled 21 consecutive PKD patients with a pathogenic variant of PRRT2 manifesting exclusively as PKD, and healthy controls (HC) matched for age and sex. HCs were recruited from the database of the Pitié-Salpêtrière Clinical Investigation Center (Paris, France). Prior to data collection, the full protocol was approved by the Ethics Committee “Comité de Protection des Personnes Sud-Méditerranée” (reference: 17.060), and was registered on clinicaltrial.gov (NCT03481491). In accordance with the Declaration of Helsinki, all participants provided written informed consent.

Study Instruments

We collected the patients’ history, demographic, genetic, and clinical information including initial misdiagnoses. Disease duration was calculated as the time in years between symptom onset and the day of the inclusion visit. Age at disease onset was taken as the age at which symptoms first occurred. Delay to diagnosis was calculated as the time in years between the patient’s first medical visit for their symptoms and their PKD diagnosis. The residual presence of paroxysmal events was defined as having at least one episode during the month prior to inclusion in the study. Patients were considered treated or non-treated depending on whether they were receiving a treatment for PKD. Non-motor aspects were investigated using standardized questionnaires: i) the Dystonia Non-motor Symptoms (DNMS) questionnaire, which can detect non-motor problems comprising sleep disorders, autonomic dysfunction, fatigue, psychiatric manifestations, stigma, and sensory symptoms (20); ii) the Stigma Scale for Chronic Illness which measures perceived stigmatization (SSCI-8)(28); iii) the Hospital Anxiety and Depression Scale (HADS) to investigate anxiety and depression with two specific sub-scales (29); iv) the Brief Fear of Negative Evaluation Scale (BFNE)(30), the Rosenberg
Self Esteem Scale (RSES)(31), and the Warwick-Edinburgh Mental Wellbeing Scales (WEMWBS)(32) which respectively quantify perceived stigmatization, fear of being judged by others, self-esteem, and mental well-being; v) the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)(33) to evaluate HrQoL; vi) the Visual Analogue Scale of Pain (34), the Fatigue Severity Scale (FSS-9)(35) and the Pittsburgh Sleep Quality Index (PSQI)(36) to measure pain, fatigue and sleep disturbances, respectively.

Component analyses showed that SF-36 measures two distinct concepts, namely a physical dimension, represented by the Physical Component Summary (PCS), and a mental dimension, represented by the Mental Component Summary (MCS). PCS is composed of four primary domains (physical functioning, physical role limitations, bodily pain, and general health). MCS is also composed of four primary domains (social functioning, emotional role limitations, mental health, and vitality). The steps for calculating the PCS and MCS have been previously described (37). The SF-36 scales are standardized using a linear z-score transformation. Z-scores are calculated by subtracting subscale means for a general US population sample from each individual's subscale scores and dividing the difference by the standard deviation of the US sample. Each of the eight z-scores is then multiplied by the corresponding factor scoring coefficient for the scale. There are two different sets of factor scoring coefficients, one for the PCS and another for the MCS. The products of the z-scores and factor scoring coefficients for the PCS are then summed together, and a similar calculation is performed for the MCS. Each resulting sum is multiplied by 10 and added to 50 to linearly transform the PCS or MCS to the T-score metric, which has a mean of 50 and a standard deviation of 10 for the US general population.

Statistical analysis
Statistical analysis was conducted with the R software (4.0.2) system. Normality in the variable distributions was assessed by the Shapiro-Wilk test. Furthermore, the Levene test was performed to probe homogeneity of variances across groups.

We performed group analyses comparing patients to controls. Variables that failed the Shapiro-Wilk or the Levene test were analyzed with nonparametric statistics. Categorical variables were compared using Pearson's $\chi^2$ test or Fisher's exact test. Quantitative variables were analyzed using the Student's t-test or the Mann-Whitney’s test.

To further explore HrQoL alteration in the patient group, we first used Spearman correlation (continuous variables) and rank-biserial correlation (binary variables: sex and treatment) coefficients to examine the associations between variables which were different between the patients and controls, and between those variables and important characteristics (age, sex, age at onset, disease duration, delay to diagnosis, treatment, or the persistence of PKD attacks) that could influence HrQoL.

Second, we performed a multivariable linear regression model. Five variables were selected to be included in the model: three variables were selected based on the statistical significance on between-group comparisons and three variables were selected because we thought they might be important to explain HrQoL (age at onset, treatment - being treated or not - and persistence of paroxysmal events). We only considered the PCS score as the dependent variable (the MCS was not different between the patient and control groups), and the above-mentioned variables as independent variables. The multivariable regression model was based on the stepwise method. Assumptions of using the linear regression method included normal distribution of PCS and lack of outlier data.

The data are expressed as mean +/- SD, and p < 0.05 was assumed to be statistically significant.
RESULTS

We analyzed data from 21 (mean age 33.7y) consecutive PKD patients with a pathogenic variant of PRRT2, and 21 matched healthy controls (HC). The patients’ characteristics and group comparisons are summarized in Table 1.

Quality of life evaluation

Compared to the HC, the patients had an altered HrQoL in four domains of the SF-36, namely physical functioning, bodily pain, energy/fatigue, and general health perceptions (Figure 1). Accordingly, the PCS score was lower showing a poorer physical component of HrQoL for the patients ($p<0.001$). There was no difference between the groups for MCS.

Global non-motor evaluation

There was a group difference for non-motor symptoms (Table 2): 100% of the patients and 29% of the HCs ($p<0.001$) reported non-motor symptoms causing impairment of activities of daily living on the DNMS questionnaire. 52% of patients and 9.5% of HCs reported at least four non-motor symptoms. In the patient group, the most prevalent non-motor symptoms were loss of self-confidence due to stigma (100%), sleep disorders (71%) (particularly difficulty to fall asleep), anxiety (48%), fatigue (43%), and depression (29%). The non-motor symptoms burden (i.e., total DNMS score) was higher in the patients ($3.76 \pm 3.33$) than in the HCs ($0.57 \pm 1.52; p<0.001$).

Psychological evaluation

HADS scores evaluating anxiety and depression related symptoms were similar between the groups ($p=0.91$), and no subject exceeded cut-off scores. The patients had lower self-esteem (RSES score) ($p=0.01$) and their fear of being judged by others (BNFE score) tended to be
higher \((p=0.067)\). Global well-being (WEMWBS) was similar in the patients and HCs \((p=0.152)\). The patients had a higher perceived stigmatization with a mean SSCI-8 score of 18.8 \((p<0.001)\).

**Sleep, fatigue, and pain**

The patients reported a poorer quality of sleep (PSQI-total score) although not significant \((p=0.116)\). They needed more time to fall asleep (30 minutes for patients and 14 minutes for HCs, \(p=0.032\)). The patients also reported more fatigue (FSS) although the difference was not significant \((p=0.133)\). They did not report more pain (VAS) \((p=1)\) compared to the HCs.

**Misdiagnosis**

62% of the patients were initially misdiagnosed. Wrong diagnoses included functional disorder (6 patients), epilepsy (4 patients), panic attack (2 patients), Tourette syndrome (2 patients), and dystonia (1 patient). Two of them sequentially received two wrong diagnoses (epilepsy and functional disorder for one; Tourette syndrome and functional disorder for the other).

**Correlation analysis**

When investigating the possible determinants of PCS alteration in the patients, we found that PCS was not related to the presence of residual PKD attacks but negatively correlated with the stigma score SSCI8 \((\rho=-0.480, p=0.028)\) and time needed to fall asleep \((\rho=-0.544, p=0.011)\). Higher stigma scores correlated with a higher NMS burden \((\rho=0.554, p=0.009)\), a greater delay to PKD diagnosis \((\rho=0.615, p=0.003)\), and lower physical components of HrQoL \((\rho=-0.480, p=0.028)\).

HrQoL was not correlated with the demographical and clinical variables of age, sex, age at onset, disease duration, treatment, or persistence of PKD attacks. Detailed information can be found in **Figure 2** and **Supplementary Material**.
Regression analysis

The independence of PCS predictors in the patients was assessed by stepwise linear regression, with PCS as a response variable and age at onset, DNMS, SSCI, RSES scores and treatment (being treated or not for PKD), and persistence of paroxysmal events as predictive variables (Table 2). From this model (Adjusted $R^2 = 0.245$), only the total DNMS was found to predict PCS in the patients ($β = -2.06$, 95% CI -3.628 - -0.487, $p = 0.013$). Finally, the global non-motor burden was inversely related to the PCS.

DISCUSSION

Patients with PKD caused by pathogenic variants of PRRT2 reported an alteration of the physical aspects of HrQoL, regardless of the presence of residual paroxysmal episodes or use of treatments. Non-motor manifestations observed in these patients were an important determinant of the alteration of HrQoL. In addition, patients perceived a high level of stigmatization positively correlated with delay in diagnosis but not with the presence of paroxysmal episodes. As observed in other dystonic syndromes, non-motor symptoms may be an entire part of the phenotype of patients with paroxysmal dystonic manifestations and should be investigated and recognized in clinical practice. Our findings have important implications for the management of these patients and for medical education about PKD.

The main strengths of our work are the clinical (typical PKD) and genetic (PRRT2 pathogenic variant) homogeneity of the patient group, the presence of a matched comparison group, and the prospective and standardized data collection. Our study was innovative in that we focused on non-motor aspects which represents an emerging concern in the field of dystonic disorders. A few limitations deserve to be mentioned. First, some patients were on chronic treatment,
mainly comprising low dose carbamazepine. Although we observed no relevant difference between medicated and non-medicated patients, chronic treatments might have influenced our results. In addition, carbamazepine is commonly used in PRRT2-related PKD and thus our results remain overall relevant for the PRRT2 population. Of note, patients with a milder form of the disease are less likely to receive medication and this should be taken into account when interpreting the lack of difference between medicated and non-medicated patients. Secondly, we binarized the presence or absence of residual PKD attacks in the past month instead of considering their exact reported frequency. The main reason for this was that frequency values are unstable and fluctuant in this disorder, being highly dependent on exposure to triggering factors in activities of daily living. Thirdly, our study only involved a small sample of patients and is thus exploratory, warranting confirmation from larger studies.

HrQoL is altered in patients with dystonia, including various idiopathic adult-onset focal dystonia (38) and genetic dystonia (14,39,40). A seminal study found an alteration of HrQoL in a large but genetically heterogeneous sample of patients with PKD (27). In this study, the patients’ data were compared with normative data in the absence of a control group. In keeping with the genetic heterogeneity of the population, the majority of these heterogeneous PKD patients had an incomplete response to treatment, which is unusual in PRRT2-PKD.

We also found an alteration of HrQoL in our group of PRRT2-PKD patients, as compared with controls. Interestingly, this altered HrQoL was not linked to the presence of residual paroxysmal events or to treatment, suggesting a contribution of non-motor manifestations. Indeed, the global non-motor burden was the only determinant of altered physical components of HrQoL retained by the stepwise regression analysis in our patients.
When screened with the DNMS, our *PRRT2*-PKD patients more frequently reported non-motor symptoms as compared to the controls, especially loss of self-confidence due to stigma and sleep problems. Investigation with semi-quantitative dedicated scales similarly identified loss of self-esteem and stigma in the patients, as well as a non-significant trend toward more fatigue and poorer sleep quality compared to the controls. The single questions related to depression and anxiety of the DNMS yielded different responses for patients and controls, which was not confirmed by the between-groups comparison on the HADS subscores. This discrepancy is not surprising as the accuracy of the specific anxiety and depression DNMS questions has not been validated against the anxiety/depression severity scales. Overall, non-motor symptoms have been identified as part of the phenotype in various dystonic disorders and they are an important determinant of quality of life (13,19). In particular, the prevalence of psychiatric disorders, pain, sleep problems and fatigue is often greater in patients with idiopathic adult-onset focal dystonia (20,21,38,41–43). For example, a controlled study using the same evaluation tool (DNMS) in patients with idiopathic adult-onset cervical dystonia revealed that pain, insomnia, and stigma were highly prevalent and that non-motor symptoms were major determinants of their HrQoL(21). A higher prevalence of psychiatric disorders, sleep problems, and fatigue was also found in a mixed group of patients with dystonia – mostly genetic dystonia (dopa-responsive dystonia, myoclonus-dystonia, and idiopathic adult-onset cervical dystonia) – as compared with controls (22). Likewise, non-motor symptoms were also linked to HrQoL in this study.

Stigmatization was perceived as important in our *PRRT2*-PKD patients. For example, perceived stigmatization evaluated with the same measurement tool was higher in our patients than in patients with multiple sclerosis or epilepsy, which can be considered to be more visible and debilitating disorders (28,44,45). The young age of our patients may have influenced this result since young patients with neurological disorders seem to be more prone to feelings of stigmatization, as demonstrated in the context of cervical dystonia and other neurological
disorders (21,28). As the perceived stigmatization was tightly linked to delay to diagnosis, we suggest that a long history of misdiagnosis – often involving a wrong diagnosis of functional disorders (29% of patients) – may play a role in the high level of perceived stigmatization (44–47). This emphasizes the need to increase knowledge about the diagnostic clues suggestive of PKD.

Interestingly, the global non-motor burden did not correlate with the presence of residual paroxysmal episodes. It is therefore possible that the additional non-motor phenotype is not a consequence of motor problems but rather reflects PRRT2-related brain dysfunction. If so, then non-motor manifestations could be related to the well-known PRRT2-related cerebellar dysfunction (8,48,49). For example, sleep disorders, especially insomnia, have been linked to structural and functional abnormalities of the cerebellum (49,50,51). Consistently, the cerebellum has sleep-related activity patterns, and its output neurons, which express clock genes, are connected with the wake-sleep brain network (49, 51). Alternatively, non-motor manifestations could be the consequence of other brain dysfunctions considering the wide expression of PRRT2 in the brain (52).

Paroxysmal disorders, such as PKD, are often seen as more “benign” compared with continuous movement disorder. Our findings indicate that early diagnosis is also critical in PKD, and suggest that more attention should be paid to the hidden non-motor part of the disease. For this reason, some patients, at least, would benefit from long-term follow-up by a neurologist even after optimal control of the paroxysmal episodes.
AUTHOR ROLES

1. Research project: A. Conception, B. Organization, C. Execution;

A.E.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
M.D.: 2A, 2B, 2C, 3A
P.J.: 1B, 1C
A.H.: 1B, 1C
C.G., Y.W, 1A, 3B
E. R. 1A, 1B, 1C, 2C, 3A

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ETHICAL COMPLIANCE STATEMENT

This study was approved by the Regional Ethics Committee “Comité de Protection des Personnes Sud-Méditerrannée” (reference 17.060) and was registered on ClinicalTrials.gov (NCT03481491). Informed consent was obtained from all study participants. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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FIGURE LEGENDS

**Figure 1:** Radar chart with the eight domains of the Quality of life (Short Form-36) for PRRT2 patients and Healthy Controls (red line: PRRT2 patients, blue line: Healthy Controls). Each spoke on the radar chart represents an SF-36 domain on a scale of 0-100, with higher scores representing better health-related quality of life. The four green domains (Physical functioning, Role physical, Bodily pain and General health) contribute to the scoring of PCS measure. The four orange domains (Vitality, Social functioning, Role emotional and Mental Health) contribute to the scoring of MCS measure. *** p<0.001, ** p<0.01, * <0.05, using Student's t-test or the Mann-Whitney’s test as appropriate.

**Figure 2:** Correlation matrix across Age, Sex, Age at onset, Disease duration, Diagnostic delay, PCS, DNMS, SSCI8, RSES, Paroxysmal events and Treatment. Color of each box indicates the significance of the correlation (Spearman's ρ or rank-biserial correlation coefficient), while size of the circles indicates its magnitude.

TABLES
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PRR2 Patients (n = 21)</th>
<th>Healthy Controls (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; Age range (years)</td>
<td>33.66 (± 12.37); 17 – 51</td>
<td>31.7 (± 12.1); 21 – 56</td>
<td>0.55†</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>7/14</td>
<td>7/14</td>
<td>1†</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>9.3 (± 3.0)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>22.4 (± 12.5)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Diagnostic delay (years)</td>
<td>9.33 (± 10.78)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Treated patients n=11) CBZ/LTG/LEV</td>
<td>9/1/1</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Residual Paroxysmal events (yes/no)</td>
<td>6/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>52.53 (± 6.34)</td>
<td>58.52 (± 4.02)</td>
<td>0.001§</td>
</tr>
<tr>
<td>MCS</td>
<td>41.57 (± 10.80)</td>
<td>42.59 (± 9.36)</td>
<td>0.743§</td>
</tr>
<tr>
<td>DNMS</td>
<td>3.76 (± 1.64)</td>
<td>0.57 (± 1.21)</td>
<td>0.000†</td>
</tr>
<tr>
<td>PSQI</td>
<td>6.19 (± 3.71)</td>
<td>4.43 (± 3.38)</td>
<td>0.116§</td>
</tr>
<tr>
<td>HA</td>
<td>2.05 (± 2.06)</td>
<td>2.38 (± 2.80)</td>
<td>0.612</td>
</tr>
<tr>
<td>HD</td>
<td>4.10 (± 2.59)</td>
<td>4.19 (± 3.87)</td>
<td>0.969‡</td>
</tr>
<tr>
<td>SSCI-8</td>
<td>18.38 (± 4.86)</td>
<td>10.00 (± 2.06)</td>
<td>0.000‡</td>
</tr>
<tr>
<td>RSES</td>
<td>21.05 (± 5.71)</td>
<td>25.52 (± 3.59)</td>
<td>0.003†</td>
</tr>
<tr>
<td>BFNE</td>
<td>39.04 (± 9.74)</td>
<td>34.76 (± 8.32)</td>
<td>0.067§</td>
</tr>
<tr>
<td>WEMWBS</td>
<td>50.57 (± 9.58)</td>
<td>53.71 (± 9.97)</td>
<td>0.152‡</td>
</tr>
<tr>
<td>VAS</td>
<td>5%</td>
<td>0%</td>
<td>1†</td>
</tr>
<tr>
<td>FSS</td>
<td>25.19 (± 17.32)</td>
<td>17.71 (± 10.32)</td>
<td>0.133‡</td>
</tr>
</tbody>
</table>
Legend: **CBZ** = carbamazepine; **LTG** = lamotrigine; **LEV** = levetiracetam; **PCS** = Physical Component Summary; **MCS** = Mental Component Summary; **DNMS** = Dystonia Non-Motor Symptoms questionnaire; **PSQI** = Pittsburgh Sleep Quality Index; **HA** = Hospital Anxiety scale; **HD** = Hospital Depression scale; **SSCI-8** = Stigma Scale for Chronic Illnesses 8-item; **RSES** = Rosenberg Self-Esteem Scale; **BFNE** = Brief Fear of Negative Evaluation Scale; **WEMWBS** = Warwick-Edinburgh Mental Wellbeing Scale; **VAS** = Visual Analogue Scale for pain; **FSS** = Fatigue Severity Scale.

Quantitative data are expressed as mean (±SD).

† Student’s t-test; † Pearson’s χ² test; ‡ Mann-Whitney test; ‡ Fisher exact test; Significant results indicated in bold: p<0.05.
Table 2: Non-motor symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients*</th>
<th>Controls*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disorders</td>
<td>61.90%</td>
<td>9.52%</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Difficulties to fall asleep</td>
<td>61.90%</td>
<td>9.52%</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42.86%</td>
<td>14.29%</td>
<td>0.040*‡</td>
</tr>
<tr>
<td>Anxiety</td>
<td>47.62%</td>
<td>19.05%</td>
<td>0.050*‡</td>
</tr>
<tr>
<td>Depression</td>
<td>28.57%</td>
<td>0%</td>
<td>0.008*§</td>
</tr>
<tr>
<td>Loss of self-confidence due to stigma</td>
<td>100%</td>
<td>0%</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Flat moods</td>
<td>28.57%</td>
<td>4.76%</td>
<td>0.038*§</td>
</tr>
<tr>
<td>Chewing/swallowing</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Unpleasant sensations</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Speech</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Vision</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>4.76%</td>
<td>0%</td>
<td>0.311§</td>
</tr>
<tr>
<td>Balance/walking</td>
<td>0%</td>
<td>0%</td>
<td>–</td>
</tr>
</tbody>
</table>

Legend: * Percentage of positive response of the subjects to the 14 items of the dystonia non motor symptoms questionnaire † Pearson’s χ² test; § Fisher exact. Significant results indicated in bold: p<0.05.
**SUPPLEMENTARY LEGENDS**

*Supplementary Table 1:* Data of the eight domains of the Short Form (36) health survey for PRRT2 patients and Healthy Controls (HC). PCS= Physical Component Summary, MCS=Mental Component Summary, PF=Physical functioning, RP=Role physical, RE=Role emotional, VT=Vitality, MH=Mental Health, SF=Social functioning, BP=Bodily pain and GH=General health, * Student’s t-test; ‡ Mann-Whitney test.

*Supplementary Table 2:* Correlations across Age, Sex, Age at onset, Disease duration, Diagnostic delay, Physical Component Summary (PCS) of the Short Form (36) health survey, Dystonia non-motor symptoms scale (DNMS), Stigma Scale for Chronic Illness (SSC18), Rosenberg Self Esteem Scale (RSES), Paroxysmal Events and Treatment.
Figure 1. Radar chart with the eight domains of the Quality of life (Short Form-36) for PRRT2 patients and Healthy Controls (red line: PRRT2 patients, blue line: Healthy Controls). Each spoke on the radar chart represents an SF-36 domain on a scale of 0-100, with higher scores representing better health-related quality of life. The four green domains (Physical functioning, Role physical, Bodily pain and General health) contribute to the scoring of PCS measure. The four orange domains (Vitality, Social functioning, Role emotional and Mental Health) contribute to the scoring of MCS measure. *** p<0.001, ** p<0.01, * <0.05, using Student’s t-test or the Mann-Whitney’s test as appropriate.
Figure 2. Correlation matrix across Age, Sex, Age at onset, Disease duration, Diagnostic delay, PCS, DNMS, SSCI8, RSES, Paroxysmal events and Treatment. Color of each box indicates the significance of the correlation (Spearman’s ρ), while size of the circles indicates its magnitude.
Supplementary Results

Quality of life

Supplementary Table 1: Quality of life (Short Form-36).

PCS= Physical Component Summary, MCS=Mental Component Summary, PF=Physical functioning, RP=Role physical, RE=Role emotional, VT=Vitality, MH=Mental Health, SF=Social functioning, BP=Bodily pain and GH=General health, † Student’s t-test; ‡ Mann-Whitney test;

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (mean±sd)</th>
<th>PRRT2 patients (mean±sd)</th>
<th>Mean difference (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>97.62±6.82</td>
<td>92.86±7.68</td>
<td>4.76 (0.23-9.29)</td>
<td>0.006‡</td>
</tr>
<tr>
<td>RP</td>
<td>80.95±30.52</td>
<td>67.86±35.48</td>
<td>13.1 (-7.56-33.75)</td>
<td>0.189‡</td>
</tr>
<tr>
<td>RE</td>
<td>73±41.69</td>
<td>69.86±43.35</td>
<td>3.14 (-23.38-29.67)</td>
<td>0.768‡</td>
</tr>
<tr>
<td>VT</td>
<td>59.05±12.81</td>
<td>48.57±16.89</td>
<td>10.48 (1.11-19.85)</td>
<td>0.029¶</td>
</tr>
<tr>
<td>MH</td>
<td>65.71±14.56</td>
<td>59.24±13.42</td>
<td>6.48 (-2.26-15.21)</td>
<td>0.142¶</td>
</tr>
<tr>
<td>SF</td>
<td>72.76±21.83</td>
<td>78.14±21.91</td>
<td>5.38 (-19.02-8.26)</td>
<td>0.417‡</td>
</tr>
<tr>
<td>BP</td>
<td>97.9±4.45</td>
<td>85±21.49</td>
<td>12.9 (2.96-22.85)</td>
<td>0.023‡</td>
</tr>
</tbody>
</table>
Supplementary Table 2: Correlations across Age, Sex, Age at onset, Disease duration, Diagnostic delay, PCS, DNMS, SSCI8, RSES, Paroxysmal Events and Treatment.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Age at onset</th>
<th>Disease duration</th>
<th>Diagnostic delay</th>
<th>PCS</th>
<th>DNMS</th>
<th>SSCI-8</th>
<th>RSES</th>
<th>Paroxysmal events</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>-0.008</td>
<td>0.122</td>
<td>0.944**</td>
<td>-0.435*</td>
<td>0.02</td>
<td>0.405</td>
<td>0.282</td>
<td>0.734**</td>
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<td>-0.075</td>
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<tr>
<td>Sex</td>
<td>1</td>
<td>0.623**</td>
<td>-0.167</td>
<td>-0.176</td>
<td>0.1</td>
<td>0.246</td>
<td>-0.295</td>
<td>-0.336</td>
<td>-0.224</td>
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<td>-0.143</td>
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<tr>
<td>Age at onset</td>
<td>1</td>
<td>-0.155</td>
<td>-0.169</td>
<td>-0.182</td>
<td>0.217</td>
<td>-0.199</td>
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<td>0.105</td>
<td>-0.488*</td>
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</tr>
<tr>
<td>Disease duration</td>
<td>1</td>
<td>0.504*</td>
<td>0.048</td>
<td>0.355</td>
<td>0.378</td>
<td>0.739**</td>
<td>-0.061</td>
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<tr>
<td>Diagnostic delay</td>
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<td>0.442*</td>
<td>0.615**</td>
<td>0.439*</td>
<td>-0.009</td>
<td>0.328</td>
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<tr>
<td>PCS</td>
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<td>-0.405</td>
<td>-0.480*</td>
<td>0.068</td>
<td>0.035</td>
<td>0.15</td>
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<tr>
<td>DNMS</td>
<td>1</td>
<td>0.554**</td>
<td>-0.044</td>
<td>-0.292</td>
<td>0.323</td>
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<tr>
<td>SSCI-8</td>
<td>1</td>
<td>0.174</td>
<td>0.203</td>
<td>0.211</td>
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<tr>
<td>RSES</td>
<td>1</td>
<td>0.053</td>
<td>-0.076</td>
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<td>Paroxysmal events</td>
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<td>-0.447*</td>
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<td>Treatment</td>
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<td></td>
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</table>