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

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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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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

Table 1
Clinical characteristics. Values are presented as mean (SD) or n (as indicated). Student t-tests were used to compute p-values. HC = healthy controls.

	Total			Adults			Children		
	Patients (n = 28)	HC (n = 28)	p	Patients (n = 18)	HC (n = 19)	p	Patients (n = 10)	HC (n = 9)	p
Gender M/F	9/19	8/20	0.77	4/14	4/15	0.93	5/5	4/5	0.81
Age median (range)	38.3 (22.3)	38.3 (22.1)	1.00	51.8 (15.7)	50.0 (16.8)	0.73	13.9 (2.1)	13.7 (2.0)	0.81
Motor symptoms	Patients (n = 28)			Patients (n = 18)			Patients (n = 10)		
Age of onset	7.6 (5.5)			8.8 (6.6)			5.9 (3.2)		
Duration of dystonia	27.4 (20.8)			40.9 (16.3)			7.9 (4.0)		
Age of diagnosis	24.0 (17.1)			33.3 (15.4)			9.1 (2.8)		
Time till diagnosis	14.0 (13)			22.2 (11.3)			3.0 (2.7)		
BFMS	6.4 (4.9)			6.9 (5.4)			5.5 (4.1)		

levodopa and carbidopa, the other 4 (19%) used levodopa with benserazide. Only 2 patients (1 adult and 1 child) have been using 5-hydroxytryptophan on top of the levodopa treatment, one of them stopped this treatment because a lack of efficacy while the other is still using 5-hydroxytryptophan. Two patients were currently under antidepressant treatment (paroxetine and mirtazapine) and one was successfully treated for depression with an SSRI in the past.

The symptomatic patients had a mean BFMS score of 6.4 (on a scale of 0–120) indicating mild dystonia, while the asymptomatic carriers had a mean score of 2.0. Symptomatic adult patients had a slightly higher score on the BFMS than the symptomatic children (6.9 vs. 5.5). No parkinsonism was observed (UPDRS = 0).

3.2. Psychiatric symptoms

The adult DRD patients had consulted mental health care professionals for psychiatric complaints twice as frequent as the adults in the control group (61% vs. 33%, p = 0.10). Reasons for these consultations were similar between groups; most frequently mood disturbances. One patient visited a psychologist because of problems with sleep and fatigue. In contrast to adults, children with DRD had consulted mental health care less frequent than controls (10% vs. 60%, p = 0.06).

A total of 17 (13 adults and 4 children) patients met the criteria for a lifetime psychiatric disorder according the DSM IV compared to 8 (5 adults and 3 children) persons in the control group (61% vs. 29%, p < 0.05). Most common were mood and anxiety disorders (see Table 2). In particular, a significantly higher prevalence of generalized anxiety and agoraphobia was found (both disorders 29% vs. 4%, p < 0.05).

On the quantitative scales the average scores of the patient group for severity of current depressive, anxiety and OCD symptoms were slightly higher compared to controls, but not significantly different (see Table 3). For children the severity scores were similar between the two groups without significant differences.

Similar to symptomatic mutation carriers, 3 of the 5 mutation carriers without dystonia met the criteria for a psychiatric disorder. This number is higher than in controls (29%), but probably due to the small sample size it did not reach statistical significance.

We assessed whether severity of motor symptoms predicts the presence of a psychiatric disorder but found no significant association between motor symptoms and the presence of a psychiatric disorder (see Supplementary Table 2).

Table 3
Severity of psychiatric symptoms. Values are presented as mean (SD) or mean (range) (as indicated). Student-t tests or Mann Whitney U tests were used to compute p-values.

Psychiatric symptoms	Patients	Healthy controls	P-value
Adults	N = 18	N = 18	
BDI	6.3 (5.1)	4.8 (4.9)	0.38
BAI	5.8 (3.3)	3.8 (3.9)	0.14
Y-BOCS (range)	2.4 (0–18)	0.1 (0–2)	0.26
Children	N = 10	N = 9	
CDI	6.9 (5.3)	7.3 (7.6)	0.91
SCARED-NL	88.7 (14.0)	94.0 (7.5)	0.35
CY-BOCS (range)	0.2 (0–2)	1.2 (0–9)	0.47
All	N = 28	N = 28	
BDI/CDI z-score	0.17 (0.93)	0.0 (0.96)	0.51
BAI/SCARED-NL z-score	−0.21 (1.2)	0.0 (0.98)	0.51
Y-BOCS (range)	1.7 (0–18)	0.5 (0–9)	0.59

Table 2
Lifetime prevalence of psychiatric disorders based on the MINI-PLUS interview. Values are presented as number of patients (%). Chi-square test or fishers exact test was used to compute p-values.

Psychiatric disorder	Patients (n = 28)	Healthy controls (n = 28)	P-value
Any psychiatric disorder	17 (61%)	8 (29%)	0.02
Generalized anxiety	8 (29%)	1 (4%)	0.03
Agoraphobia	8 (29%)	1 (4%)	0.03
Depressive disorder	9 (32%)	4 (14%)	0.11
Pain disorder	2 (7%)	2 (7%)	1.00
Specific phobia	4 (14%)	1 (4%)	0.35
Panic disorder	4 (14%)	2 (7%)	0.67
Social phobia	4 (14%)	0 (0%)	0.11
Attention deficit disorder	3 (11%)	0 (0%)	0.11
Obsessive compulsive disorder	2 (7%)	1 (4%)	1.00
Post-traumatic stress disorder	2 (7%)	1 (4%)	1.00
Substance dependence	2 (7%)	0 (0%)	0.49
Alcohol dependence	1 (4%)	2 (7%)	1.00
Body dysmorphic disorder	2 (7%)	0 (0%)	0.23

3.3. Sleep and fatigue

Patients did not report significantly more sleeping problems compared to controls (whole group 50% vs. 54%, adults 66% vs. 50%, children 20% vs. 60%). Four patients and 5 controls reported problems falling asleep, 3 patients and 5 controls had difficulties staying asleep as long as desired, but in both groups the majority had a combination of both. In the adult group significantly more patients reported fatigability (adults 55% vs. 22%, $p < 0.05$), but not in the whole (43% vs. 32%) and children's group (20% vs. 50%).

Twenty-two patients (age $\geq$ 15 yrs) completed the quantitative questionnaires about excessive daytime sleepiness (ESS), fatigue (FSS) and quality of sleep (PSQI). Patients had significantly higher scores on the ESS (11.2 vs 5.7, $p < 0.05$) but not on the FSS and the PSQI (Table 4). Significantly more patients fulfilled the criteria of excessive daytime sleepiness than controls (16 (73%) vs. 5 (24%), $p < 0.05$). More patients met the criteria for fatigue (8 (36%) vs. 5 (24%), and impaired sleep quality than the controls (17 (77%) vs. 10 (48%)), not reaching statistical significance.

The children (age <15 yrs) in the patient group and the controls had comparable scores on the parental sleep questionnaires (45.2 vs. 46.3), but significantly lower scores on the sleep self-report (28.7 vs. 36.8, $p < 0.05$), indicating less sleeping problems.

Asymptomatic mutation carriers had significantly lower scores on the ESS and the FSS than the symptomatic mutation carriers (respectively 23 vs. 39, $p < 0.05$; 5 vs. 13, $p < 0.05$). The lower scores on the PSQI did not reach significance (6 vs. 9). Scores of the asymptomatic mutation carriers were not significantly different to the scores of the control group.

A higher ESS score was positively associated with the severity of motor symptoms and depression (both $p < 0.05$; see Supplementary Table 3). A higher FSS score was positively associated with severity of motor symptoms and depression (both $p < 0.05$) and negatively with age of onset of dystonia ($p < 0.05$). The PSQI showed no association with the studied variables.

Multiple regression analysis resulted in a significant model to explain the variance in ESS score (Adjusted R^2: 0.32, $p < 0.01$; see Supplementary Table 4). The ESS score was significantly associated with severity of depressive symptoms (β: 0.6, $p < 0.01$) and also the variance in the PSQI score was explained with severity of depressive symptoms (Adjusted R^2: 0.62, $p < 0.01$; β: 0.8, $p < 0.01$).

3.4. HR-QoL

Adult patients scored significantly lower on the mental health component (perceived health) of the RAND-36 (47 vs. 54, $p < 0.05$), but not on the physical health component (47 vs. 50, see Supplementary Table 5). No significant HR-QoL differences were found in the pediatric group, nor between the asymptomatic mutation carriers and controls.

Both the univariate and multivariate analysis of the adult patient group showed that the mental health component score of the HR-QoL was negatively associated with sleep problems (PSQI score)(β: −0.54, $p < 0.05$; see Supplementary Tables 5 and 6). Univariate analysis showed that the physical HR-QoL was negatively associated with fatigue (<0.01), daytime sleepiness (<0.01), depression ($p < 0.05$) and positively associated with the age of diagnosis ($p < 0.05$). The multiple linear regression analysis showed that a high FSS score negatively influenced the physical component of HR-QoL (β: −0.77, $p < 0.01$), i.e. a lower HR-QoL was associated with more fatigue.

Table 4
Sleep and fatigue questionnaires. Values are presented a s mean (SD) or n (as indicated). Student-t test were performed to compute p-values.

	Patients	Healthy controls	p-value
Adult questionnaires	N = 22	N = 21	
Gender M/F	5/17	3/18	0.70
Age	45.2	46.2	0.88
ESS	11.2 (5.9)	5.7 (4.5)	<0.01
FSS	35.0 (16.2)	27 (14.0)	0.1
PSQI	8.4 (4.5)	5.7 (4.5)	0.06
Children questionnaires	N = 6	N = 4	
CSHQ	45.2 (3.7)	46.3 (6.7)	0.74
SSR	28.7 (4.5)	36.8 (4.5)	0.02

4. Discussion

Our study showed a significant higher lifetime prevalence of psychiatric disorders and daytime sleepiness in adult, but not pediatric DRD patients. The reported HR-QoL was low in the adult group despite good control of their motor symptoms and mainly associated with quality of sleep and fatigue.

Adult DRD patients had a significantly increased lifetime prevalence of generalized anxiety and agoraphobia compared to controls (both disorders 29% vs. 4%). Other psychiatric disorders, such as depression, panic disorder and social phobia, were also more prevalent but differences did not reach statistical significance. The prevalence of depression we found in our cohort is consistent with previous studies [11,14], but the prevalence of anxiety in our cohort is higher (57% vs. 19–25%) [11,14,16]. Similar to two previous studies [13,14], but different from the study of van Hove et al. we found a relatively low prevalence of OCD (7%). This latter difference might be explained by using a different standardized interview (MINI-PLUS vs. SCID). In line with the study of Brüggemann et al. we did not find differences in the quantitative scales assessing the current severity of depression and anxiety [15]. Based on our study we confirm that in DRD patients there is a higher lifetime prevalence of psychiatric co-morbidity, especially anxiety and agoraphobia.

Based on the pathophysiology of DRD, the higher prevalence of psychiatric co-morbidity in DRD patients is likely to be part of the phenotype instead of a secondary phenomenon of living with a motor disability [8]. The possible lack of serotonin due to GTP-CH-1 deficiency may be associated with psychiatric problems and treatment with agents that influence the serotonergic system seems effective in both anxiety and depression. In two patients of our cohort psychiatric symptoms had successfully been treated with serotonergic treatment, as was described in previous DRD patients with psychiatric complaints [11,13]. The severity of motor symptoms in our patients did not predict the presence of a psychiatric disorder. Furthermore, the prevalence of psychiatric disorders in asymptomatic and symptomatic mutation carriers was similar. These findings further support that anxiety and agoraphobia are part of the DRD phenotype.

Consistent with the study of van Hove, about half of the DRD patients in our cohort reported sleep disturbances [11], consisting of excessive daytime sleepiness, fatigue and reduced quality of sleep. In contrast to the comparable prevalence of psychiatric symptoms in symptomatic and asymptomatic mutation carriers, we didn't find more sleep problems and fatigue in the asymptomatic mutation carriers. This suggests that sleep disturbances and fatigue might be secondary to the dystonic symptoms. From literature it is known that excessive daytime sleepiness has negative effects on several behavioural, psychologic and cognitive domains [22]. Correspondingly, we found that excessive daytime sleepiness and fatigue were positively associated with depression and the severity of motor symptoms. On the other hand, serotonin

is a precursor of melatonin, a hormone known to play an important role regulating sleep [10]. The expected alterations in the serotonin metabolism in DRD patients suggest that sleep disorders can be part of the phenotype. The detected prevalence of sleep disturbances and fatigue in our DRD cohort is high. Whether this is part of the phenotype or secondary to the dystonia requires further studies.

Interestingly, children in the patient group did not have more psychiatric co-morbidity and sleep disturbances compared to controls. A study showed that psychiatric co-morbidity in DRD usually has an onset in adulthood, with a peak incidence between 41 and 50 years of age [11]. Consequently, it is possible that these children will develop more psychiatric disorders in the future.

In adult DRD patients we found a lower HR-QoL. Interestingly, not the motor symptoms, but the NMS, especially fatigue and quality of sleep, were associated with the decreased HR-QoL. This is in line with a previous study [15]. The scores of DRD patients on the HR-QoL are comparable to the scores found in different forms of focal dystonia [4]. This implicates that the NMS are, similar to focal dystonia, an important burden in daily life in DRD patients. It underscores the importance to recognize and address the NMS and initiate adequate treatment.

A limitation of our study is the small number of patients. However, the achieved sample size is relatively large seen in the light of the very low incidence of DRD (estimated 1:million worldwide); it is one of the largest cohorts of patients with genetically proven GTP-CH-1 deficiency. Due to the different questionnaires we had to use for children and adults the sample size was further reduced for some analyses. Although we did not always have enough power to reach significance, all findings did point in the same direction.

Concluding, NMS were highly prevalent in our cohort of DRD patients despite good control of the dystonic motor symptoms. Our findings support the accumulating evidence of an important non-motor phenotype in DRD. Adequate treatment of NMS will significantly contribute to a better HR-QoL and serotonin might be the missing link. This highlights the need for systematic research into NMS symptoms and the underlying neurobiology in patients with neurometabolic disorders.

Conflicts of interest

None.

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Author roles

E.R. Timmers: Organization and execution of the research project. Design and execution of the statistical analysis. Writing the manuscript.

A. Kuiper: Conception, organization and execution of the research project. Writing the manuscript.

M. Smit: Conception, organization and execution of the research project. Reviewing the statistical analysis and manuscript.

A.L. Bartels: Conception, organization of the research project. Reviewing the statistical analysis and manuscript.

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E.A.J. Peeters: Organization of the research project. Reviewing the manuscript.

T.J. de Koning: Conception and organization of the research project. Reviewing the statistical analysis and manuscript.

M.A.J. Tijssen: Conception and organization of the research project. Reviewing the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.10.005.

References

[1] M. Segawa, Y. Nomura, N. Nishiyama, Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease), Ann. Neurol. 54 (6) (2003) S32–S45, https://doi.org/10.1002/ana.10630.
[2] Y. Furukawa, A.E. Lang, J.M. Trugman, T.D. Bird, A. Hunter, M. Sadeh, T. Tagawa, P.H. St George-Hyslop, M. Guttman, L.W. Morris, O. Hornykiewicz, M. Shimadzu, S.J. Kish, Gender-related penetrance and de novo GTP-cyclohydrolase I gene mutations in dopa-responsive dystonia, Neurology 50 (1998) 1015–1020.
[3] K.J. Peall, A. Kuiper, T.J. de Koning, M.A.J. Tijssen, Non-motor symptoms in genetically defined dystonia: homogenous groups require systematic assessment, Park. Relat. Disord. 21 (2015) 1031–1040, https://doi.org/10.1016/j.parkreldis.2015.07.003.
[4] T. Pekmezovic, M. Svetel, N. Ivanovic, N. Dragasevic, I. Petrovic, D.K. Tepavcevic, V.S. Kostic, Quality of life in patients with focal dystonia, Clin. Neurol. Neurosurg. 111 (2009) 161–164, https://doi.org/10.1016/j.clineuro.2008.09.023.
[5] Y. Degirmenci, D.G. Oyekcin, C. Bakar, N. Kurklu, Anxiety and depression in primary and secondary dystonia: a burden on health related quality of life, Neurol. Psychiatry Brain Res. 19 (2013) 80–85. https://doi.org/10.1016/j.npbr.2013.01.002.
[6] H. Ichinose, T. Ohye, E. Takahashi, N. Seki, T. Hori, M. Segawa, Y. Nomura, K. Endo, H. Tanaka, S. Tsuji, Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene, Nat. Genet. 8 (1994) 236–242, https://doi.org/10.1038/ng1194-236.
[7] J.M. Monti, H. Jantos, The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking, Prog. Brain Res. 172 (2008) 625–646, https://doi.org/10.1016/S0079-6123(08)00929-1.
[8] J.J.J. Lopez-Ibor, Serotonin and psychiatric disorders, Int. Clin. Psychopharmacol. 7 (2) (1992) 5–11.
[9] M. Smit, A.L. Bartels, M. van Faassen, A. Kuiper, K.E. Niezen-Koning, I.P. Kema, R.A. Dierckx, T.J. de Koning, M.A. Tijssen, Serotonergic perturbations in dystonia disorders-a systematic review, Neurosci. Biobehav. Rev. 65 (2016) 264–275, https://doi.org/10.1016/j.neubiorev.2016.03.015.
[10] A. Brzezinski, Melatonin in humans, N. Engl. J. Med. 336 (1997) 186–195, https://doi.org/10.1056/NEJM199701163360306.
[11] J.L. Van Hove, J. Steyaert, G. Matthijs, E. Legius, P. Theys, R. Wevers, A. Romstad, L.B. Moller, K. Hedrich, D. Goriounov, N. Blau, C. Klein, P. Casaer, Expanded motor and psychiatric phenotype in autosomal dominant Segawa syndrome due to GTP cyclohydrolase deficiency, J. Neurol. Neurosurg. Psychiatry 77 (2006) 18–23 doi:77/1/18.
[12] I. Trender-Gerhard, M.G. Sweeney, P. Schwingenschuh, P. Mir, M.J. Edwards, A. Gerhard, J.M. Polke, M.G. Hanna, M.B. Davis, N.W. Wood, K.P. Bhatia, Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients, J. Neurol. Neurosurg. Psychiatry 80 (2009) 839–845, https://doi.org/10.1136/jnnp.2008.155861.
[13] H. Hahn, M.R. Trant, M.J. Brownstein, R.A. Harper, S. Milstien, I.J. Butler, Neurologic and psychiatric manifestations in a family with a mutation in exon 2 of the guanosine triphosphate-cyclohydrolase gene, Arch. Neurol. 58 (2001) 749–755 doi:noc00067.
[14] V. Tadic, M. Kasten, N. Bruggemann, S. Stiller, J. Hagenah, C. Klein, Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs, Arch. Neurol. 69 (2012) 1558–1562, https://doi.org/10.1001/archneurol.2012.574.
[15] N. Bruggemann, S. Stiller, V. Tadic, M. Kasten, A. Munchau, J. Graf, C. Klein, J. Hagenah, Non-motor phenotype of dopa-responsive dystonia and quality of life assessment, Park. Relat. Disord. 20 (2014) 428–431, https://doi.org/

10.1016/j.parkreldis.2013.12.014.
[16] E. Lopez-Laso, A. Sanchez-Raya, J.A. Moriana, E. Martinez-Gual, R. Camino-Leon, M.E. Mateos-Gonzalez, J.L. Perez-Navero, J.J. Ochoa-Sepulveda, A. Ormazabal, T. Opladen, C. Klein, J.I. Lao-Villadoniga, K. Beyer, R. Artuch, Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease, J. Neurol. 258 (2011) 2155–2162, https://doi.org/10.1007/s00415-011-6079-9.
[17] R.E. Burke, S. Fahn, C.D. Marsden, S.B. Bressman, C. Moskowitz, J. Friedman, Validity and reliability of a rating scale for the primary torsion dystonias, Neurology 35 (1985) 73–77.
[18] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129–2170, https://doi.org/10.1002/mds.22340.
[19] I.M. Van Vliet, H. Leroy, H. Van Megen, M.I.N.I. PLUS - M.I.N.I. Internationaal Neuropsychiatrisch Interview, Nederlandse Versie 5.0.0, 2000.
[20] D.V. Sheehan, K.H. Sheehan, R.D. Shytle, J. Janavs, Y. Bannon, J.E. Rogers, K.M. Milo, S.L. Stock, B. Wilkinson, Reliability and validity of the Mini international neuropsychiatric interview for children and Adolescents (MINI-KID), J. Clin. Psychiatry 71 (2010) 313–326, https://doi.org/10.4088/JCP.09m05305whi.
[21] C. Taft, J. Karlsson, M. Sullivan, Do SF-36 summary component scores accurately summarize subscale scores? Qual. Life Res. 10 (2001) 395–404.
[22] T. Roth, Effects of excessive daytime sleepiness and fatigue on overall health and cognitive function, J. Clin. Psychiatry 76 (2015) e1145, https://doi.org/10.4088/JCP.14019tx1c.