Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Non-motor symptoms and quality of life in dopa-responsive dystonia patients

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ARTICLE INFO

Article history:
Received 24 May 2017
Received in revised form
13 September 2017
Accepted 6 October 2017

Keywords:
Dopa-responsive dystonia
GTP-cyclohydrolase deficiency
Non-motor symptoms
Psychiatry
Sleep
Fatigue
Health-related quality of life

ABSTRACT

Background: In patients with GTP-cyclohydrolase deficient dopa-responsive dystonia (DRD) the occurrence of associated non-motor symptoms (NMS) is to be expected. Earlier studies report conflicting results with regard to the nature and severity of NMS. The aim of our study was to investigate the prevalence of psychiatric disorders, sleep problems, fatigue and health-related quality of life (HR-QoL) in a Dutch DRD cohort.

Methods: Clinical characteristics, motor symptoms, type and severity of psychiatric co-morbidity, sleep problems, fatigue and HR-QoL were assessed in DRD patients with a confirmed GCH1 mutation and matched controls.

Results: Twenty-eight patients were included (18 adults and 10 children), from 10 families. Dystonia symptoms were well-controlled in all patients. According to the DSM IV patients significantly more often met the criteria for a lifetime psychiatric disorder than controls (61% vs. 29%, $p < 0.05$). In particular the frequencies of generalized anxiety and agoraphobia were higher in patients (both 29% vs. 4%, $p < 0.05$). Patients scored significantly higher on daytime sleepiness than controls (ESS, 11.2 vs 5.7, $p < 0.05$). Adult patients had significantly lower scores on the mental component of the HR-QoL (47 vs. 54, $p < 0.05$) than controls mainly associated with (worse) quality of sleep.

Conclusion: NMS were highly prevalent in our cohort of DRD patients, despite adequate treatment of motor symptoms. Our findings support the accumulating evidence of an important non-motor phenotype in DRD, with possible involvement of serotonergic mechanisms. This highlights the need to address NMS and the underlying neurobiology in patients with DRD.

1. Introduction

Autosomal dominant dopa-responsive dystonia (DRD) or Segawa disease is a rare condition caused by mutations in the guanosine triphosphate cyclohydrolase 1 (*GCH1*) gene. A typical presentation comprises young-onset lower limb dystonia with subsequent generalization and parkinsonian features [1]. Patients have diurnal fluctuations and a good sustained response to levodopa treatment. Penetrance is incomplete; around 38% in men and 87% in females, with females more severely affected [2].

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https://doi.org/10.1016/j.parkreldis.2017.10.005
1353-8020/

Over the last decade there is increasing awareness for non-motor symptoms (NMS) in dystonia patients [3]. Psychiatric co-morbidity, sleep disturbances and fatigue were all shown to have a significant impact on the health-related quality of life (HR-QoL) [4,5]. In DRD, NMS are even more suspected based on the underlying pathophysiology of the genetic defect. Mutations in the *GCH1* gene result in a deficiency of guanosine triphosphate cyclohydrolase 1 (GTP-CH-1), the first and rate limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4) [6]. Since BH4 acts as co-factor for the different aromatic acid hydroxylases, GTP-CH-1 deficiency not only impairs the synthesis of dopamine, but also of serotonin. Serotonin is known to be involved in the pathophysiology of a range of psychiatric and sleep disorders [7–10].

Until now, in DRD conflicting results have been reported on NMS. In a Dutch study with 18 patients major depressive disorder and obsessive compulsive disorder (OCD) were more prevalent compared to the Dutch population (44% vs. 19% and 22% vs. 0.9%, respectively) [11]. This higher frequency of psychiatric co-morbidity was confirmed in some case series [12–14], but contradicted in others [15,16]. Subjective sleep problems were reported in 10 of the 18 Dutch DRD patients [11]. In another cohort of 23 DRD patients this was not confirmed, but impaired sleep quality and depressive symptoms were associated with a lower HR-QoL [15]. Overall, a systematic controlled design to evaluate NMS was often lacking, or findings were based on small sample sizes.

In the current study we systematically evaluate for the first time the motor and non-motor features of DRD patients and assess the impact of symptoms on HR-QoL in a large cohort of Dutch patients, and compare it with matched controls. More insight in the NMS in DRD is essential, because this allows a more integrated therapeutic approach to improve the HR-QoL in DRD patients.

2. Methods

2.1. Study population

Patients with a confirmed mutation in the *GCH1* gene were eligible, both with and without a motor phenotype. We included children (aged $\geq$ 6yrs) and adults (aged $\geq$ 18yrs) plus age and sex-matched controls. Patients were recruited from several Dutch hospitals. Controls were recruited through open advertisements. Informed consent was obtained from all participants and the study was approved by the medical ethics committee of the University Medical Center Groningen (METc 2014/034).

2.2. Clinical and neurological assessment

Clinical data included a structured interview, with medical history, evolution of symptoms, medication use and effect, and family history. In the patient group, motor symptoms were assessed with a standardized videotaped neurological examination. The severity of dystonia was independently scored by two investigators (ET, AK) using the Burke Fahn Marsden Dystonia Rating Scale (BFMS) [17]. Parkinsonian features were scored with subscale three of the Unified Parkinson's Disease Rating Scale (UPDRS) [18]. The video-based scores of both investigators were combined into a mean score (intra-class correlation 0.94). During the study, all patients continued their usual medication regime.

2.3. Assessment of NMS and HR-QoL

The presence of psychiatric disorders, as defined in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), was evaluated with the Mini International Neuropsychiatric Interview – PLUS (MINI-PLUS) [19], and in children with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [20]. Validated questionnaires were used to assess the severity of current depressive, anxiety and OCD symptoms. Impaired sleep quality, excessive daytime sleepiness, fatigue and HR-QoL were also evaluated with validated questionnaires, with age-appropriate versions for children. See Supplementary Table 1 for details of the used questionnaires.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22. A p-value <0.05 was considered statistically significant. All baseline data were quantitatively described.

A χ^2-test or Fishers' exact test was used to assess the differences in consulting mental health care and the presence of DSM-IV diagnoses between the adult patient group and controls. To assess the influence of motor symptoms on having a (lifetime) psychiatric disorder we performed a binary logistic regression analysis.

A student t-test or, in case of non-normality, a Mann Whitney *U* test was used to assess differences in psychiatric, sleep and HR-QoL scales between groups. The scores of the adult and child version of the psychiatric questionnaires were combined by computing z-scores based on the control group. The scores on the different HR-QoL domains for adults were combined into two components (mental health and physical health) using factor analysis as described previously [21].

Associations between sleep, fatigue scores, HR-QoL and clinical characteristics were assessed using univariate correlation analysis. With multivariate regression analysis, we determined the influence of the variables with a $p < 0.05$ in the univariate correlation analysis. Assumptions of the multivariate regression analysis were checked.

3. Results

We included a total of 28 patients (mean age 38 yrs, range 10–77 yrs), from 10 different families, and 28 age and gender matched controls (mean age 38 yrs, range 11–80 yrs) (see Table 1).

3.1. Clinical characteristics

Twenty-three mutation carriers experienced motor symptoms and received treatment and 5 patients were mutation carriers without dystonic symptoms. The mean age of onset of dystonia was 8 years and all symptomatic patients developed dystonia before the age of 20 years. In a majority of patients dystonia started in the lower legs (n = 20, 87%), in 2 patients in their hands (9%) and in one in the neck.

Twenty-one of the symptomatic patients reported diurnal fluctuation (91%). Some patients indicated that factors worsening dystonia were tiredness (22%) and a combination of heavy work and stress (22%).

Seven patients (30%) had been wheelchair bound before treatment with levodopa was initiated, 8 patients (35%) reported a period in which they could only walk short distances or had to use walking-devices. The remaining patients had always been able to walk independently.

Currently, 21 patients are still on levodopa. Two symptomatic patients ceased treatment because they felt the benefits no longer outweighed the effort of daily medication taking. The 21 patients all experienced a marked effect of the treatment, 6 (29%) reported complete remission of motor symptoms, but 15 (71%) still had some mild residual symptoms, such as very mild dystonic posturing of feet and neck in the evening.

The majority of patients (n = 17, 81%) used a combination of

Please cite this article in press as: E.R. Timmers, et al., Non-motor symptoms and quality of life in dopa-responsive dystonia patients, Parkinsonism and Related Disorders (2017), https://doi.org/10.1016/j.parkreldis.2017.10.005