



HAL
open science

Non-Motor Symptoms and Quality of Life in Patients with PRRT2 -Related Paroxysmal Kinesigenic Dyskinesia

Asya Ekmen, Mohamed Doulazmi, Aurélie Méneret, Prasanthi Jegatheesan, Anais Hervé, Philippe Damier, Domitille Gras, Agathe Roubertie, Juliette Piard, Eugenie Mutez, et al.

► **To cite this version:**

Asya Ekmen, Mohamed Doulazmi, Aurélie Méneret, Prasanthi Jegatheesan, Anais Hervé, et al.. Non-Motor Symptoms and Quality of Life in Patients with PRRT2 -Related Paroxysmal Kinesigenic Dyskinesia. *Movement Disorders Clinical Practice*, 2023, 10 (7), pp.1082-1089. 10.1002/mdc3.13795 . hal-04237611v2

HAL Id: hal-04237611

<https://hal.science/hal-04237611v2>

Submitted on 11 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Non-Motor Symptoms and Quality of Life in Patients with PRRT2-Related Paroxysmal Kinesigenic Dyskinesia

Asya Ekmen, MD, PhD,^{1,2} Mohamed Doulazmi, PhD,³ Aurélie Méneret, MD, PhD,^{1,2} Prasanthi Jegatheesan, PhD,^{1,2} Anais Hervé, RN,¹ Philippe Damier, MD, PhD,⁴ Domitille Gras, MD, PhD,¹ Agathe Roubertie, MD, PhD,⁵ Juliette Piard, MD, PhD,^{6,7} Eugénie Mutez, MD, PhD,⁸ Clément Tarrano, MD,^{1,2} Quentin Welniarz, PhD,^{1,2} Marie Vidailhet, MD,^{1,2} Yulia Worbe, MD, PhD,^{1,2} Cécile Gallea, PhD,¹ and Emmanuel Roze, MD, PhD^{1,2,*}

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 stigmatization 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

¹Sorbonne Université, INSERM, CNRS, Paris Brain Institute, Paris, France; ²APHP Hôpital de La Pitié Salpêtrière et Saint-Antoine, Paris, France; ³Sorbonne University, Adaptation Biologique et Vieillesse (UMR8256), Institut de Biologie Paris Seine, CNRS, Paris, France; ⁴University of Nantes, CHU Nantes CIC 1314, Nantes, France; ⁵Département Neuropédiatrie, INM, Université de Montpellier, INSERM, CHU Montpellier, Montpellier, France; ⁶Centre de Génétique Humaine, CHU, Besançon, France; ⁷INSERM UMR1231, Génétique des Anomalies du Développement, Université de Bourgogne, Dijon, France; ⁸Univ. Lille, Inserm, CHU Lille, U1172—LilInCog—Lille Neuroscience and Cognition, Lille, France

*Correspondence to: Emmanuel Roze, ICM, 47–83 boulevard de l'hôpital, 75651 Paris Cedex 13, France; E-mail: flamand.roze.75012@gmail.com

Keywords: PRRT2, paroxysmal disorders, non-motor symptoms, quality of life, stigma.

Yulia Worbe, Cécile Gallea, Emmanuel Roze equal contribution as senior authors.

This is an open access article under the terms of the [Creative Commons Attribution–NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Received 24 October 2022; revised 23 March 2023; accepted 1 May 2023.

Published online 2 June 2023 in Wiley Online Library ([wileyonlinelibrary.com](https://www.wileyonlinelibrary.com)). DOI: 10.1002/mdc3.13795

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 clinicaltrials.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: (1) the Dystonia Non-motor Symptoms (DNMS) questionnaire, which can detect non-motor problems comprising sleep disorders, autonomic dysfunction, fatigue, psychiatric manifestations, stigma, and sensory symptoms²⁰; (2) the Stigma Scale

for Chronic Illness which measures perceived stigmatization (SSCI-8)²⁸; (3) the Hospital Anxiety and Depression Scale (HADS) to investigate anxiety and depression with two specific sub-scales²⁹; (4) 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; (5) the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)³³ to evaluate HrQoL; (6) 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 χ^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 \pm 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

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 (Fig. 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

TABLE 1 Characteristics of subjects and results of the non-motor evaluation

Characteristics	PRRT2 patients (n = 21)	Healthy controls (n = 21)	P value
Age; Age range (years)	33.66 (\pm 12.37); 17–51	31.7 (\pm 12.1); 21–56	0.55 ^a
Sex (female/male)	7/14	7/14	1 ^b
Age at onset (years)	9.3 (\pm 3.0)	–	
Disease duration (years)	22.4 (\pm 12.5)	–	
Diagnostic delay (years)	9.33 (\pm 10.78)	–	
Treated patients n = 11) CBZ/LTG/LEV)	9/1/1	–	
Residual paroxysmal events (yes/no)	6/15		
PCS	52.53 (\pm 6.34)	58.52 (\pm 4.02)	0.001^c
MCS	41.57 (\pm 10.80)	42.59 (\pm 9.36)	0.743 ^c
DNMS	3.76 (\pm 1.64)	0.57 (\pm 1.21)	0.000^a
PSQI	6.19 (\pm 3.71)	4.43 (\pm 3.38)	0.116 ^c
HAHD	2.05 (\pm 2.06) 4.10 (\pm 2.59)	2.38 (\pm 2.80) 4.19 (\pm 3.87)	0.6120.969 ^a
SSCI-8	18.38 (\pm 4.86)	10.00 (\pm 2.06)	0.000^a
RSES	21.05 (\pm 5.71)	25.52 (\pm 3.59)	0.003^a
BFNE	39.04 (\pm 9.74)	34.76 (\pm 8.32)	0.067 ^c
WEMWBS	50.57 (\pm 9.58)	53.71 (\pm 9.97)	0.152 ^c
VAS	5%	0%	1 ^d
FSS	25.19 (\pm 17.32)	17.71 (\pm 10.32)	0.133 ^a

Note: Quantitative data are expressed as mean (\pm SD).

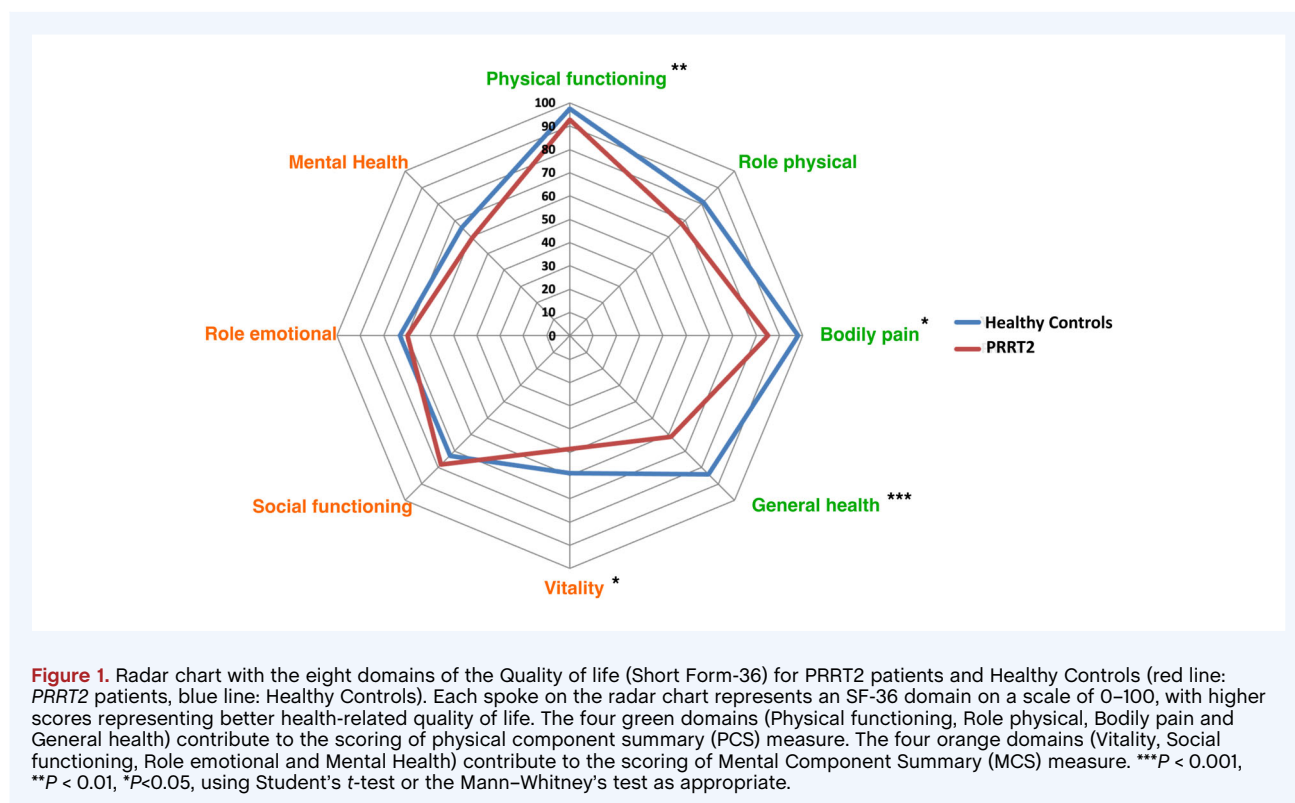
Abbreviations: CBZ, carbamazepine; LTG, lamotrigine; LEV, levetiracetam; PCS, Physical Component Summary; MCS, Mental Component Summary; DNMS, Dystonia Non-Motor Symptoms questionnaire; PSQI, Pittsburgh Sleep Quality Index; HA, Hospital Anxiety scale; HD, Hospital Depression scale; SSCI-8, Stigma Scale 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.

^aMann-Whitney test;

^bPearson's χ^2 test;

^cStudent's *t*-test;

^dFisher exact test; Significant results indicated in bold: $P < 0.05$.



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 (ie, total DNMS score) was higher in the patients (3.76 ± 3.33) than in the HCs (0.57 ± 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 (Visual Analogue Scale for 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 Data S1.

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

TABLE 2 *Non-motor symptoms*

Symptoms	Patients ^a	Controls ^a	P-value
Sleep disorders	61.90%	9.52%	<0.001 ^b
Difficulties to fall asleep	61.90%	9.52%	<0.001 ^b
Dizziness	0%	0%	–
Fatigue	42.86%	14.29%	0.040 ^{b,*}
Anxiety	47.62%	19.05%	0.050 ^{b,*}
Depression	28.57%	0%	0.008 ^{c,*}
Loss of self-confidence due to stigma	100%	0%	<0.001 ^b
Flat moods	28.57%	4.76%	0.038 ^{c,*}
Chewing/swallowing	0%	0%	–
Unpleasant sensations	0%	0%	–
Speech	0%	0%	–
Vision	0%	0%	–
Pain	4.76%	0%	0.311 ^c
Balance/walking	0%	0%	–

^aPercentage of positive response of the subjects to the 14 items of the dystonia non motor symptoms questionnaire.

^bPearson's χ^2 test.

^cFisher exact.

*Significant results indicated in bold: $P < 0.05$.

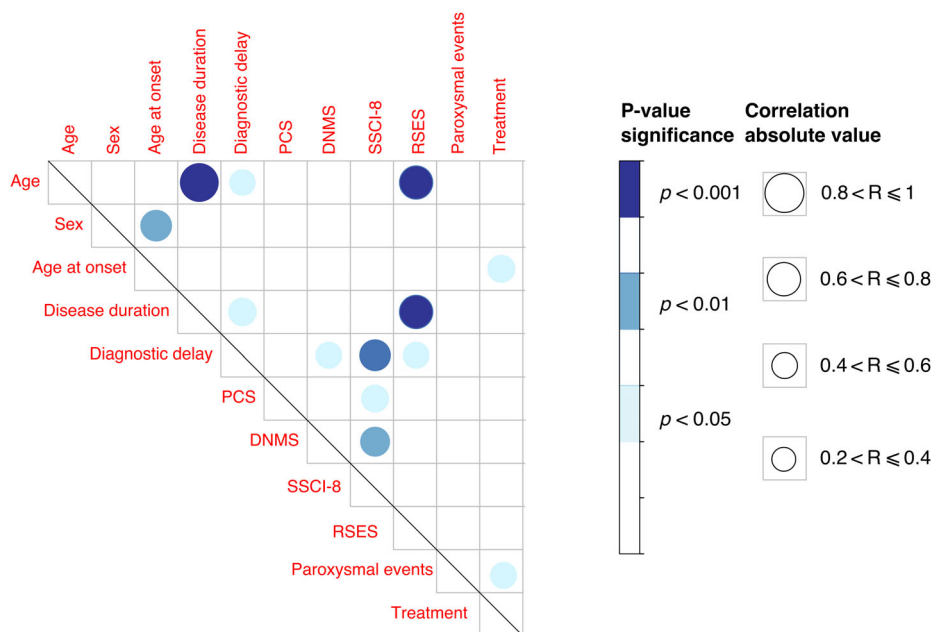


Figure 2. Correlation matrix across Age, Sex, Age at onset, Disease duration, Diagnostic delay, physical component summary (PCS), Dystonia non-motor symptoms scale (DNMS), Stigma Scale for Chronic Illness (SSCI8), Rosenberg Self Esteem Scale (RSES), Paroxysmal events and Treatment. Color of each box indicates the significance of the correlation (Spearman's ρ or rank-biserial correlation coefficient), while size of the circles indicates its magnitude.

(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 ($\beta = -2.06$, 95% CI -3.628 to -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 dystonia³⁸ 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.^{12,49,50} Consistently, the cerebellum has sleep-related activity patterns, and its output neurons, which express clock genes, are connected with the wake-sleep brain network.^{12,49} Alternatively, non-motor manifestations could be the consequence of other brain dysfunctions considering the wide expression of *PRRT2* in the brain.⁵¹

Paroxysmal disorders, such as PKD, are often seen as more “benign” compared with continuous movement disorders. 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; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

A.E.: 1A, 1B, 1C, 2B, 3A.

M.D.: 2A, 2B, 2C, 3A.

P.J.: 1B, 1C.

A.H.: 1B, 1C.

A.M., P.D., J.P., A.R., E.M., C.T., Q.W., M.V.: 1C, 3B.

C.G., Y.W., 1A, 3B.

E. R. 1A, 1B, 1C, 2A, 2C, 3A.

Disclosures

Ethical Compliance Statement: This study was approved by the Regional Ethics Committee “Comité de Protection des Personnes Sud-Méditerranée” (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.

Funding Sources and Conflicts of Interest: This work received financial support from Association des malades atteints de dystonie (AMADYS) from Fondation pour la Recherche Médicale (FRM) (prix Line-Pomaret, grant attributed to A.E.) and from MERZ-Pharma and Everpharma. This project was also supported by Agence Nationale de la Recherche (ANR) under the frame of the European Joint Programme on Rare Diseases (EJP RD, ANR-16-CE37-0003-03). In addition, this project has received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD

COFUND-EJP N° 825,575—EurDyscover. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for Previous 12 Months: A.E. has no additional disclosures to report. M.D. has no additional disclosures to report. A.M. received speaker honoraria from AbbVie and travel support from Merz. P.J. has no additional disclosures to report. A.H. has no additional disclosures to report. C.T. received a PhD research grant from the “Fondation pour la Recherche Médicale.” Q.W. has no additional disclosures to report. P.D. received honorarium for conferences from Novartis, Roche and Sun Pharma, and for participation in advisory board from Kyowa Kirin. A.R. received honorarium for advisory board from PTC Therapeutics. E.M. received honoraria for speech from Merz-Pharma. J.P. has no additional disclosures to report. M.V. has no additional disclosures to report and no conflict of interest. Y.W. has no additional disclosures to report and no conflict of interest. C.G. has no additional disclosures to report. E.R. received honorarium for speech from Orkyn, Aguetant, Elivie and for participating in an advisory board from Merz-Pharma. He received research support from Merz-Pharma, Orkyn, Aguetant, Elivie, Ipsen, Everpharma, Fondation Desmarest, AMADYS, ADCY5.org, Fonds de dotation Patrick Brou de Laurière, Agence Nationale de la Recherche, Société Française de Médecine Esthétique, Dystonia Medical Research Foundation. ■

References

- Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of *PRRT2*—associated paroxysmal diseases. *Brain* 2015; 138(12):3476–3495.
- Landolfi A, Barone P, Erro R. The Spectrum of *PRRT2*-Associated Disorders: Update on Clinical Features and Pathophysiology. *Front Neurol* 2021;12:629747.
- Méneret A, Gaudebout C, Riant F, Vidailhet M, Depienne C, Roze E. *PRRT2* mutations and paroxysmal disorders. *Eur J Neurol* 2013;20(6): 872–878.
- Méneret A, Roze E. Paroxysmal movement disorders: An update. *Rev Neurol* 2016;172(8–9):433–445.
- Méneret A, Garcin B, Frismand S, Lannuzel A, Mariani LL, Roze E. Treatable Hyperkinetic Movement Disorders Not to Be Missed. *Front Neurol* 2021;1(12):659805.
- Chen YP, Song W, Yang J, et al. *PRRT2* mutation screening in patients with paroxysmal kinesigenic dyskinesia from Southwest China. *Eur J Neurol* 2014;21(1):174–176.
- Méneret A, Grabli D, Depienne C, et al. *PRRT2* mutations: A major cause of paroxysmal kinesigenic dyskinesia in the European population. *Neurology* 2012;79(2):170–174.
- Ekmen A, Méneret A, Valabregue R, et al. Cerebellum Dysfunction in Patients With *PRRT2*—Related Paroxysmal Dyskinesia. *Neurology* 2022; 98(10):e1077–e1089.
- Lu B, Lou SS, Xu RS, et al. Cerebellar spreading depolarization mediates paroxysmal movement disorder. *Cell Rep* 2021;36(12):109743.
- Bologna M, Berardelli A. The cerebellum and dystonia. *Handbook of Clinical Neurology [Internet]*. Amsterdam: Elsevier; 2018:259–272. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780444641892000172>.
- Schmahmann JD. The cerebellum and cognition. *Neurosci Lett* 2019;688: 62–75.
- Canto CB, Onuki Y, Bruinsma B, van der Werf YD, De Zeeuw CI. The sleeping cerebellum. *Trends Neurosci* 2017;40(5):309–323.
- Junker J, Berman BD, Hall J, et al. Quality of life in isolated dystonia: non-motor manifestations matter. *J Neurol Neurosurg Psychiatry* 2021; 92(6):622–628.

14. Peall KJ, Kuiper A, de Koning TJ, Tijssen MA. Non-motor symptoms in genetically defined dystonia: Homogenous groups require systematic assessment. *Parkinsonism Relat Disord* 2015;21(9):1031–1040. <https://doi.org/10.1016/j.parkreldis.2015.07.003>.
15. Rafee S, Ndukwue I, O'Riordan S, Hutchinson M. Reliability of DNMSQUEST as a Screening Tool for Mood Disorders in Cervical Dystonia. *Movement Disord Clin Pract* 2021;8(6):925–931.
16. Smit M, Kuiper A, Han V, et al. Psychiatric co-morbidity is highly prevalent in idiopathic cervical dystonia and significantly influences health-related quality of life: Results of a controlled study. *Parkinsonism Relat Disord* 2016;30:7–12.
17. Wadon ME, Bailey GA, Yilmaz Z, Hubbard E, ALSaeed M, Robinson A, et al. Non-motor phenotypic subgroups in adult-onset idiopathic, isolated, focal cervical dystonia. *Brain Behav* 2021;11(8):e2292. <https://doi.org/10.1002/brb3.2292>.
18. Bailey GA, Martin E, Peall KJ. Cognitive and Neuropsychiatric Impairment in Dystonia. *Curr Neurol Neurosci Rep* 2022;22(11):699–708. <https://doi.org/10.1007/s11910-022-01233-3>.
19. Smit M, Albanese A, Benson M, et al. Dystonia Management: What to Expect From the Future? The Perspectives of Patients and Clinicians Within DystoniaNet Europe. *Front Neurol* 2021;3(12):646841.
20. Klingelhofer L, Chaudhuri KR, Kamm C, et al. Validation of a self-completed Dystonia Non-Motor Symptoms Questionnaire. *Ann. Clin. Transl. Neurol.* 2019;6(10):2054–2065.
21. Klingelhofer L, Kaiser M, Sauerbier A, et al. Emotional well-being and pain could be a greater determinant of quality of life compared to motor severity in cervical dystonia. *J Neural Transm* 2021;128(3):305–314.
22. Timmers ER, Smit M, Kuiper A, et al. Myoclonus-dystonia: Distinctive motor and non-motor phenotype from other dystonia syndromes. *Parkinsonism Relat Disord* 2019;69:85–90.
23. Wagle Shukla A, Brown R, Heese K, et al. High rates of fatigue and sleep disturbances in dystonia. *Int J Neurosci* 2016;126(10):928–935.
24. Ben-Shlomo Y. What are the determinants of quality of life in people with cervical dystonia? *J Neurol Neurosurg Psychiatry* 2002;72(5):608–614.
25. Gharzai L, Harney J, Higgins S, et al. Alarming levels of stigma toward generalized dystonia: A cross-cultural comparison. *Clin Park Relat Disord* 2020;3:100059.
26. Rinnerthaler M, Mueller J, Weichbold V, Wenning GK, Poewe W. Social stigmatization in patients with cranial and cervical dystonia. *Mov Disord* 2006;21(10):1636–1640.
27. Tian WT, Huang XJ, Liu XL, et al. Depression, anxiety, and quality of life in paroxysmal kinesigenic dyskinesia patients. *Chin Med J (Engl)* 2017; 130(17):2088–2094.
28. Molina Y, Choi SW, Cella D, Rao D. The Stigma Scale for Chronic Illnesses 8-Item Version (SSCI-8): Development, Validation and Use Across Neurological Conditions. *Int J Behav Med* 2013;20(3):450–460.
29. Bocéréan C, Dupret E. A validation study of the Hospital Anxiety and Depression Scale (HADS) in a large sample of French employees. *BMC Psychiatry* 2014;14(1):354.
30. Leary MR. A brief version of the Fear of Negative Evaluation Scale. *Pers Soc Psychol Bull* 1983;9:371–375.
31. Sinclair SJ, Blais MA, Gansler DA, Sandberg E, Bistis K, LoCicero A. Psychometric properties of the Rosenberg Self-Esteem Scale: overall and across demographic groups living within the United States. *Eval Health Prof* 2010;33(1):56–80.
32. Trousselard M, Steiler D, Duthel F, et al. Validation of the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) in French psychiatric and general populations. *Psychiatry Res* 2016;30(245):282–290.
33. Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30(6):473–483.
34. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *Int J Rehabil Res* 2008;31(2):165–169.
35. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. *Arch Neurol* 1989;46(10):1121–1123.
36. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
37. Ware JEJ, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 1995;33(4 Suppl):AS264–AS279.
38. Yang J, Shao N, Song W, Wei Q, Ou R, Wu Y, Shang HF. Nonmotor symptoms in primary adult-onset cervical dystonia and blepharospasm. *Brain Behav.* 2017;7(2):1–6.
39. Coenen MA, Eggink H, Tijssen MA, Spikman JM. Cognition in childhood dystonia: a systematic review. *Dev Med Child Neurol* 2018;60(3):244–255.
40. Eggink H, Coenen MA, de Jong R, et al. Motor and non-motor determinants of health-related quality of life in young dystonia patients. *Park Relat Disord* 2019;58:50–55.
41. Novaretti N, Cunha ALN, Bezerra TC, Pereira MAP, De Oliveira DS, Macruz Brito MMC, et al. The prevalence and correlation of non-motor symptoms in adult patients with idiopathic focal or segmental dystonia. *Tremor Other Hyperkinet Mov (N Y)* 2019;9:1–7.
42. Ferrazzano G, Berardelli I, Conte A, et al. Motor and non-motor symptoms in blepharospasm: clinical and pathophysiological implications. *J Neurol* 2019;266(11):2780–2785.
43. Berman BD, Junker J, Shelton E, et al. Psychiatric associations of adult-onset focal dystonia phenotypes. *J Neurol Neurosurg Psychiatry* 2017;88(7): 595–602.
44. Dayapoglu N, Ayyıldız Nİ, Şeker D. Fear of negative evaluation and the concealment of their disease by epilepsy patients. *Epilepsy Behav* 2020; 113:107539.
45. Kuramochi I, Iwayama T, Horikawa N, Shimotsu S, Watanabe S, Yamanouchi H, Yoshimasu H. Development and validation of the Epilepsy Self-Stigma Scale. *Epilepsia Open* 2021;6(4):748–756.
46. Klinke ME, Hjartardóttir TE, Hauksdóttir A, Jónsdóttir H, Hjaltason H, Andrésdóttir GT. Moving from stigmatization toward competent interdisciplinary care of patients with functional neurological disorders: focus group interviews. *Disabil Rehabil* 2021;43(9):1237–1246.
47. Ahem L, Stone J, Sharpe MC. Attitudes of neuroscience nurses toward patients with conversion symptoms. *Psychosomatics* 2009;50(4):336–339.
48. Argyropoulos GPD, van Dun K, Adamaszek M, et al. The Cerebellar Cognitive Affective/Schmahmann Syndrome: a Task Force Paper. *Cerebellum* 2020;19(1):102–125.
49. Salazar Leon LE, Sillitoe RV. Potential Interactions Between Cerebellar Dysfunction and Sleep Disturbances in Dystonia. *Dystonia* 2022;4(1): 10691.
50. Holub F, Petri R, Schiel J, Feige B, Rutter MK, Tamm S, et al. Association between insomnia symptoms and functional connectivity in the UK Biobank cohort (n = 29,423). *J Sleep Res* 2022;32:e13790.
51. Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. *Nat Genet* 2011;43(12):1252–1255.

Supporting Information

Supporting information may be found in the online version of this article.

Table S1. 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.

Table S2. 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 (SSCI8), Rosenberg Self Esteem Scale (RSES), Paroxysmal Events and Treatment.