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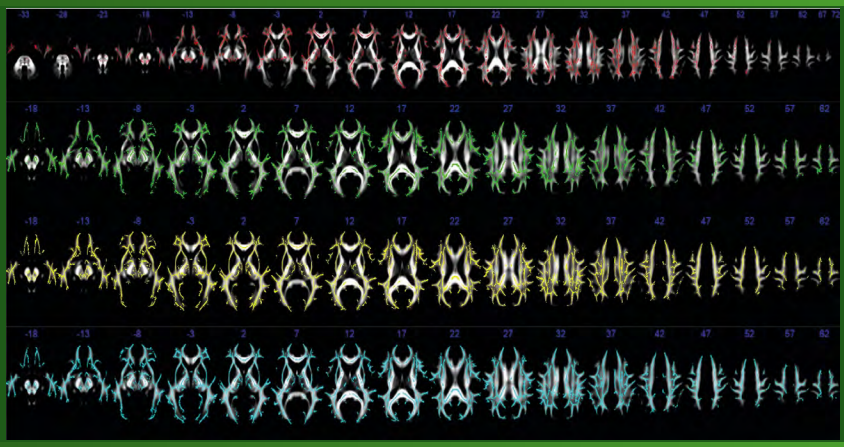

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Table of Contents

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
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Risk factors for dementia in Parkinson's Disease — the overuse of anticholinergic drugs

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ABSTRACT

Aim of the study. To determine the risk factors for dementia in a group of patients with Parkinson's Disease (PD), especially the effect of the anticholinergic burden assessed according to the Anticholinergic Cognitive Burden scale (ACB) and the CRIDECO Anticholinergic Load Scale (CALS).

Clinical rationale for the study. To provide information about factors associated with Parkinson's Disease dementia (PDD), especially the anticholinergic burden and testing the effect of both scales in an assessment of the anticholinergic burden in this group of patients.

Material and methods. A retrospective and cross-sectional analysis of medical records of patients with Parkinson's Disease admitted to the Neurology Department of the Medical University of Silesia, Katowice, Poland between 2019 and 2021 was performed. We found 418 patients with a diagnosis of PD, but 80 were excluded due to lack of a cognitive function assessment. Based on MMSE score, the remaining 338 patients were divided into two groups of patients with, and without, PDD. Next, demographic and clinical data was collected. The anticholinergic burden was assessed using the ACB and the CALS scales. According to the authors of these scales: if a scale score is of three or more points, this should be considered as a significant anticholinergic burden. Multiple logistic regression with backward elimination was used to assess factors significantly related to the presence of dementia, and two different models were used for both scales assessing the anticholinergic burden.

Results. 62 (18.3%) patients were diagnosed with PDD. Overall significant anticholinergic burden (≥ 3 points) was found in 31.95% of patients using CALS and in 18.93% using ACB. Anticholinergic burden was higher in patients with dementia (CALS 50 *vs.* 27.90%, p < 0 .001, ACB 43.5 *vs.* 13.41%, p < 0.001). According to both models, the factors significantly related to dementia were: age [ACB OR 1.114 (1.062–1.170), p < 0.001, CALS OR 1.123 (1.070–1.178), p < 0.001], significant anticholinergic burden [ACB OR 3.433 (1.746–6.750), p < 0.001, CALS OR 2.166 (1.157–4.055), p = 0.016] disease severity in the Hoehn-Yahr scale [ACB OR 1.752 (1.197–2.565), p = 0.004, CALS OR 1.831 (1.256–2.670), p = 0.002] and atrial fibrillation [ACB OR 5.593 (1.417–22.083), p = 0.014, CALS OR 5.159 (1.314–20.254), p = 0.016].

Conclusions and clinical implications. The anticholinergic burden is larger in PDD patients compared to PD patients without dementia. CALS or ACB scales are helpful in this risk assessment and might be crucial to avoid the development of PDD, especially in older PD patients with multimorbidities.

Key words: anticholinergic burden, anticholinergic drugs, Parkinson's Disease, dementia, cognitive impairment, anticholinergic burden scale, risk factors

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Introduction

Lewy body disease, including Parkinson's Disease dementia (PDD) and dementia with Lewy bodies (DLB), is one of the leading causes of cognitive impairment. The prevalence of dementia in Parkinson's Disease is c.30% and 3–4% of all patients with dementia have PDD [1]. In the course of PD, dementia usually occurs as a late, non-motor symptom. Dementia in PD is observed 2–6 times more frequently compared to the general population of the same age [1, 2]. The problem of PDD is especially important due to the fact that PD is the second most common neurodegenerative disease and that up to 80% of PD patients develop dementia [1–3]. Thus, cognitive impairment is a significant burden in this population, and significantly affects quality of life not only for patients, but also for caregivers [4].

A key aspect of developing effective preventive approaches is to identify possible strategies to modify risk factors for the development of dementia. There are many proposed risk factors of cognitive decline related to PD including: longer disease duration, older age at PD onset, male gender, disease severity, speech impairment, postural-instability-gait disorder subtype, hallucination, depression, blood pressure abnormality related to dysautonomia, REM sleep behaviour disorder, vascular risk factors, hyperhomocysteinemia, anticholinergic burden, lower level of education, low cerebrospinal fluid levels of amyloid-β42, and mutations in GBA, APOE4 or SNCA genes. However, the data from these publications is not consistent and some risk factors have been found only in single studies [5–13].

Neurochemically, the most significant deficit seems to be cholinergic, which is consistent with the view that the cholinergic system is crucially involved in cognitive function, with cholinergic dysfunction playing a pivotal role in the pathophysiology of dementia [14]. Anticholinergic drugs, which impair cholinergic pathways, are commonly used in clinical practice for the management of many conditions affecting older adults [15–17].

They affect many organs, causing adverse effects such as dry mucous membranes, constipation, urinary retention, delirium, orthostatic hypotension, as well as cognitive decline, which is the major problem associated with long-term exposure to substances having anticholinergic activity. Taking more than one anticholinergic drug has a cumulative effect and the sum of exposure to these drugs is called the 'anticholinergic burden' [16, 18, 19]. Some studies have suggested an association between anticholinergic drugs use and cognitive decline in PD [8, 9].

Therefore, there was a need to develop standardised methods for assessing the exposure to anticholinergic drugs and their impact on cognitive impairment. Multiple scales have been created, although there are significant discrepancies among them with regard to anticholinergic drugs and their anticholinergic potency [16, 20, 21]. One of the most commonly used is the Anticholinergic Cognitive Burden scale (ACB), published in 2008 and updated in 2012 [22–24]. A systematic review from 2015, which compared seven anticholinergic rating scales, showed the ACB with 88 drugs as the most frequently validated scale [24]. Also, research conducted by Lisibach et al. assessed ACB as the highest rated in the following domains: rigour of development, clarity of presentation, and applicability. With the German anticholinergic burden scale, it has reached the highest overall assessment [16]. Ramos et al. in their recent study devised the CRIDECO Anticholinergic Load Scale (CALS) for assessing anticholinergic load. They found an association between anticholinergic burden measured with CALS and cognitive impairment in patients with a subjective memory complaint, which was not confirmed using the ACB scale [20].

Clinical rationale

The aim of our study was to determine the risk factors for dementia in a group of patients with PD, especially the effect of the anticholinergic burden, and to compare the anticholinergic burden assessed according to the ACB scale and the CALS. To the best of our knowledge, this is the very first study to evaluate anticholinergic burden in patients with PD with the use of CALS. Our study provides information about potential risk factors related to PDD and tests the effect of the new tool in the assessment of anticholinergic burden in this group of patients, which will be important for future research and clinical management of PD.

Material and methods

We performed a retrospective and cross-sectional analysis of all consecutive patients diagnosed with PD and admitted to the Central Clinical Hospital of the Medical University of Silesia in Katowice, Poland between January 2019 and December 2021. The diagnosis, according to the current MDS criteria [25], was confirmed by movement disorders specialists. The initial group consisted of 418 patients. 80 patients were excluded due to lack of a cognitive function assessment. Based on the results of the neuropsychological assessment, the 338-strong study group was divided into PD with a diagnosis of dementia (MMSE score < 24 and cognitive dysfunction which interferes with the activities of daily living) and PD without a diagnosis of dementia (MMSE score ≥ 24). Other tests used in the cognitive function assessment included: the Stroop test, a trail making test, and a clock drawing test. The Addenbrooke's Cognitive Examination-Revised test was also used in some patients in the analysed period. In all cases, the patients' cognitive status was assessed in the 'ON' state, i.e.: 1–2 hours after taking the usual dose of dopaminergic drugs and with activated deep brain stimulation (if applicable).

The final study group consisted of 338 patients comprising 206 (61%) males and 132 (39%) females average age of 67 (61–72), aged from 35 to 86 years. The collected clinical data comprised sex, age, body mass index (BMI), duration

of PD, the assessment of motor status with part III of the MDS-UPDRS scale (Movement Disorder Society — Unified Parkinson's Disease Rating Scale) [26] performed without dopamine replacement therapy (DRT) and after the administration of a dose of levodopa, a rating on the Hoehn-Yahr scale, an assessment of cognitive function using the Mini Mental State Examination scale (MMSE), and the presence of depression (Beck Depression Inventory ≥ 14 pts). Data about daily levodopa equivalent dose (LEDD) was also collected [27]. An analysis of the laboratory results regarding thyroid function, lipid profile, homocysteine, vitamin D3, vitamin B12 and folate was conducted, and data on current treatment and comorbidities was collected. Anticholinergic burden was assessed using the CALS scale and the updated version of the ACB scale, with cut-off points as recommended by the authors [20, 22, 23]. ACB classifies drugs according to their serum anticholinergic activity or *in vitro* binding affinity with muscarinic receptors and clinically established anticholinergic adverse effects, and scores each drug from 0 to 3 points. A score from summation ≥ 3 is considered clinically relevant [20–24]. CALS is a scale based on a synthesis of the other scales found in a systematic review of the literature and includes 217 anticholinergic drugs each scoring 1–3 points according to their anticholinergic potency where 1 = low, 2 = medium, and 3 = high. A score from summation ≥ 3 is considered clinically relevant [20].

Statistical analysis was performed using STATISTICA 13 PL software (Tibico Software Inc.). Quantitative variables were presented as an arithmetic mean and a standard deviation (normally distributed variables) or a median and the interquartile range (variables of not normal/skewed distribution). The normality of distribution was assessed with the Shapiro–Wilk test. Qualitative variables were presented as absolute values and percentages. Intergroup differences for the quantitative variable were assessed using the U-Mann–Whitney or t-Student test, respectively. For qualitative variables, a chi-square test (Chi^2), or a chi square test with Yates correction (Chi^2YC) were used. Due to multiple comparisons, the Bonferroni correction was applied and a p-value of 0.002 was considered as significant, however the traditional cut-off point of 0.05 was also taken into account. Next, selected variables with p-value < 0.05 were analysed using a backward stepwise logistic regression model to evaluate risk factors associated with the occurrence of PDD, and two alternative models were built for ACB and CALS. The results of logistic regression were presented as odds ratios (OR) with 95% confidence intervals (CI) and Nagelkerke's R^2. The Hosmer–Lemeshow test was also performed to assess goodness of fit of final logistic regression models; its insignificant value ($p > 0.05$) suggests that the model was well-fitted. McNemar's and Cohen's kappa coefficients were used to compare scales. Agreement in Cohen's kappa was interpreted in the following way: < 0.00: poor; 0.00–0.20: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; and 0.81–1: almost perfect.

Due to the retrospective character of this work and data anonymisation, the Ethics Committee of the Medical University of Silesia waived the requirement to obtain ethical approval for this study.

Results

In the study group, 62 (18.3%) patients with PD were diagnosed with dementia. The group with dementia was older [72 (68–75) *vs.* 66 (57.5–71.5) years, p < 0.001] and presented a longer PD duration [11 (7.5–14) *vs.* 7 (3–12) years, p = 0.001] than patients without dementia. Demented patients displayed higher MDS-UPDRS part III scores both with [24.5 (18–32) *vs.* 16 (9–25), p < 0.001] and without dopamine replacement therapy [44 (40–58) *vs.* 36 (24.5–48), p < 0.001] and a higher Hoehn-Yahr score [3 (3–4) *vs.* 3 (2–3), p < 0.001], as well as LEDD [1.110 (605–1.500) *vs.* 720 (350–1.335) mg, p = 0.008].

Patients with PDD were characterised by a statistically higher occurrence of hypertension (58.06 *vs.* 42.91%, p = 0.030), atrial fibrillation (AF) (8.06 *vs.* 1.81%, p = 0.027), and the presence of two or more of the listed vascular risk factors [stroke/transient ischaemic attack (TIA), insert abbreviation (IHD), AF, arterial hypertension, and diabetes mellitus] (30.65 *vs.* 18.48%, p = 0.033) than the group of PD patients without dementia, although after the application of Bonferroni correction the differences did not reach statistical significance. They also displayed a higher frequency of anticholinergic burden defined by results ≥ 3 of the CALS (50 *vs.* 27.90%, p < 0.001) and ACB (43.5 *vs.* 13.41%, p < 0.001) scales. Overall, 108 (31.95%) patients had a significant anticholinergic burden according to CALS and 18.93% according to ACB. There was 81.7% agreement between the scales in terms of an assessment of a significant burden (Cohen's kappa = 0.53, moderate agreement). The difference between the numbers of patients who were found to have ≥ 3 points in both scales was significant in McNemar's test p < 0.001. 51.5% and 43.5% of patients took at least one anticholinergic drug according to CALS and ACB, respectively. All anticholinergic drugs according to CALS and ACB are set out in Supplementary Table 3.

PD patients with dementia showed lower BMI [24.15 (21.47–25.71) *vs.* 25.96 (24.02–29.05) kg/m^2, p = 0.01], lower total cholesterol (187.14 ± 47.37 *vs.* 204.49 ± 48.24 mg/dL, p = 0.013), lower LDL-cholesterol (LDL) (109.64 ± 39.16 *vs.* 123.42 ± 41.34 mg/dL, p < 0.028), and higher homocysteine level [16.22 (13.46–20.71) *vs.* 13.77 (11.2–17.1) µmol/L, p = 0.009], but statistical significance after the application of Bonferroni correction was not reached. There were no significant differences in terms of the sex of patients in any performed laboratory tests. No statistical difference was obtained in comorbidities such as diabetes mellitus, depression, past acute cerebrovascular conditions (stroke, TIA, SAH), ischaemic heart disease, valvular defect, cancer (past or current) or respiratory system diseases (asthma, chronic obstructive pulmonary disease, pneumoconiosis). A detailed comparison of both groups is set out in Table 1.

Table 1. Characteristics of quantitative and qualitative demographic and clinical variables comparing non-demented PD with PDD

	Non-dementia PD	PDD	P-value
Age, years	66 (57.5–71,5)	72 (68–75)	< 0.001
Duration of disease, years	7 (3–12)	11 (7.5–14)	0.001
BMI, kg/m^2	25.96 (24.02–29.05)	24.15 (21.47–25.71)	0.01
Hoehn-Yahr scale	3 (2–3)	3 (3–4)	< 0.001
MDS-UPDRS part III 'OFF'	36 (24.5–48)	44 (40–58)	< 0.001
MDS-UPDRS part III 'ON'	16 (9–25)	24.5 (18–32)	< 0.001
LEDD, mg	720 (350–1,335)	1,110 (605–1,500)	0.008
Total cholesterol, mg/dL	204.49 ± 48.24	187.14 ± 47.37	0.013
HDL cholesterol, mg/dL	59.05 (51.0–70.6)	56.05 (44.2–67.9)	0.118
LDL-C cholesterol, mg/dL	123.42 ± 41.34	109.64 ± 39.16	0.028
Triglycerides, mg/dL	85.6 (65–115)	79.8 (64.0–96.1)	0.117
TSH, µIU/mL	1.47 (1.03–2.13)	1.21 (0.93–1.80)	0.066
Vitamin B_{12}, pg/mL	344 (252–449.5)	367 (264.8–476.5)	0.405
Vitamin D_3, ng/mL	25.7 (17–33)	22.0 (14–37)	0.354
Folic acid, ng/mL	6.66 (4.84–8.96)	6.63 (4.72–10.50)	> 0.5
Homocysteine, µmol/L	13.77 (11.2–17.1)	16.22 (13.46–20.71)	0.009
Sex, % male	61.96	56.45	0.422
DBS, %	8.33	6.45	> 0.5
Depression, %	13.41	19.35	0.244
Diabetes, %	12.32	19.67	0.146
CALS ≥ 3, %	27.90	50	< 0.001
ACB ≥ 3, %	13.41	43.5	< 0.001
HT, %	42.91	58.06	0.030
Stroke/TIA/SAH, %	4.56	4.84	> 0.5
IHD, %	14.49	17.74	> 0.5
Cancer (active or in history), %	3.76	9.68	0.09
AF/AFl, %	1.81	8.06	0.027
Heart valves defect, %	3.76	8.06	0.233
Asthma/COPD/pneumoconiosis, %	3.63	4.84	> 0.5
> 1 RF of dementia (without LDL), %	18.48	30.65	0.033

BMI — body mass index; LEDD — daily levodopa equivalent dose; DBS — deep brain stimulation; ACB — Anticholinergic Cognitive Burden scale; AF — atrial fibrillation; AFI — atrial flutter; CALS — CRIDECO Anticholinergic Load Scale; IHD — ischemic heart disease, COPD — Chronic Obstructive Pulmonary Disease; RF — risk factors

Variables including age, disease duration, assessment of disease severity in the Hoehn-Yahr scale, LEDD, presence of arterial hypertension, AF, and the presence of more than one vascular risk factor (stroke/TIA, ischaemic heart disease, AF, arterial hypertension, and diabetes mellitus) were included in the stepwise logistic regression analysis to assess their association with the occurrence of PDD in two alternative models for ACB and CALS scales. The Hoehn-Yahr scale and MDS-UPDRS are measures of disease severity and we decided to use the Hoehn-Yahr scale in regression analysis due to its simplicity. BMI and homocysteine were not included due to data incompleteness. Total cholesterol and LDL were not included due to lack of data in some cases and a possible association with malnutrition that can occur in advanced PD and can coexist with dementia and older age [28–30].

The influences of age, anticholinergic burden, higher Hoehn-Yahr stage, and AF were confirmed in both models as set out in Table 2. The Hosmer–Lemeshow test revealed that both models were well-fitted (CALS p = 0.23, ACB 0 = 0.49). Nagelkerke's R^2 were 0.265 and 0.293, respectively. OR for assessment of anticholinergic burden in CALS ≥ 3 was lower than for ACB ≥ 3 [2.166 (1.157–4.055) *vs.* 3.433 (1.746–6.750)].

Table 2. Results of logistic regression with risk factors of PDD with ACB and CALS

ACB (Nagelkerke's R^2 = 0.293)				
	OR	95% CI		P-value
Age, years	1.114	1.062	1.170	< 0.001
ACB > 2	3.433	1.746	6.750	< 0.001
Hoehn-Yahr scale	1.752	1.197	2.565	0.004
AF/AFI	5.593	1.417	22.083	0.0140
CALS (Nagelkerke's R^2 = 0.265)				
	OR	95% CI		P-value
Age, years	1.123	1.070	1.178	< 0.001
CALS > 2	2.166	1.157	4.055	0.016
Hoehn-Yahr scale	1.831	1.256	2.670	0.002
AF/AFI	5.159	1.314	20.254	0.019

OR — odds ratio; CI — confidence interval; ACB —Anticholinergic Cognitive Burden scale; AF — atrial fibrillation; AFI — atrial flutter; CALS — CRIDECO Anticholinergic Load Scale

Discussion

It is well established that age, sex and genetic predispositions are non-modifiable risk factors of dementia development, not only in Alzheimer's Disease, but also in PD. Age is the primary risk factor for developing dementia including PDD, and it was significantly associated with the presence of cognitive impairment in our study [5, 7, 31]. There has beendata suggesting that sex is an important risk factor for dementia. However, this was not found in our study. Unlike Alzheimer's Disease, male gender is a risk factor for PDD and it is associated with its faster progression [31]. Lack of association between male sex and dementia might be potentially interplayed with the chosen method of cognitive function assessment. A meta-analysis of risk factors for PDD by Xu et al. indicated that advancement of motor symptoms measured with MDS-UPDRS part III scale correlates with the occurrence of PDD. However, that research presented no association with higher score in the Hoehn-Yahr scale. Other studies, like the one performed by Guo, have found it to be a predictor of cognitive impairment in PD besides MDS-UPDRS part III [7, 32]. In line with this result, Marinus et al. have described a higher severity of motor symptoms in both scales as being independently associated with the occurrence of non-motor symptoms, with PDD and cognitive impairment among these [2]. AF is a condition frequently mentioned as contributing to dementia development in the general population, in post-stroke patients, in patients with Alzheimer's Disease, and in patients with vascular dementia [33]. It is also one of the most common comorbidities in PD patients, and some research considers AF to be even more frequent in PD patients than in the general population [34, 35]. However, data confirming its potential association with PDD is scarce [36]. Our study suggests that AF might be a potential risk factor for PDD, something which should be considered in future studies, but there is also a possibility that the relation of AF and cognitive functions could be related to some potential risk factors not assessed in our study.

Vascular risk factors, other than AF/AFI, have also been considered as risk factors for PDD, but the significance for the development of PDD differs between studies [6, 7, 37]. However, our study did not display any significant difference in vascular risk factors between PD patients with and without dementia, which seems to be in agreement with a large Swedish study which revealed that PDD is less associated with diabetes mellitus and ischaemic heart disease compared to Alzheimer's Disease [37].

Literature data suggests that an increased blood level of homocysteine, frequently present in PD patients, is related to levodopa therapy [11] and is associated with cognitive decline. However there was no significant difference in homocysteine level between the groups in our study [11].

It is known that patients with PD show poorer cognitive performance if they are assessed in the 'OFF' state. Data from the literature suggests that dopaminergic treatment does not have any negative effects on cognitive function, but also might reduce the risk of cognitive decline in PD patients [38, 39]. However, there were no statistically significant negative or positive effects of LEDD in our study.

In 1996, Pondal et al. in a small sample of patients identified long-term anticholinergic therapy as a risk factor for dementia in PD [40]. In 2009, Ehrt et al. published a prospective study which displayed a larger decline in MMSE for patients taking anticholinergics [8]. Also, a large retrospective study from Taiwan revealed that patients with a high cumulative dose of anticholinergics had a higher risk of developing dementia [9]. On the other hand, some studies have not found any association between anticholinergics and cognitive decline in PD patients. However, their authors did suggest that this could be related to factors such as a low anticholinergic burden in the analysed group or a short follow-up [41–43].

Our study is in agreement with parts of the previously acquired data, and suggests that the anticholinergic burden is related to worsening of cognitive function in this group of patients. However, it is not possible to conclude that the anticholinergic burden is related to long-term cognitive decline. The differences between studies might be explained by various ways of assessing the anticholinergic burden and cognitive function, as well as differences in the assessed populations and study designs.

In two studies using ACB, 15.5–18.5% of patients had more than 2 points and 41.5–46.3% took at least one anticholinergic drug; these seem to be similar results to those in our study [42–44]. Geriatric patients from the same area of Poland hospitalised in a geriatric ward had a lower anticholinergic burden (ACB ≥ 3 13.98%, ACB ≥ 1 40.73%) than PD patients from our study, which might suggest that the topic is especially relevant for PD patients [45]. In the study population, 15 patients had used biperiden, known to be a medication having a strong anticholinergic effect, which is marked by the highest score in CALS, but however was not included in the ACB scale [22, 23]. According to the 2017 National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of Parkinson's Disease in adults, there is no indication to use anticholinergic medications in the treatment of motor symptoms in PD [19, 46]. Among medicaments presenting a medium anticholinergic potency in CALS and ACB, the greatest importance was attached to amantadine with 76 cases [20]. Amantadine is not only an antagonist of the N-Methyl-d-aspartate (NMDA) receptor, but also improves striatal dopaminergic signalling owing to the inhibition of dopamine reuptake [47]. It is widely used as a second-line drug in PD treatment in spite of the (often anticholinergic) adverse effects [35]. The NICE guidelines note no evidence of improvement of motor symptoms or activities of daily living when applying amantadine to treatment, but suggests considering amantadine if "dyskinesia is not adequately managed by modifying existing therapy" [19].

Other anticholinergics with high or medium potency include psychiatric drugs, medications for urinary incontinence, which poses a significant problem in PD, and tramadol, which is a common analgesic drug.

The basis of pharmacological treatment of motor symptoms in PD remains levodopa, which revolutionised opportunities to fight this incurable disease. Additional drugs used in this indication belong to dopamine agonists, monoamine oxidase B inhibitors (MAO-B inhibitors), or catechol-O-methyl-transferase inhibitors (COMT inhibitors) which ensures an extension of an effective treatment and L-dopa sensitivity in patients. Both Levodopa-carbidopa and alternative medications such as entacapone belonging to COMT inhibitors, selegiline as a representive of MAO-B inhibitors, or rotigotine and pramipexole which belong to dopamine agonists, are assigned to the group with low anticholinergic potency according to CALS, but not according to ACB [20]. In the conducted research, the above-mentioned drugs have been used by the vast majority of patients. Though low scores are attributed to these drugs (1 point in CALS) their frequent usage in many combinations causes a considerable increase in the anticholinergic burden measured by CALS in patients with PD.

As many as 92% of geriatric patients with PD are characterised by multimorbidities [35]. It has been shown that more than half of them struggle with polypharmacy i.e. taking 5+ drugs [48]. The common practice is that geriatric PD patients have on average more than eight drugs prescribed [49]. To avoid the deterioration of cognitive function, it seems to be necessary to apply the treatment with a low anticholinergic potential in PD patients who are already at increased risk of dementia development. ARS like CALS or ACB may provide a valuable tool in avoiding harmful side effects of anticholinergics in PD patients. Another tool, which may increase drug safety in PD patients and reduce the anticholinergic burden, could be lists of inappropriate drugs for geriatric patients like the Fit fOR The Aged (FORTA) Classification, Beer's Criteria, the START/STOPP list, or the PRISCUS list [35, 49].

In terms of the anticholinergic burden, the most relevant seems to be the conversion of medications with high or medium potency to equivalents with low or no anticholinergic potency where possible. This concerns all of the above PD-specific drugs, including biperiden (displaying high potency) and amantadine (presenting medium anticholinergic potency) which, due to their negligible action, should be replaced with dopamine agonists or a levodopa therapy. Similarly, other medications should be considered for conversion for fear of an increased risk of cognitive deterioration.

Some drugs having medium to high anticholinergic potency in CALS (amitriptyline, clozapine, olanzapine or amantadine) are in group D ('avoid') in the FORTA Classification. Considering that, it seems reasonable to follow the current guidelines concerning diagnosis and treatment combined with the use of an ARS like CALS. This will allow effective treatment of PD patients and, despite multimorbidities and polypharmacy, will permit many of them to avoid dementia.

Our study has some limitations. The first is its retrospective and cross-sectional design, meaning that it is impossible to conclude that anticholinergics are related to dementia or only worsening cognitive function which could be reversed after discontinuation of the the anticholinergic drugs.

Secondly, due to data incompleteness, it was impossible to take into account the following potential risk factors: gene mutations, hallucinations, white matter lesions or increased homocysteine.

The next major limitation of this study was the method of statistical analysis, where the cognitive function assessment was based on total MMSE score with a cut-off of 24 points. However, the diagnosis of PDD was based on a neuropsychologist's opinion and DSM-IV criteria where all demented patients had been confirmed by a caregiver as having a significant interference of cognitive dysfunction with their activities of

daily living. This is not a precise method to assess cognitive function in PD, although it is included in the Level 1 MDS Task Force Criteria for PD dementia diagnosis [1, 50]. Other scales for cognitive function assessment were also used for clinical purposes during psychological assessment. However, due to their high heterogeneity in the analysed period and the better accessibility of the MMSE results, we decided not to include them in our analysis. All PD patients with a cut-off of 24 points had dementia, but the number of patients with a diagnosis of mild PDD might have been underestimated in our study.

Clinical implications/future directions

Older age, greater severity of disease, AF, and anticholinergic burden were all significantly associated with the presence of of PDD in our study. Our study results suggest that both the ACB and the CALS scales are valid for the assessment of anticholinergic burden, although CALS contains a wider list of medications.

The results of our study have clinical implications because they suggest that anticholinergics, which are commonly used in the PD population, are associated with cognitive dysfunction, which is one of the most important non-motor symptoms related to increased mortality and significantly affects the quality of patients' lives and those of their caregivers [4]. However, we could not conclude that anticholinergics cause PDD, due to the cross-sectional design of our study and the potential reversibility of their effect after proper drug adjustments.

This implies that proper drug management using tools such as CALS or ACB might be crucial to avoid the development of cognitive decline, especially in older patients with multimorbidities and advanced PD. Avoiding anticholinergics might also prove beneficial in the context of other non-motor symptoms such as orthostatic hypotension, delirium or constipation, which they can exaggerate [18, 19]. There is an overwhelming need for in-depth studies of the anticholinergic burden in the context of PPD, and especially large prospective studies.

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Serum amino acid profiling in differentiating clinical outcomes of multiple sclerosis

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ABSTRACT

Aim of the study. Amino acid metabolism is crucial for regulating immune responses and can be monitored in blood serum samples. This study aimed to analyse serum amino acid profiles in people with multiple sclerosis (pwMS), taking into account differences depending on the disease outcomes.

Clinical rationale for the study. Serum amino acid profiling is a promising, reproducible and minimally invasive technology, available at different stages of the disease, enabling the search for a specific biomarker to differentiate MS clinical outcomes.

Material and methods. The serum concentrations of 29 amino acids were determined using high-performance liquid chromatography mass spectrometry.

Results. A total of 121 pwMS (41 relapsing-remitting MS–RRMS; 55 secondary progressive MS - SPMS; and 25 primary progressive MS–RRMS) with a median Expanded Disability Status Scale (EDSS) score of 6 and 53 healthy controls (HCs) were included. We found significantly higher serum total amino acids concentrations in pwMS compared to HCs. Serum concentrations of arginine, 1-methyl-L-histidine and proline were higher in pwMS, while circulating citrulline, α-aminobutyric acid and tryptophan were lower in pwMS. We observed significant differences in serum total amino acids concentrations depending on MS type, with the highest level in the PPMS group and the lowest in the RRMS group. We found significantly higher serum levels of beta-aminoisobutyric acid in PPMS patients compared to those with RRMS and SPMS, and significantly higher serum levels of aspartic acid in PPMS patients compared to RRMS patients. From visual inspection, no trend was observed in total amino acids concentration with respect to the EDSS score. When analysing serum total amino acids concentration in pwMS with EDSS ≤ 5 compared to those with EDSS > 5, no significant differences were found.

Conclusions and clinical implications. Amino acid metabolism is altered in pwMS and depends on the clinical type of the disease. Further studies are needed to determine whether serum metabolomic profiling of amino acids may have an application in the search for clinical phenotype-specific MS biomarkers.

Key words: metabolomics, amino acid, multiple sclerosis, disability, biomarker

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Introduction

Multiple sclerosis (MS) is an acquired, chronic disease caused by autoreactive T and B lymphocytes targeting the central nervous system (CNS) antigens, leading to the primary destruction of myelin sheaths with subsequent axonal degeneration and neuronal loss [1, 2]. MS is an unpredictable and highly heterogeneous disease, and remains the most common non-traumatic cause of permanent disability in young adults [2, 3].

Typically, MS begins with an initial relapsing-remitting course (RRMS), mediated by adaptive and innate immune responses, and characterised by the formation of acute inflammatory demyelinating areas in the CNS. Over the next 15–20 years, RRMS usually evolves into a progressive phase of the disease with underlying diffuse neurodegenerative activity, resulting in steadily increasing neurological dysfunction, defined as secondary progressive MS (SPMS) [1, 4–6]. About 15% of patients experience a gradual disability worsening from the disease onset; this is classified as primary progressive MS (PPMS) [3]. Notably, the progressive types of MS are mainly driven by a heightened innate immune mechanism within the CNS [2, 7]. Both innate and adaptive immune systems are modulated by chemical signalling networks and depend on an adequate supply of amino acids necessary to maintain basal metabolism as well as protein molecules synthesis [8, 9].

Metabolomic profiling of amino acids is a promising method of elucidating underlying mechanisms and the search for biomarkers, as well as providing data on treatment strategies of both autoimmune and neurodegenerative diseases [10–13]. Depending on the possibility of endogenous synthesis, amino acids can be classified as: essential [lysine (LYS), histidine (HIS), threonine (THR), phenylalanine (PHE), tryptophan (TRP), methionine (MET), leucine (LEU), isoleucine (ILE), valine (VAL)]; conditionally essential [glutamine (GLN), arginine (ARG), cysteine (CYS), glycine (GLY), proline (PRO) and tyrosine (TYR)]; or non-essential [glutamate (GLU), alanine (ALA), serine (SER), asparagine (ASN), and aspartic acid (ASP)] [14]. Previous studies have reported changes in amino acid profiles in serum and cerebrospinal fluid (CSF) of pwMS. However, these studies were often restricted to relatively small patient groups, limited arrays of amino acids (e.g. excitatory or non-essential), and an assessment of various biological samples derived from patients with different MS types [15–17].

Currently, MS is diagnosed based on clinical features, magnetic resonance imaging (MRI) and the presence of a molecular biomarker in the form of oligoclonal bands (OCB) in the CSF [2, 3]. Although CSF analysis is a recognised diagnostic tool for assessing the inflammatory profile of the CNS, its collection can be associated with several inconveniences [15]. Therefore, biomarkers of MS available in serum are increasingly being sought because blood sampling is more accessible, less invasive, and more reproducible at any MS stage compared to routine CSF collection [18]. There is a strong need to discover new biochemical markers in the blood serum that may be useful in MS diagnosis and monitoring clinical outcomes of the disease [19].

The aim of this study was to analyse the profile of 29 amino acids in the serum of pwMS, taking into account differences depending on the disease outcomes.

Clinical rationale for the study

MS is characterised by unpredictable and highly heterogeneous clinical outcomes. There are major differences between the relapsing-remitting and progressive MS types, especially in terms of underlying pathogenesis, treatment response, and disability progression. The differences existing between MS types must be taken into account when choosing the appropriate disease-modifying therapies (DMTs). However, they are poorly reflected in commonly available diagnostic methods.

There is therefore a strong need to identify biomarkers that facilitate an early and accurate diagnosis of MS as well as differentiation between disease types. Amino acid metabolism is involved in the modulation of autoimmune responses and can be monitored in CSF and blood samples. Serum amino acid profiling is a promising, reproducible and minimally invasive technology, available at different stages of the disease, enabling the search for a specific biomarker to distinguish MS clinical outcomes.

Material and methods

Participants and study design

We conducted a cross-sectional study. The study population consisted of 121 pwMS (80 females) and 53 healthy controls (HCs). PwMS patients were recruited from the Neurology Outpatient Clinic at Sanitas (Bydgoszcz, Poland) and the MS Rehabilitation Centre (Borne Sulinowo, Poland). HCs had no evidence of central or peripheral nervous system disorders and were recruited from the local community of Bydgoszcz. Inclusion criteria for pwMS were a diagnosis of MS according to the revised 2017 McDonald criteria and age 18 years or older [3]. Exclusion criteria for pwMS were steroid treatment and/or disease relapse within three months preceding the blood draws. A relapse was defined as the presence of new, or the recurrence of previous, MS-related symptoms lasting more than 24 hours in the absence of infection and/or fever [3, 20].

The following clinical and demographic data were obtained from available medical records: age, sex, MS type, disease duration, disability status, and the use of DMTs. Patient disability was determined based on the Expanded Disability Status Scale (EDSS) [21]. MS clinical phenotypes were classified as RRMS, SPMS, or PPMS according to the Lublin and Reingold classification [22]. Blood samples (5 mL) were drawn at 7–9 a.m. after an overnight fast and stored at –80°C until metabolomics analysis. The study participants were instructed to maintain their current dietary habits and to avoid supplementation with

products that could increase protein intake within seven days preceding blood sample collection.

Chemicals and reagents

Amino acids standards at a concentration of 200 nmol/mL and the derivatisation reagents were included in the EZ:faast™ LC-MS Free Amino Acid kit. The EZ:faast™ amino acid analysis kit was obtained from Phenomenex, Inc. (Torrance, CA, USA). High-performance liquid chromatography (HPLC) grade methanol was obtained from Merck (Darmstadt, Germany). Ammonium acetate and formic acid were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Water was deionised and purified using a Milli-Q system (Millipore, Bedford, MA, USA) and used to prepare all aqueous solutions.

Instrumentation and conditions

The HPLC system consisted of a binary Nexera XR LC-20 AD pump (Shimadzu, Kyoto, Japan) and a Nexera XR SIL-20AC autosampler (Shimadzu, Kyoto, Japan). The chromatography was performed with an EZ:faast amino acid analysis-mass spectrometry column (250 × 3.0 mm, 4 µm). The column temperature was kept at 35°C while the autosampler was maintained at 4°C. A binary gradient elution was carried out with mobile phases A (10mM ammonium formate in water) and B (10mM ammonium formate in methanol). The flow rate was 0.25 mL/min, and the injection volume was 1 µL.

Triple quadrupole tandem mass spectrometric detection was conducted on an LCMS-8045 Mass Spectrometer (Shimadzu, Kyoto, Japan). Electrospray ionisation (ESI) mass spectrometry was performed in the positive mode. Multiple reacting monitoring was used for quantification by monitoring ion transition of amino acids. LabSolutions software was used for instrument control and quantification.

Stock solutions, standards and quality control samples

A mixed stock solution of amino acids at a concentration of 100 nmol/mL was prepared using LC-MS grade water and stored for a maximum of three months at –20°C. For quantitation purposes, the stock solution was diluted in water to prepare a working range of solutions for calibration from 0.01 to 75 nmol/mL.

The kit contains as internal standard an amino acid mixture of homoarginine (HARG), methionine-d3 (MET-d3) and homophenylalanine (HPHE). The concentration in calibrators and samples was set to 200 nmol/L. The ratio between the area below the peak of the internal standard and the area below the peak of the analyte in the chromatogram was calculated. The concentration of the analyte was calculated using the slope of a calibration curve and the determined ratio.

Sample preparation

An EZ:faast amino acid analysis kit was used for serum sample preparation, and the preparation steps were as described in the user manual. The EZ:faast amino acid analysis procedure consists of a solid phase extraction step followed by a derivatisation. The solid phase extraction is performed via a sorbent-packed tip that binds amino acids while allowing interfering compounds to flow through. Amino acids on sorbent are then extruded into the sample vial and quickly derivatised with reagent at room temperature in an aqueous solution. Derivatised amino acids concomitantly migrate to the organic layer for additional separation from interfering compounds. The organic layer is then removed, evaporated, and re-dissolved in an aqueous mobile phase and analysed on a LC/MS system.

Ethics

This study complied with the principles of the 1964 Declaration of Helsinki, and was approved by the Bioethical Committee of Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun (KB 135/2019). All subjects participated voluntarily and provided written informed consent to store their data.

Statistical analysis

The Kruskal-Wallis test was used to assess differences between continuous variables distribution (age, concentration) in relation to MS types. Post-hoc analysis was further used to explore differences between means while controlling the family error rate. Considering non-normally distributed data, differences between two groups were evaluated using Mann-Whitney U test. Bonferroni correction was used to adjust for multiple testing. Pearson's correlation was used to study the linear relationship between amino acids. All analyses and figures were done in Python [Van Rossum, G., & Drake, F. L. (2009). Python 3 Reference Manual, Scotts Valley, CA, USA: CreateSpace].

Results

The clinical and demographic characteristics of the study population are presented in Table 1. We found differences in age and sex distribution between pwMS and HCs ($p = 0.001$ and $p = 0.01$, respectively). Age differences were shown between patients with different MS types ($p < 0.001$).

We found higher serum total amino acids concentration in pwMS compared to HCs. At $\alpha = 0.05$ we observed significant differences in serum concentrations of some amino acids between pwMS and HCs, i.e. GLN ($p = 0.036$), ARG ($p = 0.0001$), citrulline (CIT) ($p = 0.0001$), 1-methyl-L-histidine (1MHIS) ($p = 0.0004$), 4-hydroxyproline (HYP) ($p = 0.047$), α-aminobutyric acid (ABA) ($p = 0.0004$), PRO ($p = 0.00005$), VAL ($p = 0.01$), TRP ($p = 0.0004$), LEU ($p = 0.036$), PHE ($p = 0.032$), and cystine (C-C) ($p = 0.041$). After Bonferroni correction (corrected p-value = 0.0017), the concentrations of ARG, CIT, 1MHIS, ABA, PRO, and TRP remained significant. Serum concentrations of ARG, 1MHIS and PRO were higher in pwMS

Table 1. Demographic and clinical data of study participants

	MS	HCs
Number of subjects (n)	121	53
Sex (male/female)	41/80	30/23
Age, years	52.5 ± 11.6	58.4 ± 12.8
Disease duration (years) [range]	16 ± 8.4	n.a.
Median EDSS score (IQR)	6 (4.0–6.5)	n.a.
MS type n (%)		
RRMS	41 (34%)	
SPMS	55 (45%)	
PPMS	25 (21%)	
Type of DMT n (%)		
Interferon-beta	2 (1.5%)	
Glatiramer acetate	1 (0.6%)	
Dimethyl fumarate	4 (3%)	
Mitoxantrone	4 (3%)	
Natalizumab	2 (1.2%)	
Fingolimod	1 (0.6%)	

MS — multiple sclerosis; RRMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis; PPMS — primary progressive multiple sclerosis; EDSS — Expanded Disability Status Scale; DMT — disease-modifying therapy; IQR — interquartile range

compared to the controls. Serum levels of CIT, ABA and TRP were lower in pwMS compared to HCs (Fig. 1A). Differences in serum concentrations of ARG, CIT, 1MHIS, ABA, PRO, and TRP between pwMS and HCs remained significant after dividing the compared groups by gender and applying multiple testing correction (Bonferroni corrected p-value = 0.0083). We found significant differences in serum total amino acids concentration depending on MS type, with the highest level in the PPMS group and the lowest in the RRMS group (PPMS *vs.* RRMS p = 0.0001, SPMS *vs.* RRMS p = 0.011 and PPMS *vs.* SPMS p = 0.04). Post-hoc analysis revealed significantly higher concentrations of beta-aminoisobutyric acid (BAIB) in PPMS patients compared to RRMS and SPMS patients (p = 0.033 for both comparisons) and significantly higher serum levels of ASP in PPMS patients compared to RRMS patients (p = 0.028). In terms of BAIB concentrations, several outlying points were observed (Fig. 1B). We did not reveal significant differences regarding serum levels of other analysed amino acids between pwMS and HCs or between patients with different MS types.

The visual inspection of serum amino acid concentrations in a function of age revealed a slightly positive trend for C-C concentrations in pwMS and a slightly negative trend for SER concentrations in HCs (Fig. 2A). We observed some slightly positive trends between MS duration and serum levels of SER, HYP, GLY and PRO, and a slightly negative trend for TYR levels (Fig. 2B). From visual inspection, no trend was observed in total amino acids concentration with respect to the EDSS score (Fig. 2C). When analysing serum total amino acids concentration in patients with EDSS < 5 compared to those with EDSS ≥ 5, no significant differences were found (p > 0.05).

Discussion

This study aimed to compare profiles of 29 amino acids in serum samples from pwMS and HCs, taking into account differences depending on the disease outcomes. We found higher serum total amino acids concentrations in pwMS compared to HCs. Furthermore, serum concentrations of ARG, 1MHIS and PRO were higher in pwMS, while circulating CIT, ABA and TRP were lower in pwMS compared to the controls. We found clinical phenotype-dependent differences in serum total amino acids concentrations, with the highest values in PPMS, followed by SPMS, and then RRMS. PPMS patients had significantly higher serum levels of BAIB than RRMS and SPMS patients, as well as significantly higher serum levels of ASP compared to those with RRMS.

It has been shown that amino acid metabolism is involved in the modulation of immune mechanisms [9]. Activated immune cells require increased access to amino acids and therefore its depletion may weaken the autoimmune responses [23]. A growing body of evidence suggests that pwMS have an altered amino acid metabolism with decreased catalytic activity resulting in increased secretion of pro-inflammatory cytokines, metabotoxins production, and a reduction in Treg cell numbers [11, 23]. As patients in our group were advised to maintain their current dietary habits and to avoid protein-rich meals within seven days preceding blood sample collection, impaired metabolism may underlie the observed elevated serum total amino acids concentration. Notably, we found significantly lower ABA levels in the serum of pwMS compared to HCs, which argues against increased protein catabolism or malnutrition as potential causes [24].

We demonstrated significant differences in serum total amino acids concentration between patients with different MS clinical phenotypes, with the highest values in the progressive MS types. Therefore, our results may indicate the potential utility of such assays in accurate identifying progressive MS types as well as in highlighting the potential role of amino acids metabolism in the mechanisms underlying disease progression. Fitzgerald et al. showed greater overall metabolomic dysfunction in pwMS compared to HCs, with lower circulating lactate-related metabolites of aromatic amino acids. These differences remained consistent after excluding pwMS for whom treatment status was missing, restricting the study sample only to patients on any DMTs, and including only progressive MS patients or only those who were not on a DMT at the time of blood collection [11]. The assumptions made by Fitzgerald et al. regarding progressive MS types indicate an altered amino acid metabolism in these patients, which was also reflected in our group [11].

Several amino acids have emerged as key biological regulators of immune responses. Among these, ARG and TRP deserve special attention. Interestingly, enzymes that catabolise TRP [tryptophan dehydrogenase (TDO) and two isoenzymes of indoleamine 2,3-dioxygenase (IDO 1, IDO2)] and ARG [two

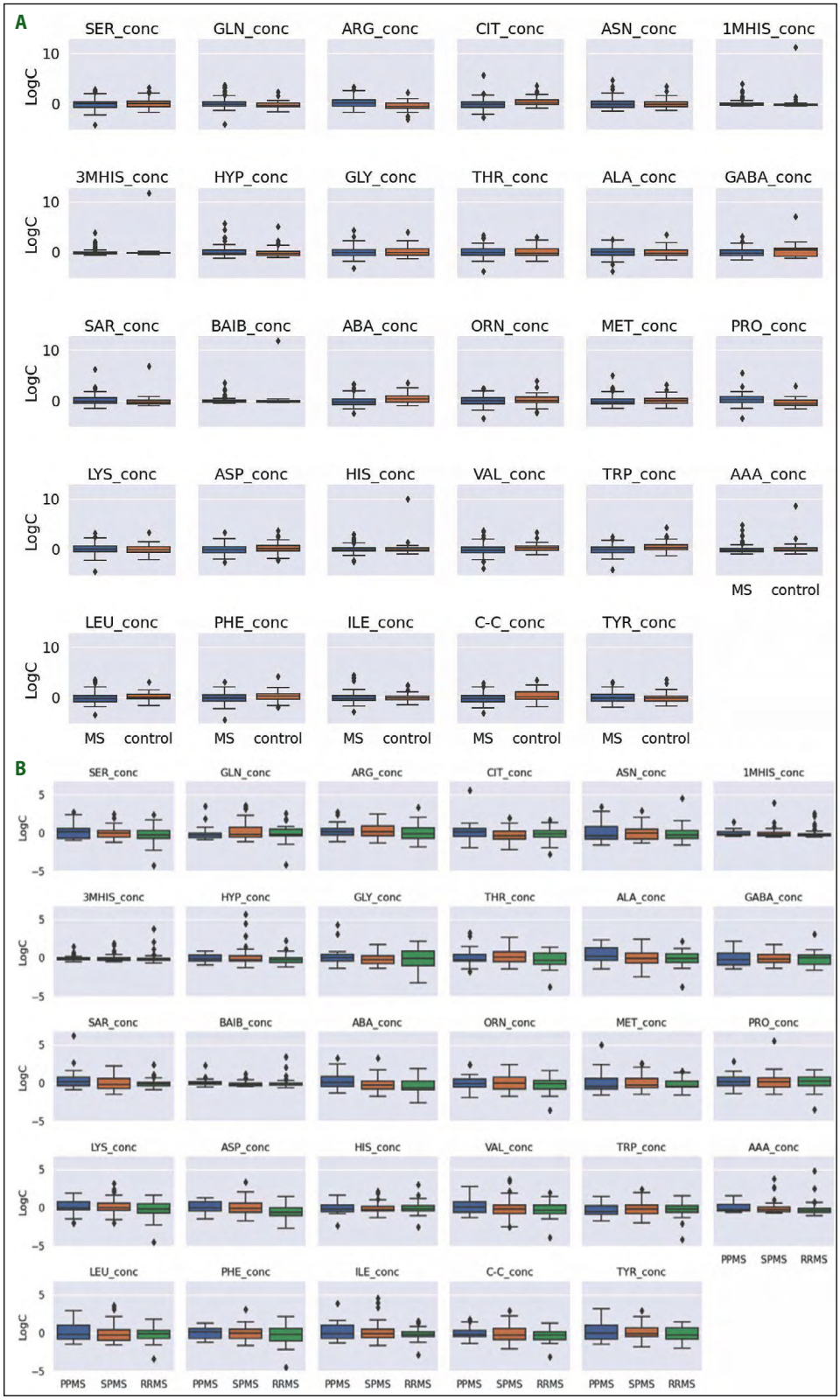

Figure 1. Centred and standardised concentrations of 29 amino acids in MS patients and controls (A), different MS types (B). Black dots represent outlying observations. MS — multiple sclerosis; RRMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis; PPMS — primary progressive multiple sclerosis; Conc — concentration; BAIB — beta-aminoisobutyric acid; ASP — aspartic acid; ARG — arginine; SER — serine; GLN — glutamine; CIT — citrulline; ASN — asparagine; 1MHIS — 1-methyl-L-histidine; 3MHIS — 3-methyl-L-histidine; HYP — 4-hydroxyproline; GLY — glycine; THR — threonine; ALA — alanine; GABA — gamma-aminobutyric acid; SAR — sarcosine; ABA — α-aminobutyric acid; ORN — ornithine; MET — methionine; PRO — proline; LYS — lysine; HIS — histidine; VAL — valine; TRP — tryptophan; AAA — α-aminoadipic acid; LEU — leucine; PHE — phenylalanine; ILE — isoleucine; C-C — cystine; TYR — tyrosine

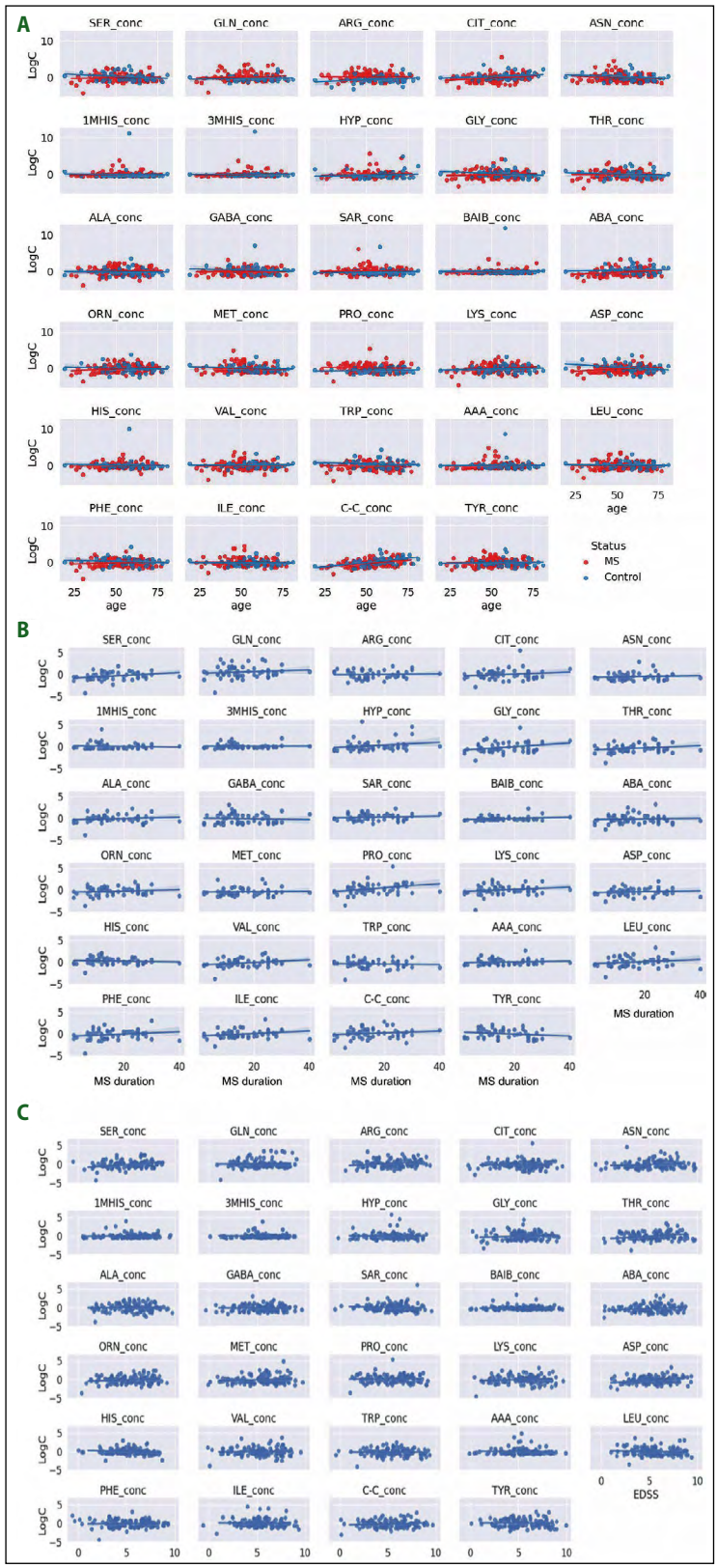

Figure 2. Centred and standardised concentrations of 29 amino acids in relation to age (**A**), MS duration (***B***) and EDSS (**C**). Red and blue lines represent linear regression lines. MS — multiple sclerosis; EDSS — Expanded Disability Status Scale; Conc — concentration; BAIB — beta-aminoisobutyric acid; ASP — aspartic acid; ARG — arginine; SER — serine; GLN — glutamine; CIT — citrulline; ASN — asparagine; 1MHIS — 1-methyl-L-histidine; 3MHIS — 3-methyl-L-histidine; HYP — 4-hydroxyproline; GLY — glycine; THR — threonine; ALA — alanine; GABA — gamma-aminobutyric acid; SAR — sarcosine; ABA — α-aminobutyric acid; ORN — ornithine; MET — methionine; PRO — proline; LYS — lysine; HIS — histidine; VAL — valine; TRP — tryptophan; AAA — α-aminoadipic acid; LEU — leucine; PHE — phenylalanine; ILE — isoleucine; C-C — cystine; TYR — tyrosine

arginase isoforms (ARG1, ARG2) and inducible nitric oxide synthase (iNOS)] have potential immunosuppressive properties [25–27]. In our study, analyses using individual amino acids showed significant differences in serum levels of TRP, ARG and two amino acids involved in ARG metabolism (PRO and CIT) between pwMS and HCs. ARG is a semi-essential amino acid that can be derived from diet, protein breakdown or synthesised from CIT. The catabolism of ARG occurs via multiple pathways, including degradation by iNOS to nitric oxide (NO) and CIT as well as arginase-mediated degradation leading to the formation of PRO, urea, ornithine and polyamines.

Thus, the higher serum concentrations of ARG and PRO with lower concentration of CIT found in our patients may indicate a shift in ARG metabolism towards decreased degradation by iNOS. This alteration of ARG metabolism may have protective effects on pwMS as polyamines and PRO are important for tissue repair, while the excessive production of NO causes nitroxidative stress and contributes to neurodegeneration in MS [28, 29, 30]. Furthermore, we showed a slightly positive trend for serum PRO concentration in relation to disease duration, which may confirm the significant role of altered ARG metabolism at different stages of the disease.

Conversely, serum TRP concentrations were significantly reduced in pwMS compared to HCs and a slightly negative trend of TRP levels was observed in relation to the disease duration. In line with our findings, decreased TRP levels in plasma obtained from pwMS have been previously reported [31, 32]. Recent studies have shown that activation of the kynurenine pathway (KP), responsible for more than 95% of TRP degradation, plays a key role in MS pathogenesis by modulating cell-mediated immune responses and may be associated with disease progression [33, 34]. Lim et al. found decreased serum TRP concentrations and a significantly higher kynurenine/tryptophan ratio in pwMS compared to HCs, and this was more pronounced in those with progressive disease types, suggesting that abnormalities in the KP may be associated with the conversion from early-mild stage to progressive MS forms, which is consistent with our findings [35].

The dominance of mechanisms mediated by excitatory amino acids may contribute to neurodegeneration within the CNS through excitotoxic injury of neurons and glial cells [17]. Murgia et al. identified ALA, ASP, and GLU metabolism among the most altered pathways in serum samples between patients with PPMS and RRMS [17]. In our study, patients with PPMS had higher serum ASP concentrations compared to RRMS patients. In this context, our findings are in line with the results reported by Murgia et al., and confirm a shift towards excitatory amino acids dominance in the progressive types of MS [17].

In the present study, patients with PPMS were characterised by higher serum BAIBA levels compared to those with SPMS and RRMS. BAIBA has been categorised as a myokine produced and secreted by skeletal myocytes during physical activity [36]. Recent studies have shown that BAIBA can inhibit hypothalamic inflammation and reverse the inflammatory processes in animal models of diet-induced obesity, protecting against vascular inflammation by enhancing the gene expression of the antioxidants and mitochondrial biogenesis-related molecules in humans. Therefore, the antiatherogenic properties of BAIBA could explain the beneficial effects of exercise on obesity and vascular endothelial function [37, 38]. So far, the impact of elevated serum BAIBA concentrations on MS pathogenesis and disability progression has not been reported. In our study, the increase in BAIBA concentrations in the serum of PPMS patients may have resulted from more intensive physical rehabilitation in this group compared to patients with an initial relapsing-remitting disease onset. Future studies are needed to address the potential role of BAIBA in MS, taking into account the intensity of physical rehabilitation.

Although we adopted dietary restrictions prior to blood sampling, we did not consider differences in the frequency and intensity of physical rehabilitation as potential factors influencing serum amino acid concentrations, which is a limitation of our study. Another limitation is a relatively large number of patients with progressive MS types, which made it possible to specify the profile of amino acids involved in neurodegenerative mechanisms, although this translates into overrepresentation of this group of patients and demographic heterogeneity of the entire study cohort.

Notably, age differences between the analysed groups found in our study were also observed in previous reports evaluating the metabolic alterations in MS and may confirm the overall heterogeneity of the disease [11, 17, 39]. So far, studies evaluating age- and sex-related differences in serum amino acid concentrations have used different methodologies, their results have been inconsistent, and they have not identified specific metabolic patterns [40–44]. These issues remain insufficiently addressed in relation to pwMS as well. In our study, the observed differences in serum concentrations of ARG, CIT, 1MHIS, ABA, PRO, and TRP between pwMS and HC remained significant after dividing the compared groups by gender. Furthermore, no linear trends (positive or negative) with ageing were found for the serum concentrations of the above-mentioned amino acids in pwMS and HCs.

With respect to MS type, the majority of our patients had a progressive MS course (66%) with reduced ambulatory ability (median EDSS score was 6, interquartile range 4.0–6.5), and 14 (11.5%) of them used DMTs. The lack of assessment of demyelinating lesions on magnetic resonance imaging and the low percentage of pwMS using DMTs can be considered as further limitations of our study. However, the negligible exposure of patients to DMTs at the time of blood sample collection may more reliably represent the changes in amino acid metabolism underlying the pathogenesis of various MS types. Finally, an undoubted limitation of this study is the lack of a prospective assessment of changes in plasma amino acid profiles in pwMS, including clinical phenotype-dependent differences.

Clinical implications/future directions

Our study revealed different patterns of serum amino acid profiles between pwMS and HCs as well as between patients with various disease types. The demonstrated differences may result from the participation of amino acids in immune responses, neurodegeneration processes and construction of muscle proteins. Therefore, serum amino acids may be considered as potential molecular biomarkers of MS, components of individualised therapeutic agents, or laboratory indicators to monitor the intensity of physical rehabilitation.

Future studies on amino acid profiling in MS involving a larger group of patients with different disease types are needed, taking into account the type of DMTs used, the profile of amino acids that best discriminates RRMS from progressive MS types and HCs, as well as the prospective evaluation of blood samples.

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Association between within-visit blood pressure variability, stroke, coronary heart disease, and cardiovascular mortality

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ABSTRACT

Introduction. Long-term variability in systolic blood pressure (SBP) is associated with a higher risk of cardiovascular events. Little is known about any association between within-visit SBP variability, stroke, coronary heart disease (CHD), and cardiovascular (CV) death.

Material and methods. Participants included adults ≥ 18 years who participated in the US National Health and Nutrition Examination Surveys from 1999 to 2012 linked to the national death index in 2012. Stroke was self-reported. SBP was obtained up to four times by a physician, using a manual sphygmomanometer according to standard procedures. Within-visit SBP variability was defined as the standard deviation of the BP measurements, stratified into quartiles. We evaluated the relationship between within-visit SBP variability and the odds of stroke or CHD using multivariable logistic regression, and with CV mortality, using multivariable Cox regression.

Results. Of the 27,987 adults, 16.4% were aged ≥ 65 years, 51.3% were female, 71.2% were white, and 10.7% were black. Factors associated with higher mean SBP variability included older age, hypertension, chronic kidney disease, peripheral artery disease, and smoking (all $p < 0.05$). The prevalence of stroke significantly increased across SBP variability quartiles, from 2.1% for quartile 1 to 3.7% for quartile 4 ($p < 0.001$). High SBP variability was associated with higher odds of stroke [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.4–2.2], coronary heart disease (OR 2.0, 95% CI 1.6–2.4), and increased risk of CV mortality [hazard ratio (HR) 2.7, 95% CI 2.3–3.1]. The relationships were not observed after adjusting for covariables.

Conclusions. Within-visit variability in SBP is associated with increased risks of stroke, coronary heart disease, and cardiovascular mortality, but the relationship is confounded by age and covariates.

Key words: blood pressure variability, stroke, coronary heart disease, cardiovascular mortality

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Introduction

Blood pressure (BP) variability has been recognised as a potential risk factor for stroke and coronary heart disease (CHD) [1, 2]. With hypertension being the most prevalent treatable risk factor for stroke and other vascular events [3, 4], its diagnosis and treatment should be of primary importance. The role of hypertension and the incidence of stroke and CHD have been investigated in several major prospective studies [5, 6]. Most of these studies have relied on a single blood pressure reading, but the prognostic value of visit-to-visit and within-visit variability and episodic hypertension has not been reliably established.

This prompted us to hypothesise that higher within-visit systolic blood pressure (SBP) variability is associated with higher odds of a stroke. In this study, we conducted a retrospective study using data from the National Health and Nutrition Examination Survey (NHANES) from 1999–2012 to evaluate the relationship between within-visit SBP variability and the risk of stroke, coronary heart disease, and CV mortality.

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Material and methods

Study population

The National Health and Nutritional Examination Survey (NHANES) is a series of cross-sectional, stratified surveys of the non-institutionalised civilian population in the United States. Individuals selected for inclusion in NHANES undergo an interview followed by a physical examination and laboratory testing administered by trained personnel. A detailed description of the plan and operations of each survey has been published [7]. Our study received approval from the National Centre for Health Statistics Research Ethics Review Board, and participants were asked to sign an informed consent form. For this study, we used the survey data from NHANES 1999–2012, including only individuals ≥ 18 years of age, and where there was available data on blood pressure, stroke, and CHD.

Blood pressure measurement and variability

Each person had 1–4 blood pressure measurements within the same visit. After at least five minutes of rest in the sitting position, brachial BP was measured by using either a sphygmomanometer or an oscillometer with a cuff of appropriate size monitored by a trained clinician based on the Seventh Joint National Committee recommendations [8]. We defined within-visit systolic blood pressure (SBP) variability using the standard deviation (SD) of the up to four SBP measurements, stratified into quartiles (Q1-4), with Q1 being the group with the lowest SBP variability and Q4 being the group with the highest SBP variability.

Assessment of stroke, CHD and CV mortality

Prevalence of stroke among the subjects was determined by any self-reported history of stroke in the NHANES 1999–2010 survey database. We considered an answer of "Yes" to the question, "Has a doctor or other health professional ever told you that you had a stroke?" in the Medical Conditions (MCQ) section of the NHANES questionnaire, as a positive self-reported history of stroke. The participants were asked if they had been told by a doctor or another health practitioner that they had CHD. If the individuals replied yes to this question, they were considered positive for CHD existence.

We calculated the CV mortality rates. We used data from NHANES III linked mortality file, in which the NHANES III eligible participants were matched, using a probabilistic matching algorithm, to the National Death Index up until the end of 2012 to determine their mortality status. Deaths from cardiovascular diseases were identified by using the International Classification of Disease 10th revision (ICD-10), codes I00-I99. A detailed description of the methodology is described elsewhere [9].

Covariates

Demographic and comorbid covariates included were age, sex, education (≤ 12th grade, > 12th grade), ethnicity (i.e. Caucasian, African-American, Mexican-American, or other), poverty income ratio (≤ 200%, > 200%), smoking status (ever smoker), hypertension, diabetes, hypercholesterolemia, myocardial infarction (MI), and chronic kidney disease (CKD).

Hypertension was defined as a self-reported history of hypertension, being on antihypertensive medication, or a blood pressure recording of > 140/90 mmHg. Diabetes was defined as a self-reported history of diabetes, being on antidiabetic medication, or haemoglobin A1C ≥ 6.5%. Hypercholesterolemia was defined as a history of anti-cholesterol medication or a total serum cholesterol ≥ 240 mg/dL. CKD was defined as a urine albumin to urine creatinine ratio > 30 mg/dL.

Statistical analyses

Baseline characteristics were presented as a percentage for categorical variables and compared across the SBP variability quartiles using the Rao-Scott Chi-Square test. Survey-weighted prevalence rates of self-reported stroke and CHD/MI were calculated and compared across SBP variability quartiles. To evaluate the relationship between the severity of SBP variability and odds of stroke and CHD/MI, univariable and multivariable logistic regression analyses were performed. To evaluate the association between the severity of SBP variability and the risk of CV mortality, the Cox regression model, before and after adjusting for covariables was performed. Model 1 was adjusted for demographic factors including age, sex, education, ethnicity, and poverty index ratio. Model 2 was also adjusted for medical conditions including hypertension, diabetes, myocardial infarction, chronic kidney disease, and smoking. The statistical significance was defined as p for interaction < 0.1 and a 2-side p value of < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Study characteristics

We identified 27,987 patients who met the inclusion criteria from NHANES 1999–2010. The baseline characteristics of the sample population are set out in Table 1. Age distribution was 49.2%, 34.4%, 12.6%, and 3.8% for patients aged 18–44, 45–63, 65–79, and ≥ 80, respectively. The proportion of patients with increased BP variability across severity quartiles decreased in the youngest age group (18–44), while the proportion of patients with increased severity of BP variability increased in the oldest age groups (65–79, ≥ 80; Tab. 1). Participants with the highest BP variability (Q4) were more likely to be Caucasian and to have more prevalent comorbid conditions, including hypertension, diabetes, MI, CKD, and smoking history (p < 0.05).

Risk of stroke and coronary heart disease across within-visit BP variability

Of the 27,987 subjects, 986 had a self-reported history of stroke. The prevalence of stroke in the sample population

Table 1. Patient characteristics across SBP variability quartiles (Q1–4), NHANES 1999–2010

	Overall	Q1	Q2	Q3	Q4	p-value
	N%	N%	N%	N%	N%	
Age						< 0.001
18–44	49.2%	58.4%	55.2%	48.3%	32.2%	
45–64	34.4%	30.6%	32.9%	36.2%	38.9%	
65–79	12.6%	8.7%	9.6%	12.3%	21.1%	
≥ 80	3.8%	2.3%	2.3%	3.2%	7.7%	
Sex						0.100
Male	48.7%	48.5%	49.6%	49.6%	47.2%	
Female	51.3%	51.5%	50.4%	50.4%	52.8%	
Ethnicity						< 0.001
Mexican-American	7.8%	8.7%	8.3%	7.7%	6.4%	
Caucasian	71.2%	69.5%	70.7%	71.1%	74.0%	
African-American	10.7%	11.1%	11.2%	10.4%	9.9%	
Other	10.3%	10.7%	9.9%	10.8%	9.7%	
Education						0.072
≤ 12th grade	44.6%	44.0%	44.1%	43.9%	46.5%	
> 12th grade	55.3%	55.8%	55.8%	56.0%	53.4%	
Unknown	0.1%	0.2%	0.1%	0.0%	0.1%	
PIR						0.566
≤ 200%	31.5%	32.4%	31.0%	31.4%	31.0%	
> 200%	61.6%	60.6%	61.9%	62.1%	61.8%	
Unknown	6.9%	7.0%	7.1%	6.5%	7.1%	
Medical history						
Hypertension*	35.5%	28.9%	30.9%	33.8%	50.3%	< 0.001
Diabetes†	9.4%	7.4%	8.3%	10.0%	12.3%	< 0.001
Hypercholesterolemia‡	27.6%	24.0%	25.3%	27.9%	34.5%	< 0.001
Myocardial infarction	3.3%	2.5%	2.8%	3.4%	4.7%	< 0.001
Chronic kidney disease§	8.8%	8.2%	6.9%	7.9%	12.4%	< 0.001
Peripheral arterial disease**	16.1%	14.6%	15.8%	16.1%	17.4%	0.102
Ever smoker	48.5%	47.7%	47.1%	49.0%	50.5%	0.040

*BP > 140/90 or on anti-hypertensive medications, or self-report; †Haemoglobin A1C ≥ 6.5% or on diabetes medications, or self-report; ‡Total serum cholesterol ≥ 240 mg/dL or on anti-cholesterol medications; §Urine albumin to urine creatinine ratio > 30 mg/g; ** ABI < 0.9 or ABI > 1.3. Myocardial infarction, ever smoking: self-report

was 2.6% [standard error (SE) 0.12] overall. Those with the highest SBP variability (Q4) had a higher prevalent stroke compared to those with the lowest (Q1) BP variability (3.7% *vs.* 1.8%; p < 0.001).

In our crude analysis, we observed that subjects with the highest BP variability (Q4) had higher odds of stroke compared to another group (OR 1.75, p < 0.001, Tab. 2). After adjusting for covariables, a relationship between BP variability and stroke was no longer observed.

In our study sample, 1,742 reported a history of CHD (Tab. 2). The prevalence of CHD in the overall cohort was 4.8% ± 0.19%. The prevalence increased from 3.6% ± 0.25% in the lowest quartile of SBP variability (Q1) to 6.9% ± 0.40% in the highest quartile of SBP variability (Q4) (p < 0.001, Tab. 2). In our crude analysis, the risk of having a MI/CHD was 1.99--fold in the subjects in the highest quartile of SBP variability (p < 0.001, Tab. 2). On further adjustment with demographics (Model 1) and vascular risk factors (Model 2), there was no significance seen for both stroke and CHD/MI.

CV-mortality across BP variability

CV mortality was highest in the patients with the highest quartile of BP variability (2.9%, SE 0.39, p < 0.001). The HR in our unadjusted model was also highest in the Q4 group (HR 2.73, SE 0.39, p < 0.001). After adjustment, these associations were no longer statistically significant; the adjusted HR in the highest quartile (Q4) compared to the lowest quartile (Q1) was 0.87 (p = 0.937, Model 2) for CV-related mortality.

Table 2. Rate and odds ratio (OR) of stroke, coronary heart disease/myocardial infarction, and cardiovascular mortality across within-visit SBP variability quartiles, NHANES 1999–2010

		Overall cohort	Q1	Q2	Q3	Q4	p-value
Stroke	No. of stroke/No. at risk	986/27,987	214/7,890	162/6,393	238/6,688	372/7,016	–
	Prevalence rate – % (SE)	2.6 (0.12)	2.1 (0.20)	1.8 (0.20)	2.7 (0.24)	3.7 (0.24)	< 0.001
	Crude OR	–	1.00	0.82	1.27	1.75	< 0.001
	Model 1 OR*	–	1.00	0.77	1.03	0.90	0.854
	Model 2 OR**	–	1.00	0.77	1.03	0.84	0.407
CHD/MI	No. of CHD and MI/No. at risk	1,742/27,987	381/7,890	329/6,393	427/6,688	605/7,016	–
	Prevalence rate – % (SE)	4.8 (0.19)	3.6 (0.25)	4.1 (0.28)	5.1 (0.26)	6.9 (0.40)	< 0.001
	Crude OR	–	1.00	1.13	1.42	1.99	< 0.001
	Model 1 OR*	–	1.00	1.06	1.13	0.99	0.940
	Model 2 OR**	–	1.00	1.07	1.11	0.95	0.620
CV-mortality	No. of CV deaths / No. person-years	305/118,447	63/34,256	50/27,403	63/27,697	129/29,089	
	Rate – CV deaths per 1,000 person-yrs (SE)	1.5 (0.14)	1.0 (0.23)	1.1 (0.26)	1.1 (0.29)	2.9 (0.39)	<0.001
	Crude HR	–	1.00	1.08	1.05	2.73	<0.001
	Model 1 HR*	–	1.00	1.02	0.77	0.94	0.640
	Model 2 HR**	–	1.00	1.09	0.72	0.87	0.937

CHD — coronary heart disease; CV — cardiovascular; MI — myocardial infarction; OR — odds ratio; *Model 1 (demographic): adjusted for age, sex, race, poverty index ratio, education; **Model 2 (demographic + comorbidities): model 1 + hypertension, diabetes, hypercholesterolemia, chronic kidney disease, peripheral artery disease, smoking

Discussion

In our study, we demonstrated that subjects with high within-visit SBP variability had a higher risk of stroke, CHD, and CV mortality. However, the relationship was not observed after adjusting for age and risk factors. We also noticed that those with the highest quartile of SBP variability (Q4) had the highest prevalent vascular risk factors.

This study addressed for the first time the prognostic implications of within-visit blood pressure variability.

In our study, we observed that the proportion of older age groups increased with each quartile. This can be explained in part by ageing, and chronic hypertension, which both lead to stiffening of the arteries. This stiffening of the large arterial wall results in an attenuation of the baroreflex function, which then causes a larger BP variability [10]. With ageing, the elastin-rich medial layer of the arteries undergoes damage or degradation of the elastic fibres (elastin and elastin-associated glycoproteins such as fibrillin-1) and increased aggregation glycosaminoglycans or collagen fibres, or both [11]. Other conditions such as diabetes which lead to increased crosslinking of the collagen via glycosylation have also been associated with increased stiffness of arteries [12]. Sasaki et al. [13] and Lacolley et al. [14, 15] demonstrated that an increase in BP variability induced by arterial baroreceptor denervation in rats, without an increase in mean blood pressure, was linked to aortic atherosclerosis, decreased arterial distensibility, and increased collagen content and density in arterial walls.

Another possible explanation could be conditions such as autonomic dysfunction that can also cause swings in haemodynamic variables [16], particularly in conditions such as diabetes, synucleinopathy, and Alzheimer's Disease which are known to cause autonomic dysfunction and have been associated with BP variability [17, 18]. Thus, high SBP variability may serve as a marker, rather than an independent risk factor, for these conditions. In our study, we similarly observed that the prevalence of diabetes mellitus increased with every quartile, concurring with the results of other studies [19, 20] showing that diabetes is associated with autonomic dysfunction manifested as high BP variability.

The presence of untreated hypertension, along with common behaviours such as smoking, low physical activity levels, and high obesity rates among young individuals, has a notable impact on the prevalence of cardiovascular diseases like myocardial infarction and atrial fibrillation [21]. It is widely acknowledged by clinicians that these conditions increase the risk of cerebrovascular events in the young population. Considering the known association between blood pressure variability and cardiovascular outcomes, it is plausible to suggest that the high prevalence of cardiovascular diseases and risk factors in young individuals, as mentioned above, may also contribute to variations in blood pressure readings.

It should be noted that a previous study (conducted in Poland) revealed a higher prevalence of arterial hypertension and peripheral arterial disease in the lower limbs among patients with DM [22]. This could lead to a compromised

bloodflow and vascular function in peripheral arteries that may lead to fluctuations in blood pressure readings. While DM and other systemic vascular risk factors could also cause baroreceptor denervation resulting in blood pressure variability, the causal pathway may also be reversed. Hyperglycaemia could directly harm the ischaemic brain by causing the build-up of lactate and intracellular acidosis. Additionally, the inflammatory response triggered by stress might elevate the levels of circulating free fatty acids in individuals with acute illnesses, which can negatively affect the ability of the endothelium to dilate blood vessels. Moreover, hyperglycaemia can contribute to reperfusion injury by intensifying oxidative stress and inflammation [22].

Brain injury such as stroke is known to cause central autonomic dysfunction, particularly lesions affecting the bilateral insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus [23]. Previous studies have shown an association between an excessive drop in nocturnal blood pressure and silent cerebrovascular lesions [24, 25]. The explanation for this could be pre-existing cerebral ischaemia that could lead to both altered central autonomic control of blood pressure [26, 27] and an increased risk of stroke. Furthermore, BP variability is also known to associate with pro-inflammatory cytokine production, hyperglycaemia, and increased blood-brain-barrier permeability [28–31], all of which can contribute to an increased risk of stroke. Haemodynamic instability caused by high BP variability can also increase shear stress, resulting in small vessel disease, cerebral hypoperfusion, and neuronal cell damage [32].

Blood pressure variability may have a different effect on different vascular beds (cerebrovascular *vs.* cardiovascular). For instance, Hata et al. [33] demonstrated that the coefficient of variation between clinic SBP was slightly greater in 138 patients with stroke than in healthy controls [34], but not in patients with myocardial infarction, suggesting that the mechanism involved in larger office BP variability and the incidence of a stroke may be different from the mechanism that links 24-h BP variability and cardiovascular complications. A previous study found that home BP variability, as measured by SD of SBP, was related to CVD events in 2,455 individuals from a typical Japanese community who did not have a CVD risk [35]. These studies have indicated that environmental factors (mental and physical stress), poor compliance of arteries, and adherence to drug therapy by the patients were thought to be the possible reasons for causing BP variability leading to increased risks of MI and CV mortality [33]. However, another reasonable explanation is that the relatively quick BP variations assessed by this method have a traumatic impact on the CV system, encouraging the formation and progression of atherosclerosis.

Similar to our study, Verdecchia et al. [36] were unable to show an independent association between baseline BP variability, which was defined as the SD of ambulatory BP, and cardiovascular morbidity after adjusting for associated confounding factors such as ageing, diabetes mellitus, and severity of hypertension. Also in another study there was no significant association seen between the excessive circadian amplitude of BP and the occurrence of CHD [37]. This suggests the prognostic significance of 24h BP variability may have organ specificity.

Our study has several strengths, including a nationally representative sample of US adults with a long follow-up for mortality, rigorous and validated survey and examination procedures, adjustment for numerous possible confounders, and robust estimations of absolute mortality and cumulative 10-year mortality rates, with multiple models adjusting for various potential confounders. An advantage of using the NHANES data to explore a mechanistic hypothesis is that the results apply to the US population. By utilising within-visit blood pressure measurements, we successfully accounted for significant potential confounding factors, specifically mean blood pressure levels and the influence of antihypertensive medications. Our blood pressure measurements were conducted by extensively trained staff using a validated electronic device and standard protocols, thereby minimising any potential imprecision and bias in the data collection process.

This study also has several limitations. The available data on risk factor prevalence, including both our study and the NHANES, rely on self-reporting. However, it is important to acknowledge the limitations of self-reporting, such as potential biases associated with telephone surveys and the exclusion of individuals with health conditions. Additionally, in our population survey, we did not collect data on body mass index (BMI), preventing us from assessing the impact of obesity within our population over time.

The assessment of stroke relied on self-reporting, and crucial details such as stroke type, duration since stroke, severity, and functional status were not available. These factors, which could potentially impact upon mortality, were not accounted for in our study. Moreover, the absence of CT or MRI findings in the patients may have led to the inclusion of individuals with asymptomatic cerebrovascular lesions as control patients. However, it is important to note that the limitations arising from self-reported illness are probably mitigated to some extent. A previous study has demonstrated the validity of using self-reported illness as a measure of objective health [38]. NHANES only captures non-institutionalised individuals and those who can comprehend and respond to surveys, resulting in a possible bias towards a healthier population. This study used only four BP readings to calculate the variability.

In conclusion, the findings of this study provide evidence of significant associations between within-visit SBP variability and an increased risk of stroke, coronary heart disease, and CV mortality. Our results indicate that patients with the highest quartile of blood pressure variability are particularly susceptible to these adverse health outcomes. These findings underline the need for vigilant monitoring and management of blood pressure to minimise the risk of stroke.

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Differences in diffusion tensor imaging parameters of brain white matter tracts between patients with myotonic dystrophy type 1 and type 2 — a retrospective single-centre study

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ABSTRACT

Introduction. The main aim of our study was to compare diffusion tensor imaging (DTI) parameters in patients with myotonic dystrophy types 1 and 2 (DM1 and DM2).

Clinical rationale for the study. To ascertain whether DTI could be used to assess the integrity of white matter tracts in the brain and identify any abnormalities or disruptions in connectivity between different brain regions in patients with DM. By providing a more detailed understanding of the structural changes in the brain associated with DM, could DTI potentially be used to develop more effective treatments for the cognitive and neurological symptoms of the disorder?

Material and methods. We retrospectively compared MRI scans of 19 patients with DM1 to those of 23 healthy, matched controls, and of 16 patients with DM2 to those of 20 healthy, matched controls, and finally compared the DM1 and DM2 samples. Fraction anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) values were assessed using Tract Based Spatial Statistics (TBSS).

Results. In patients with DM1, a statistically significant decrease in the values of the FA parameter was revealed in 45/48 white matter tracts compared to patients with DM2. There was no statistically significant decrease in the values of the FA parameter in patients with DM2 compared to DM1. The values of MD and RD were significantly higher in 47 tracts in DM1 patients compared to DM2 patients. AD values were significantly higher in all 48 tracts in DM1 patients compared to DM2 patients. There were no tracts with increased MD, AD, or RD values in DM2 patients compared to DM1.

Conclusions. Our results indicate diffuse disintegration of white matter pathways in DM patients, especially in the DM1 group. The damage to all types of fibres (association, commissural, and projection) may explain the diversity of clinical symptoms, which were more severe in the DM1 group of patients than in the DM2 group.

Clinical implications. DTI in patients with DM may help us to understand the neural mechanisms underlying brain involvement during the disease. In future, it may help to identify biomarkers for disease progression and treatment response.

Key words: myotonic dystrophy 1, myotonic dystrophy 2, diffusion tensor imaging, brain imaging

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Introduction

Myotonic dystrophy (DM) is the most common type of muscular dystrophy in adults, characterised by progressive muscle degeneration because of a genetic defect. The main, muscular symptoms in DM are accompanied by problems with the heart and digestive system, and hormonal disorders.

Two types of DM have been identified as taking different courses [1, 2].

In type 1 DM, the pathology results from a mutation in the gene encoding the protein kinase DPMK (dystrophia myotonica protein kinase) consisting of a CTG repeat expansion, while a CCTG repeat expansion in the zinc finger protein 9 gene (ZNF9) has been identified in myotonic dystrophy type 2 [3, 4]. Type 1 occurs in young patients, including children, and the severity of its course is associated with the amount of CTG repeat numbers [5]. In this type, the peripheral muscles and the voluntary (striated) muscles of the face are mainly affected, but also the independent muscles such as the heart and diaphragm, and the smooth muscles (gastrointestinal tract etc.) gradually also become involved.

Type 2 has a milder course with adult onset only, and it involves exclusively proximal voluntary muscles. This means that the disability may be greater even with less advanced disease [1, 2].

Central nervous system involvement occurs in both types of myotonic dystrophy, with type 1 being more severe and manifested by intellectual disability, reduced intelligence quotient (IQ), memory disorders, visual and hearing impairment, excessive daytime sleepiness, avoidant personality, and low self-esteem [6–10]. In type 2, the IQ is usually normal, while visual-spatial disturbances, excessive daytime sleepiness, and a profile of psychological disorders (avoidant personality) occur at a similar frequency as in DM1, but to a lesser degree [7, 11, 12].

The pathogenesis of the involvement of the central nervous system is not fully understood. Some authors include myotonic dystrophies in the subgroup of neurodegenerative diseases called tauopathies because of intraneuronal accumulation of abnormally modified microtubule-associated tau protein in the brains of patients with DM [13–19].

Magnetic resonance imaging (MRI) is the best tool to assess the brain in patients with DM. In both types of DM, the lesions mainly concern white matter and are visible on T2/FLAIR images as white matter hyperintense lesions (WMHL). In type 1, they are located in the frontal and temporal lobes, while in type 2 they are located in the periventricular white matter in the frontal and parieto-occipital lobes. Characteristics for type 1 lesions located in the anterior part of the temporal lobes (anterotemporal white matter lesion, ATWML) are usually not observed in type 2 [20].

Novel techniques, such as T2 relaxometry, magnetisation transfer (MT), voxel-based morphometry (VBM), and diffusion tensor imaging (DTI), can specifically and more deeply analyse structural changes within white matter (WM), and they demonstrate extensive white matter involvement compared to morphological images [5]. In particular, DTI, based on a region of interest (ROI) approach or with the use of more advanced tract-based spatial statistics (TBSS), proves that white matter abnormalities in DM patients are more frequent and pronounced than has been previously suggested [21]. The DTI technique has been effectively used to assess the integrity of white matter pathways in various physiological conditions, including the learning process, memory, and brain ageing, as well as in numerous neurological diseases. It is also valuable in preoperative planning prior to the removal of a brain tumour or a cavernous haemangioma [22, 23].

The aim of our study was to compare DTI parameters in patients with DM1 and DM2 to those of sex- and age-matched healthy controls, and between DM1 and DM2 patients. Afterwards, we checked how the DTI parameters in DM1 and DM2 patients correlated with the duration of the disease.

Clinical rationale for the study

A study on DTI in patients with DM could provide important insights into the neural mechanisms underlying CNS involvement in DM. Specifically, DTI could be used to assess the integrity of white matter tracts in the brain and identify any abnormalities or disruptions in connectivity between different brain regions in patients with DM.

By providing a more detailed understanding of the structural changes in the brain associated with DM, DTI could potentially be used to develop more effective treatments for the cognitive and neurological symptoms of the disorder. Additionally, DTI might serve as a useful biomarker for monitoring disease progression and treatment response in patients with DM.

Material and methods

Participants

From the 37 MRIs performed in DM patients in the 2nd Department of Clinical Radiology of the Medical University of Warsaw, Poland between 2009 and 2020, we selected 35 adolescents for further analysis.

Only patients with a genetically confirmed mutation were included in the study, and they were assigned to the appropriate DM group (DM1 or DM2) according to the mutation type. The other inclusion criteria were: a good quality DTI examination using at least 20 diffusion directions, the absence of focal lesions other than those typical of DM on morphological sequences, and age above 18 years. Patients without a DTI sequence or with poor image quality were excluded from the study.

We formed two control groups (HC1 and HC2) age- and sex-matched to each type of DM.

It has been demonstrated that there are age-related changes in the integrity of white matter tracts, which are manifested

by alterations in DTI parameters. In older patients, there is a decrease in FA and an increase in MD [24].

Because of the significant difference in age between DM1 and DM2 patients, we introduced two age-matched control groups, to avoid the effect of age-related changes on the DTI parameters.

The control groups consisted of healthy subjects without any neurological symptoms and with no pathological lesions within the brain on structural MR images.

All procedures were performed in compliance with the Declaration of Helsinki. Ethical approval was not required due to the retrospective study design.

Data acquisition

All patients and controls underwent an MRI examination on a 1.5-T scanner (Avanto, Siemens, Erlangen, Germany). A 12-channel head coil was used. The examination protocol started from morphological sequences: 2D T2 TSE in transverse, coronal, and sagittal planes, 2D T2 FLAIR, 2D T1 SE, DWI in transverse plane, and sagittal 3D MPR T1 followed by DTI sequence. Detailed image parameters are included in Supplementary Table 1.

The DTI protocol differed depending on the date of acquisition: we started with a single-shell 20-direction protocol (between 2009 and 2011), but from 2012 we upgraded this to 30 directions of diffusion. Only six patients with DM1 and three with DM2 underwent a DTI study with the use of 20 directions of diffusion. The remaining 26 patients (13 with DM1 and 13 with DM2) underwent a DTI study with a 30-direction protocol. Accordingly, in the control group for DM1 there were six examinations with 20 directions and three in the control group for DM2.

Diffusion-weighted images were collected using a gradient echo-planar imaging sequence (echo time TE = 86 ms, repetition time TR = 3,300 ms with the two diffusion weightings of b1 = 0 s/mm^2 and b2 = 1,000 s/mm^2, voxel size 1.8 × 1.8 × 5 mm, FoV 230 mm, 25 slices per volume). The acquisition time was 5.05 minutes for 20 directions and 6.59 minutes for 30 directions of diffusion.

All patients and controls gave written informed consent for the examination and for the use of MRI data for research.

Data processing

Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) maps were calculated after susceptibility-induced distortion, eddy current, and head motion correction. DTI data was corrected by applying an affine transformation of each image to the B0 image using the Oxford FSL toolkit (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html). For each voxel, tensor eigenvectors and corresponding eigenvalues as well as FA, MD, RD, and AD values were computed.

FA, MD, RD, and AD maps were then fed into standard TBSS skeletonisation using the Oxford FSL toolkit [25].

Next, each subject's FA, MD, RD, and AD data was projected onto FMRIB58_FA standard space (which is in the same space as the MNI152 standard space). Each subject's FA and maps were visually inspected for the quality of this registration. Then, TBSS skeletons were segmented according to the Johns Hopkins ICBM-DTI-81 atlas containing 48 white matter tracts. For each region, average FA, MD, RD, and AD values were extracted.

Statistical analysis

Averaged FA, MD, RD, and AD values in the ROI were compared between DM1 and HC1, DM2 and HC2, and finally between DM1 and DM2 samples using a standard non-parametric test. False discovery rate (FDR) p values were computed using Freeman & Lane (1983) (default in FSL GLM randomize) to control the FDR for multiple tests.

To detect between-group differences, we used a cluster-based thresholding, a voxel-wise thresholding, and a threshold-free cluster enhancement approach (TFCE). We have presented the results based on threshold-free cluster enhancement, which provides better sensitivity and richer and more interpretable output than cluster-based and voxel-wise thresholding [26].

The number of permutations was set to 5,000. P-value < 0.05 after family-wise error corrections for multiple comparisons was applied.

The effect associated with the diffusion-encoding gradient directions (20 or 30 in this case) was included as an additional regressor in the statistical model. In this way, any differences due to the number of diffusion-encoding directions were regressed out during statistical comparisons.

FA, MD, RD, and AD values in white matter tracts were compared with disease duration.

Results

Patients

The final patient cohort consisted of 19 patients with DM1 (aged 20 to 57 years; mean age 39; median age 39; female/male 4/15) and 16 patients with DM2 (aged 20 to 64 years; mean age 50; median age 54; female/male 12/4).

There was a statistically significant difference in the mean age between the two groups of patients at p = 0.009.

Out of 53 people, we selected 23 healthy individuals aged between 19 and 57 years (median age 39; female/male 4/19) as the control group for DM1, and 20 healthy individuals aged 22 to 62 (median age 54; female/male 12/8) for comparison to DM2.

Diffusion tensor imaging — comparing myotonic dystrophy type 1 to healthy controls 1

Supplementary Table 2 sets out the detailed differences between DM1 and HC1 in all tested white matter tracts. Compared to HC1, patients with DM1 had reduced FA and

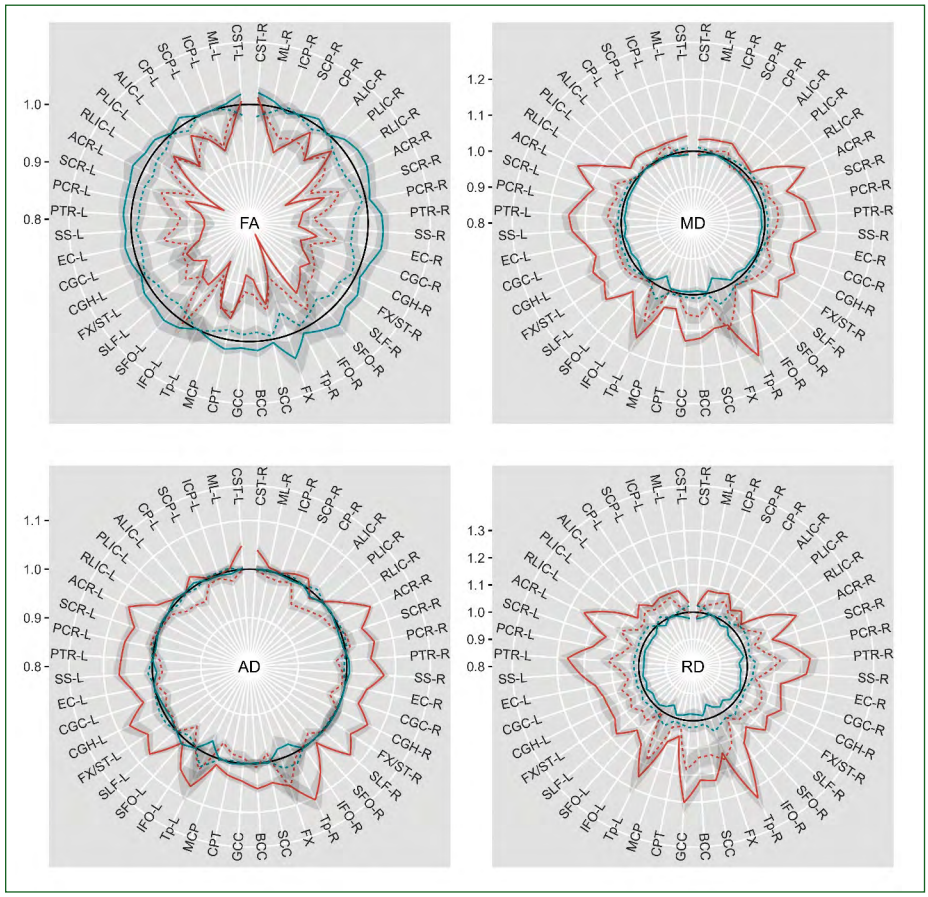

Figure 1. Radar chart illustrating in detail differences between DM type 1 and type 2 patients for all regions altogether. Solid red line — DM1 patient; solid blue line — HC1; dashed red line — DM2 patient; dashed blue line — HC2; grey fields — standard error; solid black line is average value of two control groups. Thus, average of two control groups is reference value, and is 1. MCP — middle cerebellar peduncle; CPT — pontine crossing tract; GCC — genu of corpus callosum; BCC — body of corpus callosum; SCC — splenium of corpus callosum; FX — fornix; CST-R — corticospinal tract r; CST-L — corticospinal tract l; ML-R — medial lemniscus r; ML-L — medial lemniscus l; ICP-R — inferior cerebellar peduncle r; ICP-L — inferior cerebellar peduncle l; SCP-R — superior cerebellar peduncle r; SCP-L — superior cerebellar peduncle l; CP-R — cerebral peduncle r; CP-L — cerebral peduncle l; ALIC-R — anterior limb of internal capsule r; ALIC-L — anterior limb of internal capsule l; PLIC-R — posterior limb of internal capsule r; PLIC-L — posterior limb of internal capsule l; RLIC-R — retrolenticular part of internal capsule r; RLIC-L — retrolenticular part of internal capsule l; ACR-R — anterior corona radiata r; ACR-L — anterior corona radiata l; SCR-R — superior corona radiata r; SCR-L — superior corona radiata l; PCR-R — posterior corona radiata r; PCR-L — posterior corona radiata l; PTR-R — posterior thalamic radiation (include optic radiation) r; PTR-L — posterior thalamic radiation (include optic radiation) l; SS-R — sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) r; SS-L — sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) l; EC-R — external capsule r; EC-L — external capsule l; CGC-R — cingulum (cingulate gyrus) r; CGC-L — cingulum (cingulate gyrus) l; CGH-R — cingulum (hippocampus) r; CGH-L — cingulum (hippocampus) l; FX/ST-R — fornix (cres)/ /Stria terminalis (cannot be resolved with current resolution) r; FX/ST-L — fornix (cres)/Stria terminalis (cannot be resolved with current resolution) l; SLF-R — superior longitudinal fasciculus r; SLF-L — superior longitudinal fasciculus l; SFO-R — superior fronto-occipital fasciculus (could be a part of anterior internal capsule) r; SFO-L — superior fronto-occipital fasciculus (could be a part of anterior internal capsule) l; IFO-R — uncinate fasciculus r; IFO-L — uncinate fasciculus l; Tp-R — tapetum r; Tp-L — tapetum l

increased MD and RD in all white matter tracts. Increased AD was found in 45 white matter tracts.

There was no increase in FA and no decrease in MD, AD, or RD parameters in any white matter tracts in the HC1 group compared to DM1 patients.

Detailed results are set out in Figure 1 and Table 1.

Diffusion tensor imaging — comparing myotonic dystrophy type 2 to healthy controls 2

Supplementary Table 3 sets out detailed differences between DM2 and HC2 in all tested white matter tracts. Compared to HC2, patients with DM2 had decreased FA values revealed in 41 white matter tracts. No decrease in FA values

Table 1. Differences of FA, AD, RD, and parameter in white matter tracts between tested groups. Red indicates tracts with decreased values and green indicates tracts with increased values

FA				
vs.	**DM1**	**DM2**	**HC1**	**HC2**
DM1	–	0	0	–
DM2	45	–	–	0
HC1	48	–	–	–
HC2	–	41	–	–
AD				
vs.	**DM1**	**DM2**	**HC1**	**HC2**
DM1	–	0	0	–
DM2	45	–	–	7
HC1	44	–	–	–
HC2	–	0	–	–
RD				
vs.	**DM1**	**DM2**	**HC1**	**HC2**
DM1	–	0	0	–
DM2	47	–	–	
HC1	48	–	–	–
HC2	–	17	–	–
MD				
vs.	**DM1**	**DM2**	**HC1**	**HC2**
DM1	–	0	0	–
DM2	47	–	–	0
HC1	48	–	–	–
HC2	–	0	–	–

in any white matter tract was demonstrated in subjects from the HC2 group compared to DM2.

No statistically significant difference in the value of the MD parameter was found between DM2 and HC2 or between HC2 and DM2 in any white matter tract.

RD was higher in 28 out of 48 white matter tracts and AD was lower in 9 out of 48 white matter tracts in DM2 patients compared to HC2.

Detailed results are set out in Figure 1 and Table 1.

Diffusion tensor imaging — comparing myotonic dystrophy types 1 and 2

Table 2 sets out detailed differences in all tested white matter tracts. In patients with DM1, a statistically significant decrease in the values of the FA parameter was revealed in 45 out of 48 white matter tracts compared to patients with DM2.

There was no statistically significant decrease in the values of FA parameter in patients with DM2 compared to DM1.

The values of MD and RD were significantly higher in 47 tracts in DM1 patients compared to DM2 patients. AD values were significantly higher in all 48 tracts in DM1 patients compared to DM2 patients.

There were no tracts with increased MD, AD, or RD values in DM2 patients compared to DM1.

Detailed results are set out in Figures 1 and 2 and in Table 1.

Diffusion tensor imaging — considering disease duration

The mean age at disease onset in patients with DM1 was 27.2 years, and the mean disease duration was 11.3 years (range 2–34). In DM2 patients, the mean age at disease onset was 35.1 years, and the mean disease duration was 13.4 years (range 1–33). The disease duration in patients with DM1 and DM2 was compared to the average FA, MD, RD, and AD values of white matter tracts. Only the FA parameter in DM2 patients showed negative correlation with the duration of the disease. A statistically significant FA decrease was noted in 7 out of 48 white matter tracts; namely, body of corpus callosum, splenium of corpus callosum, left cerebral peduncle, left anterior limb of internal capsule, left posterior limb of internal capsule, left superior corona radiata, and superior fronto-occipital fasciculus.

We did not find any relationship between DTI parameters and disease duration in the group of DM1 patients.

Discussion

This study presents an analysis of white matter tract integrity in patients with DM1 and DM2 based on DTI parameters using TBSS — an unbiased automated technique in which whole-brain-based voxel-wise comparison between groups can be made. We used two different control groups matched for both types of dystrophy first in order to eliminate the age differences that occur between patients with types 1 and 2.

We found a statistically significant reduction of FA in all 48 analysed white matter tracts in DM1 patients compared to HC1 and in 41 of 48 white matter tracts in DM2 patients compared to HC2. A comparison of patients with DM1 and DM2 revealed lower values of the FA parameter in the DM1 group in 45 out of 48 white matter tracts. The values of MD, RD, and AD were significantly higher in 47, 47, and 48 tracts respectively in DM1 patients compared to DM2 patients.

These results indicate diffuse disintegration of white matter pathways in DM patients, especially in the DM1 group. The damage to all type of fibres (association, commissural, and projection) may explain the diversity of clinical symptoms, which were more severe in the DM1 group of patients compared to the DM2 group.

When comparing disease duration, there was no statistically significant relationship with FA, MD, RD, or AD in DM1 patients, whereas in 7/48 DM2 patients, white matter tracts showed an FA decrease. This may suggest that the damage in DM1 is more severe from the onset of the disease, while in DM2 the process is gradual, which perhaps makes it possible to find a way to delay or stop progression of the disease.

Table 2. Differences in 48 white matter tracts according to Johns Hopkins ICBM-DTI-81 atlas

No.	White matter tract	TBSS TFCE FA DM2 > DM1 (p-value)	TBSS TFCE MD DM1 > DM2 (p-value)	TBSS TFCE AD DM1 > DM2 (p-value)	TBSS TFCE RD DM1 > DM2 (p-value)
1	Middle cerebellar peduncle	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
2	Pontine crossing tract	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
3	Genu of corpus callosum	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
4	Body of corpus callosum	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
5	Splenium of corpus callosum	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
6	Fornix	p = 0.0048	p < 0.0002	p < 0.0002	p < 0.0002
7	Corticospinal tract R	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
8	Corticospinal tract L	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
9	Medial lemniscus R	p = 0.0022	p < 0.0002	p < 0.0002	p < 0.0002
10	Medial lemniscus L	–	p < 0.0002	p < 0.0002	p = 0.0004
11	Inferior cerebellar peduncle R	p = 0.0024	p < 0.0002	p = 0.0156	p < 0.0002
12	Inferior cerebellar peduncle L	–	p < 0.0002	p = 0.0156	p = 0.0004
13	Superior cerebellar peduncle R	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
14	Superior cerebellar peduncle L	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
15	Cerebral peduncle R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
16	Cerebral peduncle L	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
17	Anterior limb of internal capsule R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
18	Anterior limb of internal capsule L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
19	Posterior limb of internal capsule R	p = 0.0008	p < 0.0002	p < 0.0002	p < 0.0002
20	Posterior limb of internal capsule L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
21	Retrolenticular part of internal capsule R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
22	Retrolenticular part of internal capsule L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
23	Anterior corona radiata R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
24	Anterior corona radiata L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
25	Superior corona radiata R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
26	Superior corona radiata L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
27	Posterior corona radiata R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
28	Posterior corona radiata L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
29	Posterior thalamic radiation R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
30	Posterior thalamic radiation L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
31	Sagittal stratum R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
32	Sagittal stratum L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
33	External capsule R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
34	External capsule L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
35	Cingulum (cingulate gyrus) R	p = 0.0012	p < 0.0002	p < 0.0002	p < 0.0002
36	Cingulum (cingulate gyrus) L	–	p < 0.0002	p < 0.0002	p < 0.0002
37	Cingulum (hippocampus) R	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
38	Cingulum (hippocampus) L	p = 0.0372	p < 0.0002	p < 0.0002	p < 0.0002
39	Fornix (cres) R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
40	Fornix (cres) L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
41	Superior longitudinal fasciculus R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
42	Superior longitudinal fasciculus L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
43	Superior fronto-occipital fasciculus R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
44	Superior fronto-occipital fasciculus L	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
45	Uncinate fasciculus R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
46	Uncinate fasciculus L	p = 0.0004	p < 0.0002	p < 0.0002	p < 0.0002
47	Tapetum R	p = 0.0006	p < 0.0002	p < 0.0002	p < 0.0002
48	Tapetum L	p = 0.0380	–	p = 0.0156	–

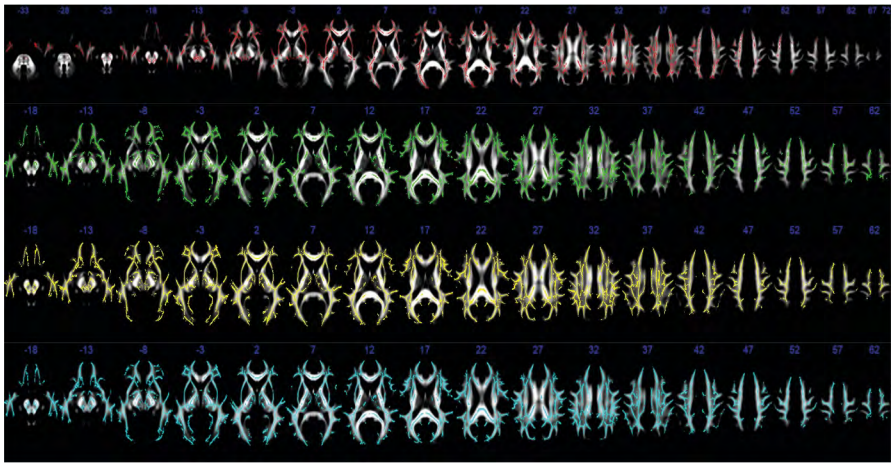

Figure 2. Tract-based spatial statistics map using TFCE approach: white matter tracts with FA reduction in DM1 patients compared to DM2 patients (shown in red), white matter tracts with AD (shown in green), RD (shown in yellow) and MD (shown in blue) increase in DM1 patients compared to DM2 patients

There have only been a few studies on DTI in DM1 patients [21, 27–29], with only two publications to date comparing DTI parameters between both types of DM and between DM patients and a control group.

Minnerop et al. [5] analysed 22 patients with DM1, 22 with DM2, and 22 age- and sex-matched healthy controls. Using TBSS, they compared DM1 to the controls, DM2 to the controls, and both types to each other. According to their results, association fibres throughout the whole brain, limbic system fibre tracts, the callosal body, and projection fibres were affected in DM1 and DM2; however, white matter occupation in DM1 was more prominent than in DM2, which is in accordance with our findings. According to Minnerop et al. [5], central motor pathways were exclusively impaired in DM1, whereas in our study, in DM1 in both corticospinal tracts, FA increased; a decrease in MD, AD, and RD was noted only in DM2, and a decrease of FA in the left corticospinal tracts was found.

The group of patients studied by Franc et al. [30] consisted of only 20 subjects (five for each group i.e. congenital-onset DM1, adult-onset DM1, DM2, and controls). A significant difference in FA in each brain compartment among all four groups ($p < 0.003$) was revealed, and pair-wise significant differences of mean FA within the brain compartments were observed between each of the three DM groups compared to controls. However, DM1 patients had significantly lower FA than controls in the inferior frontal, supra-callosal, and occipital regions ($p < 0.05$), while DM2 and controls did not. An ROI-based approach was applied to analyse DTI parameters, which is a less accurate, and more observer-dependent, method compared to the TBSS technique we used in our analysis.

A limitation of our study is the lack of clinical information and correlation with muscle status and intellectual assessment, as well as with psychological tests and the length of sleep during the day. Knowing that the severity of the course is associated with the amount of CTG repeat numbers, it would also be interesting to correlate genetics with the DTI characteristics of white matter tracts. Therefore, we are planning in our further study to focus on finding the association between diffusion parameters and physical and mental status, as well as with genetics results, to better understand the pathogenetic processes of central system involvement.

Conclusions

DTI allows us to better understand the neural mechanisms underlying CNS involvement in myotonic dystrophy. The application of DTI may help to identify biomarkers for disease progression and treatment response, and ultimately to develop more effective treatments for the cognitive and neurological symptoms of DM.

Article information

Data availability statement: *Data available upon request from the authors.*
Ethics statement: *All procedures were performed in compliance with the Declaration of Helsinki. Ethical approval was not required due to the retrospective study design.*
Authors' contributions: *EM — study conception and design, draft manuscript preparation; TW — analysis and interpretation of results, statistics; JdeM, KJ — data collection; MW — editing; AK-P, MG — critical article revision for important intellectual content; AL — data collection, revision of article and approval of publication. All authors approved final version of manuscript.*
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RESEARCH PAPER

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To know or not to know? Opinions of patients with Parkinson's Disease on disclosing risk of phenoconversion in RBD

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ABSTRACT

Introduction. The aim of our study was to find out the opinion of patients with Parkinson's Disease (PD) whose disease was preceded by REM sleep behaviour disorder (RBD) regarding early information about the high risk of phenoconversion in RBD.

Clinical rationale for the study. RBD is an early clinical manifestation of α-synucleinopathies with a more than 90% risk of phenoconversion to PD, dementia with Lewy bodies (DLB) or multiple system atrophy (MSA). It remains a subject for debate as to whether and how RBD patients should be informed about the high risk of phenoconversion.

The patient's right to full knowledge regarding his or her health conflicts with the potentially destructive impact of this information on his or her mental state and quality of life of them and their relatives.

Material and methods. Thirty-nine patients with PD whose disease was preceded by RBD were surveyed. Data on the course of RBD and PD was collected. Questions were asked about early information about the high risk of phenoconversion to patients with RBD and factors determining the opinion of the surveyed persons.

Results. The majority (> 60%) of respondents gave a positive answer when asked whether patients should be informed about their high risk of developing PD once diagnosed with RBD. Only a few (7.7%) respondents believed that disclosing such information to the patient should be possible only after obtaining his or her consent. Respondents associated consent to information about the high risk of developing PD in people with RBD with high expectations of the healthcare system. We were unable to determine whether factors such as the gender of the subject, the clinical course of the PD, and the RBD duration had an impact on patients' opinions regarding disclosing knowledge about phenoconversion.

Conclusions and clinical implications. Our study provides important information that should influence physicians' communication with patients with RBD, especially regarding how they communicate about the high risk of phenoconversion.

Keywords: REM sleep behaviour disorder, phenoconversion, risk disclosure, patients' expectations, physician-patient relationship

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Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia that affects less than 2% of the adult population, as shown by studies using polysomnography [1–3]. RBD is characterised by violent motor and vocal activity closely related to the content of the patient's nightmares (dream-enactment behaviour) [4–6]. Motor activity is the result of loss of atonia during REM sleep [7].

RBD is an early clinical manifestation of α-synucleinopathies. Within 15 years from the onset of RBD, more than 90% of patients will experience phenoconversion, i.e. they will develop symptoms of Parkinson's Disease (PD) — most often, dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) [8–10].

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There is ongoing discussion as to whether and how patients with RBD should be informed about the high risk of phenoconversion. The patient's right to full knowledge about his or her health conflicts with the potentially destructive impact of this information on the mental state and quality of life of the patient and his or her relatives [11–14].

Doubts arise from the fact that it is impossible to predict what the effect of phenoconversion (PD, MSA or DLB) will be, and how long it will take until the first motor and/or cognitive symptoms appear. Furthermore, there is no treatment available to modify the natural course of the neurodegenerative process.

Previous research on disclosing information about a high risk of phenoconversion to RBD subjects has focused on the views and expectations of the patients themselves, as well as preferences and practices of physicians. The aim of our study was to find out the opinions of patients with PD, in whom the disease was preceded by RBD.

Material and methods

Patients were recruited from the outpatient clinic of the Central University Hospital, Medical University of Lodz, Poland. The study was conducted according to the guidelines of the Declaration of Helsinki. The study protocol was submitted to the Ethics Committee of the Medical University of Lodz, which issued an opinion that the study was not a medical experiment and did not require approval. Written informed consent was obtained from all participants.

In all patients, PD was diagnosed according to the MDS clinical diagnostic criteria [15].

Inclusion criteria for the study were: a diagnosis of PD within the previous seven years, and a 'yes' answer to a screening question during a routine visit to a neurology clinic [RBD Single-Question Screen (RBD1Q): '*Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)*?' [16]. Those who met these criteria, and agreed to participate, were surveyed at a specially arranged visit to the clinic or in their own home.

Firstly, to confirm the diagnosis of RBD, each patient completed an REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) [17], Polish version); a result ≥ 5 points confirms a diagnosis of RBD.

Next, the investigator conducted an interview with the patient, obtaining all the data necessary to complete a questionnaire about demographic data and the course and diagnostic process of both RBD and PD. The next questions concerned the respondents' views on disclosing information about a high risk of phenoconversion to patients with RBD, both in principle and in their own case, and any related expectations towards the healthcare system.

Results

Two neurologists asked the RBD1Q question to a total of 132 PD patients during a routine visit. Eighty patients gave a positive response and tentatively agreed to participate in the study. Later, during an interview with the investigator, 41 patients denied having a sleep disorder, refused to participate in the study, and/or or had a negative RBDSQ score (< 5 points).

Eventually, 39 patients (23 women and 16 men) were included in the study. The mean age was 68.9 ± 7.9 (range 45–85) years. The education of the patients was as follows: higher — 17 persons (43.6%), secondary — 20 (51.3%), primary — 2 (5.1%). The study group was dominated by retirees (33 persons, 85%); two patients (5%) were unemployed, retirees (n = 2; 5%), and two patients (5%) were professionally active.

Loud vocalisations were indicated as the most bothersome symptom by most patients (51%) and most household members (59%). Violent motor activity was mentioned in this context by 38% of patients and 33% of household members. After waking up, 31 (80%) of the subjects always or occasionally remembered the content of their dreams. Three persons (8%) confirmed that dream enactment caused minor injuries, and eight (21%) respondents reported falling out of bed during RBD incidents. In four cases, the partner was forced to sleep separately due to the patient's RBD symptoms. Nine patients (23%) sought medical help because of the bothersome symptoms of RBD. Clonazepam was administered in one case, and melatonin in four cases.

In all studied patients, the result of the RBDSQ confirmed the diagnosis of RBD: the mean score was 9.10 ± 1.96 (5–13) points. The time from the onset of sleep disorders, the picture of which could be consistent with RBD, to participation in the study, ranged from 48 to 684 (mean 215.1 ± 125.5) months. Only four respondents reported that this was shorter than 100 months, but in the majority of participants (51.3%) it did not exceed 200 months. The diagnosis of PD was made 1–564 (mean 171.7 ± 119.3) months after the onset of RBD symptoms. The time from the diagnosis of PD to participation in the study ranged from 1–75 (mean 42.6 ± 21.4) months. In 22 (56.4%) patients, tremor (isolated or in combination) was the first symptom, and we called this group the PD (tremor+) subgroup. In the remaining 17 (43.6%) participants, tremor was neither the first nor an early manifestation of the disease, and we called this group the PD (tremor–) subgroup.

To test an association between gender (men *vs.* women), early clinical manifestation of PD (tremor *vs.* no-tremor) and RBD duration (≤ 10 years *vs.* > 10 years), these variables were cross-tabulated with patients' beliefs about PD risk disclosure in RBD patients. Since more than 20% of the cells had an expected number of less than 5, we abandoned the calculation of the chi-square independence test and analysed the data only qualitatively.

The question: '*Do you think patients should be informed about their high risk of developing Parkinson's Disease once*

Table 1. Results of cross tabulation of patient characteristics (gender, first PD manifestation, and duration of RBD) and beliefs about disclosure regarding high risk of Parkinson's Disease in RBD patients

Question	Do you think patients should be informed about their high risk of developing Parkinson's Disease once diagnosed with REM sleep behaviour disorder?			Would you like to be informed about the high risk of developing Parkinson's Disease at the time of the diagnosis of REM sleep behaviour disorder?	
Participants	Answers			Answers	
	Yes, in any case n (%)	No, never n (%)	Only with patient's consent n (%)	Yes, in any case n (%)	No, never n (%)
All	25 (64.1)	11 (28.2)	3 (7.7)	27 (69.2)	12 (30.8)
Men (n = 16)	12 (75.0)	3 (18.8)	1 (6.3)	13 (81.3)	3 (18.8)
Women (n = 23)	13 (56.5)	8 (34.8)	2 (8.7)	15 (65.2)	8 (34,8)
PD (tremor+) (n = 22)	15 (68.2)	6 (27.3)	1 (4.5) 2 (11.8)	16 (72.7)	6 (27.3)
PD (tremor–) (n = 17)	10 (58.8)	5 (29.4)		11 (64.7)	6 (35.3)
Duration of RBD before onset of PD					
≤ 10 years (n = 19)	12 (63.2)	6 (31.6)	1 (5.3)	12 (63.2)	7 (36.8)
> 10 years (n = 20)	13 (65.0)	5 (25.0)	2 (10.0)	15 (75.0)	5 (25.0)

diagnosed with REM sleep behaviour disorder?' was answered 'yes' by 25 (64.1%) respondents, regardless of gender, first manifestation of PD, or duration of RBD before phenoconversion. Only occasionally did respondents believe that disclosing such information to the patient should be possible only after obtaining his/her consent (Tab. 1).

Also, in response to the more personal question: '*Would you like to be informed about the high risk of developing Parkinson's Disease when you are diagnosed with REM sleep behaviour disorder*?', most respondents (27; 69.2%) answered 'yes' (Tab. 1).

Study participants were presented with seven factors that might have an impact on their own positive attitude towards being informed about the high risk of PD. Respondents were asked to indicate any number of factors that influenced their positive opinion. These were the following (in parentheses we show the percentage of patients indicating a given factor as being significant in making a positive decision):

a. To help advance knowledge about RBD (70.4%);
b. To help other patients in the future (44.4%);
c. The possibility to plan future life (81.5%);
d. Time to build relationships with family and friends (74.1%);
e. Ability to change life priorities (59.3%);
f. Getting help and support (77.8%);
g. To prepare for the coming illness (70.4%).

Thus, all factors except one were confirmed by more than 59% of the respondents. The exception was *Helping other patients in the future,* indicated by only 44.4% (Fig. 1).

The patients were also presented with seven factors that would make them unwilling to be informed about the high risk of PD (in parentheses we show the percentage of patients indicating a given factor as significant in making a negative opinion). Only 3/7 were indicated by more than half of the respondents (Fig. 2).

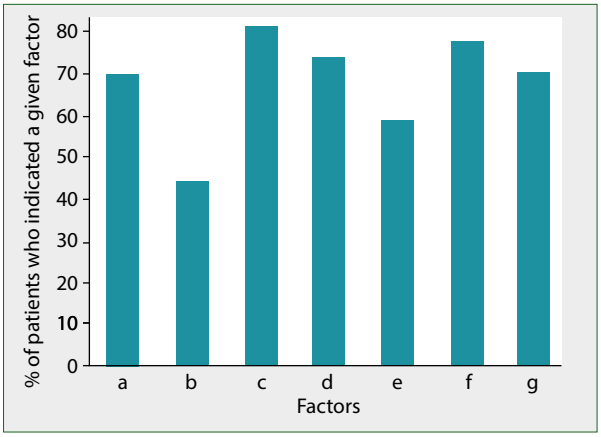

Figure 1. Factors relevant for respondents when making positive opinion on informing RBD patients early about risk of phenoconversion. a) To help advance knowledge of RBD; b) To help other patients in future; c) Possibility to plan further life; d) Time to build relationships with friends and family; e) Ability to change life priorities; f) Getting help and support; g) To prepare for coming illness

a. Fear of lowering mood and quality of life (75.0%);
b. Impact of information on life plans (33.3%);
c. Impact of information on life priorities (16.7%);
d. Feeling of powerlessness (66.7%);
e. Impact of information on relationships with relatives (16.7%);
f. Uncertainty of diagnosis (83.3%);
g. Seeking help and support (33.3%).

Consent to being informed about the high risk of developing PD in people with RBD was associated with high

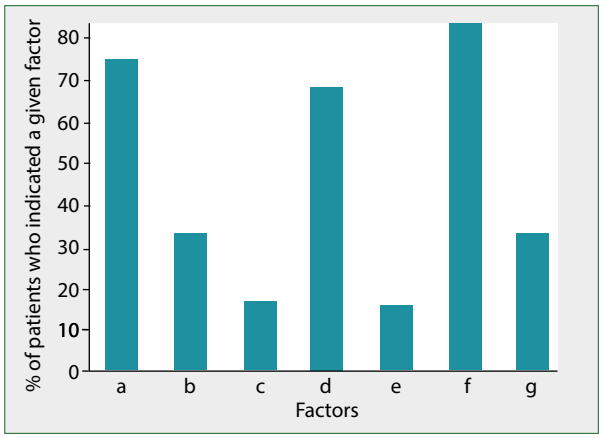

Figure 2. Factors relevant for respondents when making a negative opinion on informing RBD patients early about risk of phenoconversion. a) Fear of lowering mood and quality of life; b) Impact of information on life plans; c) Impact of information on life priorities; d) Feeling of powerlessness; e) Impact of information on relationships with relatives; f) Uncertainty of diagnosis; g) Seeking help and support

expectations of the healthcare system. All the proposals presented to them in this regard were accepted by ≥ 60% of the respondents:

a. Regular follow-up visits (100.0%);
b. Constant contact with the same doctor (100.0%);
c. Family doctor included in the treatment team (76.9%);
d. Access to new treatment options or participation in clinical trials of new therapies (92.3%);
e. Recommendations on lifestyle (physical activity, nutrition) that may affect the risk of developing PD (87.2%);
f. Information about PD (64.1%);
g. Opportunity to receive additional support (e.g. psychological, participation in self-help groups) (69.2%).

Discussion

RBD is an early manifestation of synucleinopathy with an over 90% probability of phenoconversion to PD, LBD, or MSA [8–10]. All three of these neurodegenerative diseases inevitably lead to motor and/or cognitive impairment and force affected patients to change their life plans. There is ongoing discussion as to whether and how patients with RBD should be informed about the high risk of phenoconversion. The patient's right to full knowledge about his or her health conflicts with the potentially destructive impact of this information on the mental state and quality of life of the patient and their relatives [11–14].

Doubts about informing patients are raised by the fact that it is impossible to predict what the outcome of phenoconversion (PD, MSA or DLB) will be, and how much time will elapse before the appearance of the first motor and/or cognitive symptoms. Furthermore, there is no treatment available to modify the natural course of the neurodegenerative process.

Respecting the patient's autonomy should consist, on the one hand, in providing them with access to full information about their health, and on the other hand in respecting their decision to ignore the existence of this information. Patients and their doctors should be partners in this process.

Previous research on disclosing information about a high risk of phenoconversion has focused on the views and expectations of RBD patients themselves. In one study [18], as many as 92.5% of RBD patients expressed the opinion that knowledge about possible future neurodegenerative disease was important to them. According to 75.3% of them, a lack of information about the risk of phenoconversion — after the diagnosis of RBD was made — would result in a loss of trust in the physician. More than half (56.7%) of the respondents believed that the physician should ask the patients about their preferences in this regard [18].

On the other hand, and perhaps surprisingly, 54% of patients with Parkinson's Disease expressed the opinion that they would not like to be informed about suspected PD early in the diagnostic process, before a final diagnosis is made (e.g. when only the diagnostic criteria for prodromal PD were met) [19]. Moreover, the vast majority (87%) of respondents accepting early information believed that disclosing such information to the patient should be preceded by obtaining his or her consent. Thirty seven percent of patients were willing to accept early disclosure of risk only if it opened access to new therapies for the patient [19].

The aim of our study was to obtain opinions on disclosing the risk associated with RBD among PD patients for whom this form of sleep disturbance was the first clinical manifestation of the neurodegenerative process. It might be expected that the opinion of PD patients on disclosing a high risk of phenoconversion would be different than that of those with RBD. Patients with PD can retrospectively assess at what point in their lives they received information about the risk of developing a neurodegenerative disease, and what impact it had on their decisions at that time. They also know when the first symptoms of PD appeared and how these symptoms determined their future lives. Moreover, they have been through an entire diagnostic process.

To both questions regarding early disclosure of the risk of PD to people with RBD, the majority (64.1% and 69.2%) of our respondents gave positive answers. Study participants were able to indicate many more arguments supporting this position than arguments justifying not providing patients with information. In this respect, our respondents' views were much closer to those of persons with RBD [18] than to those of patients with PD [19].

It is likely that patients' different perspectives and experiences influence their views on early disclosure of RBD-related conversion risk and communication of suspected PD before a final diagnosis is made. In our study group, the time from the diagnosis of PD ranged from 1 to 75 (42.6 ± 21.4) months, while in the material [19] with which we compared

our patients, it ranged from 1 to 24 (median 6) years. The longer duration of disease meant that a greater number of patients represented an advanced stage of the disease. They had experienced the limited effectiveness of oral therapies, motor fluctuations and dyskinesias, and they had experienced a significantly higher incidence of non-motor symptoms. For many of them, progressive disability and social isolation were challenges.

Both the patients in our study group, and those in the groups presented by other authors [18, 19], expressed the belief that consent to early disclosure of a high risk of phenoconversion should be associated with special support from the healthcare system.

Significant discrepancies concern patients' opinions about the physician obtaining the patient's consent before providing complete information about the risk of neurodegenerative disease. In our material, only 7.7% of respondents made disclosing the risk of PD dependent on the patient's consent. Just over half (56.7%) of Mayo Clinic RBD patients did not see a need for their physician to obtain consent from them to provide information about phenoconversion [18].

On the other hand, the vast majority (87%) of German PD patients — who accepted information about the disease before the final diagnosis — indicated obtaining the patient's consent as a condition that should be met [19]. It is likely that these significant differences reflect, at least to some extent, differences in physician-patient relationships across different healthcare systems.

Several limitations of our study must be acknowledged. Although a much larger number of patients were prescreened, the size of the study group was ultimately limited. We were unable to determine whether factors such as the gender of the subject, the clinical picture of PD, and the RBD duration had an impact on patients' opinions regarding disclosing knowledge about phenoconversion. Our study was retrospective and concerned the distant past. The extreme values of some data (e.g. duration of RBD until phenoconversion) may raise doubts. However, these were not important in evaluating respondents' opinions on disclosing the risk of phenoconversion.

Despite the above-mentioned limitations, our study, the first to assess the opinions of PD patients on informing persons with RBD about the risk of phenoconversion, provides important information that should influence physicians' communication with patients.

In practice, the approach of physicians in this respect varies significantly. While most physicians involved in the diagnosis and treatment of patients with RBD provide patients with information about phenoconversion, only a few routinely ask patients about their preferences for receiving this information [20], and an even smaller group attempts to provide the patient with a quantitative estimate of risk.

The means by which, and the extent to which, knowledge about conversion should be disclosed to patients remains a subject of debate [12, 14, 21]. The solutions that will be adopted should take into account the preferences of patients themselves.

Article information

Data availability statement: *Original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.*

Ethics statement: *The study protocol was submitted to the Ethics Committee of the Medical University of Lodz, which issued an opinion that the study was not a medical experiment and did not require approval.*

Authors' contributions: *A.M.: Conception, organisation and execution of study, writing first draft of manuscript.*

A.B.: Conception and execution of study, review and critique of manuscript.

A.K.: Conception of study, review and critique of manuscript.

A.G.: Conception and execution of study, review and critique of manuscript.

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A.G. has served on advisory boards for, consulted for, and/or been a speaker for, Allergan/AbbVie, Krka and GE, outside the submitted work.

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POINT OF VIEW

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Potential use of glucocorticosteroids in *CSF1R* mutation carriers — current evidence and future directions

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ABSTRACT

We recently found that glucocorticosteroids (GCs) have protective effects in *CSF1R* mutation carriers against developing symptomatic *CSF1R*-related leukoencephalopathy. Our findings were subsequently confirmed in a mouse model study.

We have received many questions from patients, their families, patient organisations, and healthcare practitioners about the optimal type of GCs, the dose, the route of administration, and application timing. This paper attempts to answer the most urgent of these questions based on our previous studies and personal observations. Despite the promising observations, more research on larger patient groups is needed to elucidate the beneficial actions of GCs in *CSF1R* mutation carriers.

Keywords: leukoencephalopathy, glucocorticosteroids, spheroids, hereditary

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CSF1R-related leukoencephalopathy (CRL) is an autosomal dominant neurodegenerative disease with worldwide prevalence, rapid progression, and an ominous prognosis, with death ensuing within a few years [1]. Currently, treatment options are limited to supportive care and possibly hematopoietic stem cell transplantation [2]. Our previous observations on pathogenic *CSF1R* mutation carriers exposed to long-term immunosuppressive therapy who did not develop symptomatic disease prompted us to evaluate the effects of glucocorticosteroids (GCs) on the disease course [3].

We conducted a retrospective cohort study on 41 *CSF1R* mutation carriers, of which eight took GCs for various unrelated medical reasons at the *asymptomatic stage* of the disease [4]. We found that individuals exposed to GCs were less likely to develop symptomatic disease, or to become dependent in the activities of daily living, and less frequently had white matter lesions and corpus callosum involvement on neuroimaging [4]. Our findings were confirmed in an animal model, in which mice carrying an inactivated allele of *CSF1R* and exposed to GCs did not develop symptomatic disease, nor demyelination, neurodegeneration nor microgliosis, on neuropathological evaluation [5].

These promising results from our studies on a possible protective effect of GCs against symptomatic CRL sparked considerable interest among patients, their families, patient organisations, and healthcare practitioners. We have received many questions about the optimal type of glucocorticosteroid, the dose, the route of administration, and application timing in asymptomatic and symptomatic *CSF1R* mutation carriers. We suggested that more research needs to be done before implementing GCs in clinical practice [4]. Generally speaking, there is limited interest within the pharmaceutical industry in performing clinical trials on already FDA-approved medications. Even more importantly, conducting such a medication trial would take many years (definitely beyond the timeframe of currently conducted medication trials). Based on our previous studies and personal observations, we here attempt to answer the most important questions.

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Our thoughts presented below have significant limitations and must be read only as our personal views, and not as forming any recommendations or guidelines.

GCs differ in terms of their anti-inflammatory potency, hormonal activity (mainly mineralocorticoid effects), and duration of hypothalamic-pituitary-adrenal axis suppression (HPA) (ranging from hours to days) [6, 7]. Based on the duration of HPA axis suppression, GCs are classified as short-acting (hydrocortisone), intermediate-acting (prednisone, prednisolone, methylprednisolone, triamcinolone), or long-acting (dexamethasone, betamethasone) [7]. It is important to note that as GC effects are mainly mediated through intracellular and nuclear mechanisms, their therapeutic effects persist beyond their plasma elimination time [6, 8]. Chronic GC therapy is associated with a number of side effects, including increased mortality, psychiatric (anxiety, irritability, mood liability, insomnia, psychosis), cognitive (memory impairment), musculoskeletal (osteoporosis, fractures, myopathy), endocrine (adrenal suppression, Cushingoid features), metabolic (hyperglycaemia, diabetes, dyslipidemia, obesity), cardiovascular (hypertension), ophthalmological (cataracts, glaucoma), gastrointestinal (gastritis, peptic ulcer disease, dyspepsia), dermatological (skin thinning, purpura, red striae), and immunosuppressive (predisposition to infection) complications [7].

In addition, GCs may interact with other non-steroid medications, leading to decreased or increased exposure to GCs or non-steroid medications, resulting in a higher risk of side effects and drug toxicity [7]. As the harm associated with GC therapy and GC-related toxicity depends on the dose and duration of the therapy, the goal is the lowest effective dose for the shortest duration [7, 9]. Short-term GC courses (i.e. less than two weeks) are unlikely to suppress the HPA axis, and steroid tapering is not needed [10, 11]. In most studies, adverse effects have been linked to long-term treatment with a prednisone equivalent daily dose of more than 5–7.5 mg [8]. In a recent consensus paper of the European League Against Rheumatism's task force group, the authors concluded that a daily dose of ≤ 5 mg prednisone equivalent conveyed an acceptably low level of harm in rheumatic diseases, with the exception of patients at high risk for cardiovascular disease (i.e. older age, male sex, obesity, hypertension, diabetes, dyslipidemia) [9]. A daily prednisone equivalent dose of > 10 mg was linked with elevated harm, whereas the benefit-risk balance of daily prednisone equivalent doses between 5 and 10 mg was determined by patient-specific conditions (i.e. risk factors, comorbidities) [9]. The general risk of GC-related complications is higher in older individuals with concurrent medical problems, unhealthy lifestyles, those who smoke, have high alcohol consumption, and bad nutrition [8, 9]. The risk of GC-related complications can be lowered by adopting healthy behaviours such as regular physical exercise, a healthy diet (low in saturated fat and sodium), stopping smoking, lower alcohol consumption, sufficient vitamin D and calcium intake, and weight loss [9]. Monitoring for potential complications, preventive and therapeutic measures is recommended to address the most common serious GC-related side effects [9]. Influenza, pneumococci, and herpes zoster vaccinations are proposed in patients on chronic GC therapy [9]. Patients at high risk for osteoporosis may be prescribed bisphosphonates, osteoanabolic drugs, or selective oestrogen receptor modulators, whereas statins and angiotensin-converting enzyme inhibitors may benefit patients at high cardiovascular risk [9].

Therefore, the ultimate benefit-*versus*-risk balance depends on the GC therapy regimen (dose and duration) and the individual patient profile.

Based on basic science studies, at least partial preservation of microglia is a prerequisite for GCs to exert their positive effects in CRL [4, 5]. In line with this, we demonstrated the beneficial effects of GCs in asymptomatic human and mouse *CSF1R* mutation carriers [4, 5]. The age at GC therapy onset ranged from 21–50 years, with a median 34.5 years in our retrospective clinical study [4], and 3 months in the mouse model study [4], which corresponds to 20 human years [12, 13]. In the clinical study, the group treated with GCs was heterogeneous regarding the type of medication, dose, route of administration, therapy duration (median of 14.5 years, range 2–25 years), and mono- or poly-GC therapy [4]. In the animal study, the mice received slow-release subcutaneous prednisone 1.8 mg/kg/day for 12 months [5], corresponding to human exposure of 0.146 mg/kg (8.75 mg in a 60-kg adult) [5, 14] for 30 years [12, 13].

It is challenging to convert subcutaneous prednisone to its oral equivalent, as such a formula is not available for humans. However, another glucocorticoid, dexamethasone, is converted in a 1:1 or 0.825:1 ratio between oral and subcutaneous applications [15]. Hence, the translated dose from the mouse model study [5] equals an approximate oral daily prednisone dose of 7.2–8.75 mg/kg in a 60-kg (132 lbs) adult human.

The age at onset in CRL has been previously calculated at 43 ± 11 years (mean ± 1 SD, range 18–78 years) for both sexes [16]. Women develop symptomatic disease on average seven years earlier than men, with an age at onset of 40 ± 10 compared to 47 ± 11 years (mean ± 1 SD), respectively [16]. One possible explanation for the observed dichotomy in symptomatic onset may be hormonal differences. As some studies have shown that men display higher cortisol levels compared to women [17, 18], we hypothesise that physiological differences in GCs levels between men and women may lead to later symptomatic onset in men.

The age at onset may also depend on *CSF1R* mutation, and kindred studies may help in better understanding genotype-phenotype associations and predicting the timing of symptomatic disease onset in carriers of specific mutations. Ideally, the GCs would be initiated a few years before the predicted symptomatic onset, limiting the lifetime exposure to GCs. However, in carriers of *CSF1R* mutations that are not well characterised, a general (based on all *CSF1R* mutation

carriers) [16] age at onset would determine the GCs initiation. The application of age at onset encompassing two standard deviations (2 SD) would allow the inclusion of c.95% of all cases. Thus, starting ages for prophylactic GCs initiation of 20 years for women and 25 years for men seem reasonable.

We speculate that GCs could also be of potential benefit in the early stages of CRL when a substantial fraction of microglia still functions properly. As no systematic studies have addressed GCs use in symptomatic *CSF1R*, we searched the literature and our records for reports of symptomatic CRL mutation carriers treated with GCs, finding a total of 12 patients (Tab. 1). Unfortunately, in most cases, the information on the GC regimen was scarce. However, as more than half of the cases (n = 7) received GCs for misdiagnosed multiple system sclerosis, it can be assumed that it was a pulse therapy. The timing of the treatment varied, but in most cases, patients received GCs when they were already severely affected. Three cases received repeated courses of intravenous methylprednisolone followed by oral therapy with downward titration starting in the first two years of their disease, and did not benefit from the treatment [19, 20]. However, they presented rapidly progressive phenotypes, and could have been already advanced when initially exposed to GCs. In the whole group, a lack of benefit was observed in all but one case, who received pulse therapy with GCs and immunoglobulins, "which slightly relieved his dementia symptoms" [21]. However, the improvement in this patient is questionable, because at the 3-month follow-up, the authors noted worsening of the symptoms [21]. Based on arguments from the previous studies, we speculate that GCs may also be beneficial at the early stages of symptomatic disease; however, no benefit can be expected at the advanced stages of the disease, when already most microglia are damaged and dysfunctional; and not as a one-time dose (pulse therapy). More studies are needed to gain insight into these important aspects in the early disease stages of CRL.

The annual incidence of short-term oral GC treatment in the United States has been estimated at 7%, with approximately one in five adults receiving at least one course of therapy in three years for various medical reasons [22]. The chronic oral GC intake has been estimated at 0.6–1.2%, with more than 70% of patients using prednisone [23, 24].

Due to systemic action, high bioavailability, non-invasiveness, and relatively low cost, oral prednisone would be the first choice among GCs for use in *CSF1R* mutation carriers. Since most serious side effects are associated with prednisone equivalent doses of higher than 5 mg/day, we speculate that the initial oral dose for asymptomatic *CSF1R* mutation carriers would not exceed 5 mg per day. Repeated short-term courses would obviate the need for steroid tapering, and limit the side effects.

Any biomarkers of disease progression would be invaluable for deciding upon the optimal timing of GC initiation, monitoring the therapy effects, and allowing appropriate titration of GCs according to individual needs. However, the role of both non-specific (e.g. neurofilament light chain, glial fibrillary acidic protein, tau protein) or specific to microglia (e.g. positron emission tomography imaging of the translocator protein, not yet discovered proteins unique to microglia) biomarkers is yet to be verified in *CSF1R* mutation carriers. Thus, an annual comprehensive clinical assessment with neurological, neuropsychological, and neuroimaging (preferably with 7 Tesla magnetic resonance imaging [25]) evaluations, remains the best strategy to monitor asymptomatic *CSF1R* mutation carriers, detect early first signs of conversion from asymptomatic to symptomatic disease, and monitor symptomatic disease progression.

Given all these considerations, we hypothesise that the starting GC regimen in asymptomatic *CSF1R* mutation carriers would include a 7-day prednisone course of 5 mg per day every 3–4 months. However, if signs of disease progression are detected, as they are today by means of neurological, neuropsychological, or neuroimaging (7-Tesla brain MRI) assessments, or by means of biomarkers as they may be tomorrow, an intensified GC regimen would be introduced. That could involve an increased duration of GC courses, an increased daily dose, or a transition to more potent GCs (e.g. methylprednisolone pulses).

Despite the promising results from earlier studies, more research on larger patient groups is needed to elucidate the beneficial actions of GCs in asymptomatic and symptomatic *CSF1R* mutation carriers. We cannot exclude that an unidentified confounder impacted upon previous observations, particularly the clinical ones, which were based on a small number of patients. As a randomised clinical trial would be challenging, in terms of time, cost and ethics, a retrospective meta-analysis based on a multicentre collaboration is the ultimate means we would use to provide further evidence, or a lack thereof. Additional basic science studies of novel targets downstream of GCs are underway. The last decade has seen the discovery of the genetic cause underlying the disease; hopefully, our observations will hasten the emergence of preventive therapy.

Table 1. Demographic, genetic, and clinical characteristics of symptomatic patients with *CSF1R*-related leukoencephalopathy treated with glucocorticosteroids (based on literature review and our records)

No	Paper	Sex	Ethnicity	CSF1R mutation	Age at onset	Initial diagnosis	Clinical course	Treatment	Age at treatment	Benefit
1	Sundal et al. [19, 20]	F	Norwegian	c.1754-2A > G (splicing mutation)	38 years	Multiple sclerosis	Rapid progression, bedridden at 41 years, died six months later	Three courses: intravenous methylprednisolone (1,000 mg/day for three days) followed by oral prednisolone 60 mg/day with downward titration over three weeks	38–41 years	None
2	Sundal et al. [19, 20]	F	Norwegian	c.1754-2A > G (splicing mutation)	36 years	Multiple sclerosis	Rapid progression, bedridden at 38 years, died at 40 years	Three courses of intravenous methylprednisolone (1.000 mg/day for three days) followed by oral prednisolone 60 mg/day with downward titration over three weeks; Interferon β-1b 44 μg three times/week for six months	37–39 years	None
3	Inui et al. [26]	M	Japanese	Arg777Gln	24 years	Multiple sclerosis	Enteral feeding tube at 30 years; bedridden with occasional respiratory support at 32 years	Methylprednisolone, cyclophosphamide	N/A	None
4	Saitoh et al. [27]	F	Japanese	Ile782Thr	28 years	HDLS	Rapid progression, wheelchair-bound at 1.5 years from onset	Methylprednisolone pulse therapy (1,000 mg/day for three days)	29 years	None
5	Kitani-Morii et al. [28]	F	Japanese	Ile794Thr	20 years	Multiple sclerosis	Rapid progression, wheelchair-bound at 21 years	Intravenous and oral glucocorticosteroids, plasmapheresis	20 years	None
6	Konno et al. [29]	F	Japanese	Gly589Arg	37 years	Multiple sclerosis	Rapid progression, bedridden at 41 years	Glucocorticosteroids, interferon β-1b	N/A	None
7	Konno et al. [29]	F	Japanese	Gly589Arg	30 years	N/A	Rapid progression, severe dementia at 31 years	Glucocorticosteroids	31 years	None
8	Konno et al. [29]	F	Japanese	c.2442 + 5G > A (splicing mutation)	27 years	N/A	Progressive gait disturbances, frontal lobe dysfunction, spasticity, alien hand syndrome by 28 years	Glucocorticosteroids	28 years	None
9	Shi et al. [21]	M	Chinese	p.His899fs (frame-shift mutation)	42 years	HDLS	Dependent in activities of daily living in second year of disease	Glucocorticosteroids (pulse therapy), immunoglobulin	43 years	Slight improvement of dementia, but then worsening at 3-months follow-up
10	Breningstall & Asis [30]	M	N/A	Gln481Term	14 years	Inflammatory or metabolic disorder	Fast progression, incapable of independent walking at three months after presentation, gastrostomy at eight months after presentation	Glucocorticosteroids	14 years	None
11	(unpublished)	F	White European	Gly589Glu	47 years	Multiple sclerosis	Rapid progression, wheelchair = bound at 48 years, died at 49	Three courses: — intravenous — methylprednisolone (1,000 mg/day for five days) followed by — oral therapy for one week	48–49 years	None
12	(unpublished)	F	White European	Gly589Glu	42 years	Multiple sclerosis	Rapid progression, wheelchair-bound at 43 years	Intravenous glucocorticosteroids	44 years	None

F— female; HDLS — Hereditary diffuse leukoencephalopathy with spheroids; M — male

Article information

Conflict of interest: *None.*
Data availability statement: *Additional data that supports the findings of this study is available from the corresponding author, ZKW, upon reasonable request.*
Ethics statement: *The patient data was collected and investigated under approval by the Mayo Clinic institutional review board (1087-98 and 21-006198) and by means of a literature review. 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.*
Authors' contributions:
1. Research project: A. Conception, B. Organisation, C. Execution;
2. Statistical analysis: A. Design, B. Execution, C. Review and critique;
3. Manuscript preparation: A. Writing of first draft, B. Review and critique;
JD: 1A, 1B, 1C, 3A, 3B; ERS: 1A, 1B, 1C, 3B; VC: 1A, 1B, 1C, 3B; ZKW: 1A, 1B, 1C, 3B.
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Atypical motor presentation of Huntington's Disease

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To the Editors

Huntington's Disease (HD; OMIM# 143100) is a genetic neurodegenerative disorder classically characterised by motor symptoms including chorea, psychiatric and behavioural disturbances, and progressive cognitive deterioration [1]. Chorea, flowing from one body part to another in a non-patterned fashion, is the most characteristic clinical phenomenon in adult-onset HD. On the other hand, patients may also develop an akinetic-rigid syndrome, which is the most common presentation of juvenile HD (known as Westphal variant) in addition to representing the advanced stage of HD when chorea is often no longer present. Less common initial motor presentations of HD exist, e.g. dystonia can be the first noticeable symptom of HD, as well as tics, and cerebellar and pyramidal signs [2].

Here, we describe an uncommon clinical manifestation of HD in a genetically proven case and underline the fact that HD can display a much wider phenotypic spectrum than is usually considered.

A 53-year-old male developed progressive walking difficulties with marked postural instability and balance impairment over a six-month period, in addition to dysarthria, clumsiness in the upper limbs with dystonic posturing, and memory impairment. The patient's grandmother had been affected by a similar condition without a formal diagnosis, his mother had been affected by dementia, and his daughter had a diagnosis of Down's syndrome. On examination, the patient presented with hypomimia, and his eye movements disclosed broken smooth pursuit. He had bilateral upper limb bradykinesia and mild apraxia. Additionally, he presented with generalised dystonia mainly affecting the trunk and upper extremities. His gait was only minimally broad-based, and he was unable to perform tandem gait. Brain MRI revealed prominent putaminal atrophy, and iron deposition in the basal ganglia on T2 sequences, with FC/CC of 1.5 and an increased CC/IT ratio to 0.22 (Fig. 1). The patient was screened for iron storage diseases and Wilson's Disease, both of which came back as negative. Molecular analysis of *HTT* showed a mutant allele with 43 CAG repeats, consistent with a diagnosis of HD. Six months after his initial presentation, he developed generalised chorea.

Here we report a patient with atypical presenting features of HD, namely dystonia. Despite chorea being the most prominent motor symptom of adult-onset HD, recent studies have shed light on non-choreatic movement disorders in HD, either at onset or throughout the disease course [3]. Interestingly, non-choreatic presentations have been correlated with longer CAG repeat expansions and earlier onset [4]. Additionally, MRI has revealed elevated brain iron accumulation (Fig. 1), which had been previously described in HD patients as a result of alteration in metal homeostasis. However, no specific motor presentation has been associated with this brain image [5].

The most common manifestations of HD, other than chorea, seem to be dystonia, ataxia, parkinsonism and tics, although exact numbers are lacking. Parkinsonian signs of HD are less often reported than chorea, but seem to progress

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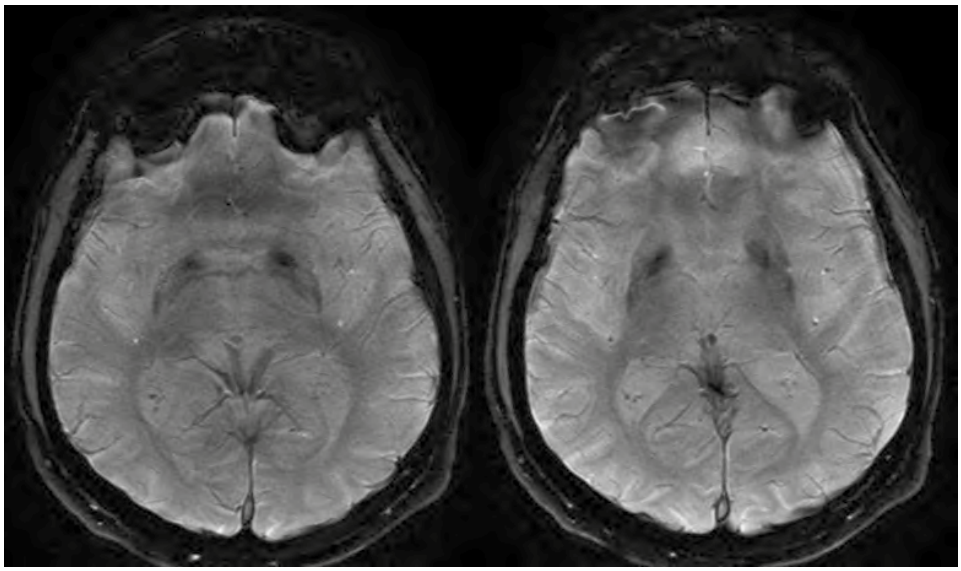

Figure 1. Magnetic Resonance Imaging showing brain iron deposition

in a fairly linear pattern. Becker et al. reported one patient with segmental dystonia, while Hu et al. reported one patient with early-onset blepharospasm followed by cervical dystonia with torticollis and retrocollis; approximately 12% of adult-onset HD patients manifest with prominent dystonia [3].

In conclusion, diagnostic difficulties may arise when HD manifests atypically with non-choreatic motor symptoms. Greater awareness of rare presentations of HD, especially when symptoms overlap with psychiatric co-morbidities, and diligent history-taking regarding the patient's family, will improve diagnosis and aid management. Our case serves to highlight that HD can display a much wider phenotypic spectrum than that which is classically considered, especially in extending to symptoms beyond chorea.

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Neurologists should retain diagnostic and therapeutic management of migraines

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To the Editors

I read with interest Boczarska-Jedynak's article on a cross-sectional online survey using an electronic questionnaire among 81 aesthetic medicine professionals (AMPs) on knowledge and the standard of treatment of chronic migraine with botulinum toxin (BTX), brand OnaBoNT-A [1].

It turned out that only a third of the AMPs rated the effectiveness of BTX as good, and that most respondents wanted to expand their knowledge and skills regarding BTX treatment of migraine [1]. It was concluded that while there is willingness to treat migraine among AMPs, current knowledge and skills in migraine are limited, and that programmes should be established to educate physicians authorised to administer BTX to treat migraine with BTX [1]. Boczarska-Jedynak's study is excellent, but has limitations that should be discussed.

I disagree with the suggestion that AMPs should inject OnaBoNT-A for migraine [1]. Firstly, migraine is a neurological disorder and diagnostic and therapeutic management should remain in the hands of the neurologist. Secondly, migraine is often complicated by pre- or post-headache phenomena such as aura, hemiplegia, visual impairment, ophthalmoplegia, dizziness or gait disturbance, that require evaluation by a neurologist. Migraine can sometimes even be complicated by stroke or seizures [2]. Therefore, adequate post-ictal management [electroencephalogram (EEG), magnetic resonance imaging (MRI), prophylaxis] of migraine patients can only be carried out by neurologists. Thirdly, migraine can be a feature of a syndrome (e.g. MELAS) that requires extensive evaluation by specialised neurological centres. Another argument against AMPs for the treatment of migraine is that 13% of AMPs in the index study used BTX, regardless of whether the patients were diagnosed with migraine or not [1]. In addition, 21% responded that they knew nothing about migraine and seven respondents did not know the diagnostic criteria of migraine [1]. In addition, a non-neurologist may not be able to correct the diagnosis when symptoms and signs no longer meet the diagnostic criteria [3]. I also disagree with the statement in the introduction that AMPs have extensive BTX treatment experience [1]. Given that 26% of the index study respondents were dentists [1], it cannot be guaranteed that they were familiar with the use of BTX in migraine.

A limitation of the study is that it was conducted using an electronic questionnaire. The disadvantages of electronic questionnaires are that it is impossible to check whether the data provided is reliable, whether the addressees actually answered the questions themselves, that missing data cannot be replaced, and that additional, interesting, data cannot be obtained.

Another limitation is that alternative and less expensive therapy options for the treatment of migraine were not discussed. These include diet, the avoidance of triggering factors including certain medications, adequate water intake, nonsteroidal, anti-inflammatory drugs (NSAIDs), tryptanes, and monoclonal antibodies (e.g. erenumab). BTX should only be administered in refractory cases, in which neither prophylactic measures nor acute treatment lead to an adequate therapeutic response.

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The indication for BTX in migraine mentioned in the discussion is contradictory, since the indication also included tension-type headaches [1]. If chronic migraine is defined as the "presence of headache (tension-type and/or migraine) for at least 15 days/month during the last three months", patients with isolated tension-type headache, or a mixture of both migraine and a tension-type headache, could be treated with BTX. This discrepancy should be clarified.

Finally, it is questionable whether BTX is really effective for migraines or rather only for tension-type headaches or mixed headaches. In addition, it is conceivable that the effect of BTX in migraine patients is based on a placebo effect. As societies around the world are stressed and neuroticised by external influences or internal strains, they are affected by stress and therefore prone to muscle tension. In addition, it is possible that non-neurologists tend to interpret headaches more often as migraines simply for commercial reasons. If a migraine is diagnosed, BTX treatment is reimbursed but may not necessarily be indicated.

Overall, I feel that this interesting study has limitations which challenge the results and their interpretation. Addressing these limitations could further strengthen and reinforce the study. AMPs should not be included in the treatment of migraines. Headaches, whether primary or secondary, should remain the domain of the neurologist. The diagnostic and therapeutic management of chronic and episodic migraine is complex and constantly requires new considerations. For many patients, treatment cannot be standardised but must be individualised to achieve the optimal individual outcome.

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RESPONSE TO LETTER
TO THE EDITORS

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Response to 'Neurologists should retain diagnostic and therapeutic management of migraines'

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To the Editors

I would like to thank Dr. Finsterer for his interest in my article, and I welcome his comments [1]. I am happy that it has provoked a discussion on treating chronic migraine (CM) with botulinum toxin (BTX) by specialists other than neurologists. This article is the first to have assessed the actual situation in Poland [2], although the topic is of concern to many other countries also. The commercial market of BTX treatment for CM is continually developing, trying to meet patient needs and overcome barriers to accessing treatment. Based on labels, the use of products is not restricted to professionals experienced in treating CM. As a result, BTX is used to treat CM by neurologists, but also by aesthetic medicine practitioners (AMPs), orthopaedic surgeons, anaesthetists, and dentists. Any licensed physician can use BTX for various indications, including CM. My article looked at real-life practice and neither suggested nor approved treatment of CM with BTX by specialists other than neurologists. It did include a discussion of some weaknesses in today's practice; however, it did not suggest it should either be prohibited or stigmatised. Physicians have the right to use a medication registered for a given indication to help their patient. I merely wish those practitioners using BTX to treat CM to know the diagnostic criteria, the principles of injection technique, and good patient management. The results map areas of improvement, at least in Poland, where the therapy was not reimbursed for 12 years. This led to the development of a commercial market for the treatment of CM in Poland, primarily owned by AMPs.

Undoubtedly, the diagnosis of migraine, especially CM, should be the domain of neurologists. Similarly, the management of patients with complicated migraine, especially those with a coexisting medication overuse headache, must be left in the hands of a neurologist. However, there is no reason why other specialists, including AMPs, could not perform the BTX injections after a neurologist has qualified the patient and provided that the procedure is performed correctly, following the PREEMPT protocol.

Patients might benefit if a neurologist avoids performing such a procedure, and instead cooperates with an AMP. There is an important reason for that. Due to the anatomical distinctiveness of each patient's face, the injection, according to the PREEMPT protocol, can cause the patient's appearance to alter unfavourably e.g. brow ptosis or the Mephisto symptom. This is especially important for women, and is sometimes the reason for discontinuing BTX for CM therapy. AMPs deal with such complications of BTX application much better than do most neurologists. Andrew Blumenfeld and I recently described an individualised approach for combining neurological and aesthetic treatments [3].

This preliminary study, performed using an online questionnaire, has many limitations. However, it might provide guidelines for further education directions among physicians in Poland. Given that every doctor in Poland, by law, can use BTX for CM, although they sometimes lack the knowledge and experience to do so correctly, it is surely safer to train those who do it anyway and encourage them to cooperate with neurologists regarding the diagnosis, qualification, and management of CM patients.

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