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Trimetazidine and parkinsonism: A prospective study

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ABSTRACT

Background: Although trimetazidine may induce parkinsonian symptoms in some patients, no systematic characterization has been reported on parkinsonism occurring during trimetazidine treatment since the first case reports.
Objective: To systematically investigate parkinsonism occurring during trimetazidine use.
Methods: Thirty-three consecutive patients on trimetazidine treatment with previously unrecognized parkinsonian symptoms were enrolled. Detailed neurological and neuropsychological examinations were performed at baseline and 1 and 12 months after trimetazidine withdrawal. In cases with persisting parkinsonian symptoms and suspected de novo Parkinson's disease, antiparkinsonian treatment was initiated. Twenty of the 33 patients underwent DaTSCAN imaging.
Results: After trimetazidine withdrawal, parkinsonism was completely resolved in 11 cases. The comparison of baseline data of patients with reversible and persisting parkinsonism showed that trimetazidine-induced reversible parkinsonism was mainly characterized by akinesia, rigidity, postural instability and gait disturbances (PIGD; PIGD scores: 5.3 ± 3.8 vs. 2.0 ± 1.6 points, p = 0.006) rather than tremors (tremor scores: 1.5 ± 2.2 vs. 7.7 ± 4.6 points, p = 0.000). Trimetazidine-induced reversible parkinsonism was also more symmetrical (asymmetry index: 3.1 ± 3.6 vs. 40.1 ± 22.2, p = 0.000) and milder in severity (MDS-UPDRS Part III. scores: 10.5 ± 19. vs. 30.5 ± 11.3, p = 0.040) than nonreversible parkinsonism. DaTSCAN images were normal in all trimetazidine-induced reversible parkinsonism patients, while these images were abnormal in every patient with nonreversible parkinsonism. In cases of nonreversible parkinsonism, preexisting, incipient Parkinson's disease was suspected by clinical appearance and a good response to antiparkinsonian medication.
Conclusions: Mild and symmetrical appearance of parkinsonism with normal DaTSCAN results can indicate drug-induced parkinsonism. Trimetazidine discontinuation generally results in permanent remission in such cases.

1. Introduction

Trimetazidine (1-[2,3,4-trimethoxibenzyl]-piperazine, TMZ) is one of the most frequently prescribed cardiologic drugs, and it is a well-established add-on therapy for stable coronary heart disease (CHD) [1]. Based on epidemiological data and a national health-insurance database, there are approximately 400,000 patients with stable CHD in Hungary. Of these patients, approximately 157,000 (39%) were on TMZ between July 2017 and June 2018 [2]. Consequently, one-third of CHD patients are treated with TMZ in Hungary, which is comparable with use in other European countries [3].

Although TMZ is generally well tolerated and its safety profile is considered to be good, some adverse drug reactions (ADRs), including gastrointestinal disturbances, nausea, vomiting, headache, liver dysfunction, thrombocytopenia, and agranulocytosis, have also been observed. These ADRs are reported to be rare and generally reversible,

Abbreviations: ACS, acute coronary syndromes; ADRs, adverse drug reactions; AI, asymmetry index; CHD, coronary heart disease; CHF, chronic heart failure; TMZ, trimetazidine; EMA, European Medicines Agency; ESC, European Society of Cardiology; LARS, Lille Apathy Rating Scale; NMSS, Non-Motor Symptoms Scale; NRP, nonreversible parkinsonism; MADRS, Montgomery-Asberg Depression Rating Scale; MDS-UPDRS, Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PAD, peripheral artery disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; PAS, Parkinson Anxiety Scale; PD, Parkinson's disease; PIGD, postural instability and gait difficulty; RP, reversible parkinsonism; TGI, transient global ischemia; TS, tremor score

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and most of them are not considered to be directly linked to TMZ treatment [4,5]. However, ADRs requiring more careful evaluation have also been reported. In 2004, Marti Masso et al. described reversible parkinsonism in eight patients treated with TMZ [6]. In 2005, the same authors provided more evidence for the putative relationship between TMZ and parkinsonism. Based on their assumptions, approximately 40% of patients treated with TMZ were reported to develop movement disorders. TMZ was also found to cause deterioration of the clinical status of patients with Parkinson's disease (PD) [5]. The warnings given by Marti Masso et al. have been reinforced by further reported cases of supposed TMZ-related movement disorders [7–11]. The growing number of reported cases requires reassessment of the risk-benefit ratio of TMZ treatment. In 2012, the European Medicines Agency (EMA) made a recommendation for the regular investigation of parkinsonian symptoms in patients on TMZ, especially in those aged more than 75 years old with severe renal failure (creatinine clearance < 30 ml/min). TMZ became contraindicated in patients with PD, and it was de-licensed as a treatment option in the management of vertigo, tinnitus and vision disturbances due to its parkinsonism-inducing side-effects. According to EMA, TMZ-related parkinsonian symptoms persisting more than 4 months after drug discontinuation should be evaluated by a neurologist [12].

The exact mechanism of action by which TMZ induces or worsens parkinsonism is not yet fully understood. This metabolic modulator with cytoprotective capabilities against ischemic cell damage via various mechanisms [13] has a piperazine core. The piperazine structure is also found in cinnarizine and flunarizine, which have been found to be able to induce movement disorders via dopamine receptor antagonism [14]. Therefore, it is thought that TMZ also performs its parkinsonism-inducing or -aggravating effect via interacting with dopamine D2 receptors of the striatum [10]. Further evidence for TMZ interacting with central dopamine receptors may be its potential antipsychotic-like effects that were found in a rodent model [15].

Although the first cases of parkinsonism related to TMZ treatment were published fourteen years ago, very few systematic studies have been conducted on parkinsonism occurring during TMZ use. Therefore, the aim of the present study was an in-depth systematic investigation of parkinsonism observed during TMZ treatment. The findings by Marti Masso et al. from 2005 [5] allowed the authors to hypothesize that, on the one hand, TMZ can unmask subclinical neurodegenerative parkinsonism and, on the other hand, it can also induce secondary and reversible parkinsonism.

2. Materials and methods

In the present study, consecutive patients were enrolled between 2013 and 2016 in the Department of Neurology, University of Pecs, Hungary, who presented with previously unrecognized parkinsonism and were on TMZ treatment. The definition of the International Parkinson's Disease and Movement Disorder Society for parkinsonism was used for clinical diagnosis [16]. The study was approved by the Regional and Institutional Ethical Committee (3617.316–24987/KK41). In addition to demographic-, medication- and disease-related data, the validated Hungarian versions of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [17], the 39-item Parkinson's Disease Questionnaire (PDQ-39) [18], the Montreal Cognitive Assessment (MoCA) [19], the Lille Apathy Rating Scale (LARS) [20], the Parkinson Anxiety Scale (PAS) [21], the Montgomery-Asberg Depression Rating Scale (MADRS) [22] and the Non-Motor Symptoms Scale (NMSS) [23] were used for assessments. On the basis of their MDS-UPDRS scores, patients were classified as mild, moderate or severe using the cut-off points determined by Martinez-Martin et al. [24]. The MDS-UPDRS cut-off values between mild/moderate and moderate/severe levels were the following: Part I: 10.5 and 21.5; Part II: 12.5 and 29.5; Part III: 32.5 and 58.5; Part IV: 4.5 and 12.5.

The asymmetry index (AI) was calculated by the following formula:

$$AI = \frac{\text{Left} - \text{Right}}{(\text{Left} + \text{Right})/2} \times 100$$

where left is the sum of left-sided scores of MDS-UPDRS Part III (Motor Examination) and right is the sum of the right-sided scores. For judging the symmetry of symptoms, the absolute values of AI were used; larger numbers represent more pronounced asymmetry. Subsequently, the Tremor score (TS) and Postural Instability/Gait Difficulty (PIGD) scores were calculated as described by Stebbins et al. [25].

In addition, brain magnetic resonance imaging (MRI) was performed and an ^{123}I-FP-CIT SPECT (DaTSCAN®, G.E. Healthcare, Eindhoven, Netherlands) examination was offered for all patients. The procedure of the DaTSCAN examination was previously described in full detail elsewhere [26].

As its usage may be associated with drug-induced parkinsonism, we first stopped TMZ use and patients were reassessed 1 month later. If the parkinsonian features completely disappeared, the patients were asked to attend regular follow-ups and no specific dopaminergic medication was introduced. In those cases where the parkinsonian symptoms improved but did not completely resolved 4 months after TMZ withdrawal and de novo PD could be suspected based on the UK Brain Bank criteria, antiparkinsonian treatment was initiated in accordance with the current guidelines.

All patients were re-evaluated one year after the initial examination. Based on the clinical data and symptoms, the diagnosis of TMZ-induced reversible parkinsonism was established in those patients where the parkinsonian symptoms completely resolved and the patients did not require any antiparkinsonian medication.

The IBM SPSS software package (version 24.0.2, IBM Inc, Armonk, NY, USA) was used for statistical analysis. To test normality, the Shapiro-Wilk test was used. Because data from the applied scales followed the normal distribution, the mean and standard deviation were calculated and independent samples t-tests were applied for group comparisons. For categorical variables (e.g., the severity of symptoms measured by different parts of MDS-UPDRS) a chi-squared test was used. The statistical significance level was set at 5%.

3. Results

We identified 37 patients with previously unrecognized parkinsonism and concomitant TMZ use. Because four patients were lost to follow-up for unknown reasons, the data of 33 patients (14 females, mean age: 70.7 ± 6.6 years) who underwent both baseline and 1-year follow-up were subsequently utilized. The duration of TMZ usage at baseline examination varied between 18 and 120 months. The average time between the onset of parkinsonian symptoms and the baseline examination was 9.7 ± 5.2 months. In all cases, the brain MRI did not reveal any specific abnormalities that were capable of producing parkinsonism. Other specific causes for parkinsonism (e.g., usage of other dopamine receptor blocking agents, previous serious head trauma or encephalitis, or stroke-induced parkinsonism) were also excluded.

At the 1-year follow-up, 11 patients (33.3%) had no parkinsonian symptoms nor need for any antiparkinsonian medication; therefore, these patients were diagnosed with TMZ-induced reversible parkinsonism (reversible parkinsonism, RP). In 22 patients (66.7%), the parkinsonian symptoms improved but did not completely disappear after TMZ withdrawal (nonreversible parkinsonism, NRP) and, in these cases, antiparkinsonian treatment was initiated: levodopa monotherapy in 17 cases, dopamine agonist monotherapy in 3 cases, and combination therapy with levodopa and a dopamine agonist in 2 cases.

Twenty of 33 patients (7 patients with RP and 13 patients with NRP) underwent DaTSCAN imaging. The result was normal in every patient with TMZ-induced RP, while all patients with NRP had abnormal results (grade 2 in 10 cases, and grade 3 in 3 cases). A representative scan of both normal and abnormal cases can be seen in Fig. 1.

Demographic and disease-related data of patients with RP and NRP

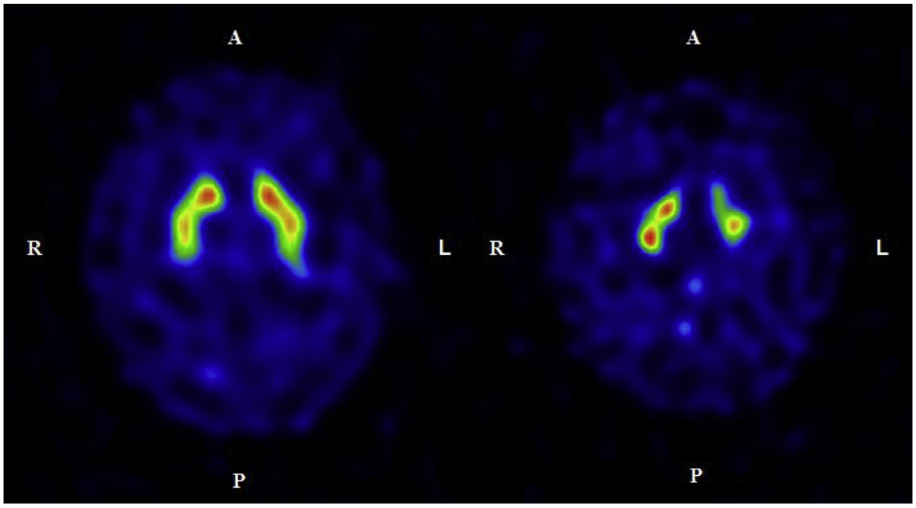

Fig. 1. A representative DaTSCAN of a patient with reversible TMZ-induced parkinsonism (left), and an abnormal scan of a patient with nonreversible parkinsonism (right).

at baseline are compared in Table 1. The duration of the TMZ usage did not differ between the two groups. In patients with RP, more symmetrical symptoms were observed, while parkinsonism was more asymmetrical in patients with NRP (absolute value of the AI: 3.1 ± 3.6 vs. 40.1 ± 22.2, p = 0.000). In addition, less pronounced tremors (TS: 1.5 ± 2.2 vs. 7.7 ± 4.6 points, p = 0.000) and more severe postural instability and gait disturbances (PIGD scores: 5.3 ± 3.8 vs. 2.0 ± 1.6 points, p = 0.006) were observed in the RP group than in the NRP group. The severity of parkinsonian motor symptoms measured by the MDS-UPDRS Part III was also milder in the RP group than in the NRP group (10.5 ± 19.0 vs. 30.5 ± 11.3 points, p = 0.040). However, worse health-related quality of life (PDQ-39 summary index) and cardiovascular problems (1st section of the NMSS) were be measured in the PR group. Age, sex, handedness, education and scores of further neurological and neuropsychological tests were comparable.

4. Discussion

Symptoms of drug-induced secondary parkinsonism show improvement or may completely disappear after drug discontinuation. According to the EMA statement [12], approximately 4 months withdrawal is necessary for the complete resolution of TMZ-induced RP. In the present study, one-third of patients achieved complete remission after TMZ withdrawal. These cases were considered to belong to TMZ-induced secondary parkinsonism characterized by milder and more symmetrical motor symptomatology with more pronounced rigid-akinetic features.

The results of the present study support previous findings on the motor features of TMZ-induced parkinsonism [5,7,10]. We confirm that the generally complete remission of the parkinsonian symptoms after drug discontinuation is one of the main characteristic features of TMZ-induced parkinsonism [6,7,10]. Although it has also been reported that TMZ can induce dyskinesia including choreiform movements, periodic leg movements, and buccolingofacial dyskinesia [9,10], we did not identify such cases.

As far as the authors are aware, this is the first study investigating the nonmotor features of TMZ-induced parkinsonism. Considering the Hungarian threshold values of 18 points on the MADRS and 13 points on the PAS, depression does not seem to be a characteristic feature for TMZ-induced parkinsonism. However, anxiety may occur in patients with TMZ-induced RP. The presence of anxiety may result from the development of gait disturbances and postural instability, which can lead to falls. Anxiety disappeared after TMZ discontinuation and it therefore may be an actual nonmotor feature of TMZ-induced parkinsonism.

The average MoCA score in the TMZ-induced RP group was below the previously established normal values measured in the general PD population (23.6 ± 3.6) [23]. Cognitive impairment has been found to occur commonly in patients with drug-induced parkinsonism; however, the underlying cause for this is not fully known yet. It is suggested that cognitive impairment is not related to the metabolic effects of the drug [27]. In the present study, cognitive functioning did not improve significantly after TMZ withdrawal; therefore, cognitive impairment may not be associated with TMZ treatment. As patients on TMZ with angina pectoris may have several vascular risk factors, the potential role of these risk factors in cognitive decline cannot be excluded.

In the Hungarian population, the cut-off value of −19.5 points on the LARS can be utilized for detecting apathy [20]. Using this threshold value, apathy also appears to be a nonmotor feature of TMZ-induced parkinsonism. The remission of apathy due to TMZ withdrawal may affirm the association of apathy with TMZ-induced parkinsonism.

As the other nonmotor symptoms of patients with RP measured by the NMSS did not improve after TMZ discontinuation, they may not be actual nonmotor features of reversible TMZ-induced parkinsonism. Comorbidities (e.g., diabetes mellitus) and other drugs (e.g., diuretics) may be responsible for the presence of these symptoms. However, the small number of patients with reversible TMZ-induced parkinsonism might limit the generalization of these findings. Therefore, larger prospective studies are warranted to confirm and explain these results.

The severity of apathy, depression, anxiety, cognitive decline and other nonmotor symptoms measured by the NMSS, with the exception of cardiovascular problems, were comparable between the RP and NRP groups. Therefore, nonmotor symptoms seem to be less helpful for differentiating TMZ-induced parkinsonism from neurodegenerative parkinsonism.

The most remarkable result of our data is the impact of TMZ-induced parkinsonism on the health-related quality of life (HRQoL). Although motor symptoms of TMZ-induced parkinsonism are considered to be generally mild, and MDS-UPDRS Part III scores were lower in the RP group, they had worse HRQoL measured by the PDQ-39. Therefore, the recognition and the treatment of TMZ-induced parkinsonism are of great importance.

TMZ has only modest effects on the symptoms of angina pectoris [28]. In the case of TMZ-induced parkinsonism, it should be discontinued and replaced by other antianginal drugs, including certain beta-blockers and calcium-channel blockers, which are not considered to cause parkinsonism [28]. This approach is generally well-tolerated and leads to complete remission of parkinsonian symptoms.

Table 1
Demographic and disease-specific data of patients with reversible and non-reversible parkinsonism at baseline.

		Reversibility of parkinsonism		p-value
		Yes (n = 11)	No (n = 22)	
Age (years)		68.4 ± 4.8	71.8 ± 7.2	p = 0.248
Handedness (R/L)		10/1	21/1	P = 0.606*
Sex (M/F)		4/7	15/7	p = 0.081*
Length of TMZ usage (months)		48.5 ± 20.3	50.7 ± 16.5	p = 0.386
Education (years)		12.7 ± 2.9	12.1 ± 3.2	p = 0.665
DATSCAN**	Normal	7/7 (100.0%)	0/13 (0.0%)	p = 0.000*
	Abnormal	0/7 (0.0%)	13/13 (100.0%)	
MDS-UPDRS I. nM-EDL		12.3 ± 5.0	11.6 ± 5.2	p = 0.585
MDS-UPDRS I. nM-EDL severity	Mild	4 (36.4%)	10 (45.5%)	p = 0.640*
	Moderate	7 (63.6%)	11 (50.0%)	
	Severe	0 (0.0%)	1 (4.5%)	
MDS-UPDRS II. M-EDL		10.4 ± 6.1	8.2 ± 6.0	p = 0.375
MDS-UPDRS II. M-EDL severity	Mild	6 (54.5%)	18 (81.8%)	p = 0.097*
	Moderate	5 (45.5%)	4 (18.2%)	
	Severe	0 (0.0%)	0 (0.0%)	
MDS-UPDRS III. ME		22.6 ± 10.5	30.5 ± 11.3	p = 0.040
MDS-UPDRS III. ME severity	Mild	10 (90.9%)	12 (54.5%)	p = 0.037*
	Moderate	1 (9.1%)	10 (45.5%)	
	Severe	0 (0.0%)	0 (0.0%)	
MDS-UPDRS IV. MC		4.0 ± 0.8	4.0 ± 1.2	p = 0.836
MDS-UPDRS IV. MC severity	Mild	9 (81.8%)	17 (77.3%)	p = 0.763*
	Moderate	2 (18.2%)	5 (22.7%)	
	Severe	0 (0.0%)	0 (0.0%)	
MDS-UPDRS Total score		49.3 ± 19.1	54.2 ± 13.0	p = 0.218
MDS-UPDRS AI (absolute value)		3.1 ± 3.6	40.1 ± 22.2	P = 0.000
Tremor score		1.5 ± 2.2	7.7 ± 4.6	P = 0.000
PIGD score		5.3 ± 3.8	2.0 ± 1.6	p = 0.006
LARS		−20.6 ± 6.5	−24.9 ± 5.1	p = 0.048
MADRS		12.9 ± 5.9	10.5 ± 6.4	p = 0.248
PAS		13.6 ± 7.0	13.0 ± 6.6	P = 0.560
MoCA		21.9 ± 5.1	22.2 ± 3.8	p = 0.977
PDQ-39				
Mobility		37.7 ± 26.1	9.2 ± 9.1	P = 0.003
ADL		15.9 ± 14.6	5.9 ± 9.1	P = 0.097
Emotional well-being		24.6 ± 11.4	18.9 ± 15.9	p = 0.063
Stigma		9.1 ± 19.2	1.7 ± 4.4	p = 0.355
Social support		10.6 ± 11.8	7.2 ± 9.0	p = 0.510
Cognition		20.5 ± 12.5	15.0 ± 11.0	p = 0.233
Communication		8.3 ± 15.4	5.3 ± 8.4	p = 0.895
Bodily discomfort		25.0 ± 23.9	25.0 ± 19.6	p = 0.807
SI		18.7 ± 9.8	11.1 ± 7.7	p = 0.021
NMSS				
Cardiovascular problems		6.0 ± 5.0	1.9 ± 2.7	p = 0.021
Sleep problems		8.1 ± 7.9	13.4 ± 10.6	p = 0.178
Mood problems		17.0 ± 14.7	14 ± 17.3	p = 0.317
Hallucinations		1.8 ± 5.4	0.8 ± 2.4	p = 0.836
Memory problems		4.7 ± 8.6	5.4 ± 6.3	p = 0.721
Gastrointestinal problems		3.3 ± 4.3	2.5 ± 4.5	p = 0.440
Urinary problems		11.1 ± 8.4	10.4 ± 9.4	p = 0.749
Sexual problems		0.0 ± 0.0	0.5 ± 1.4	p = 0.534
Miscellaneous		2.2 ± 3.7	2.5 ± 4.7	p = 0.985
Total score		54.2 ± 42.2	51.4 ± 43.0	p = 0.510

Data are mean ± standard deviation or n (%) unless otherwise indicated.
MDS-UPDRS cut-off values between mild/moderate and moderate/severe levels are the following: Part I: 10/11 and 21/22; Part II: 12/13 and 29/30; Part III: 32/33 and 58/59; Part IV: 4/5 and 12/13.
*Based on Chi-square statistics.
**Based on results of 20 out of 33 patients.
Abbreviations: **R/L** = right/left; **M/F** = male/female; **MDS-UPDRS** = Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; **MDS-UPDRS I. nM-EDL** = Non-motor Experiences of Daily Living (Part I of MDS-UPDRS); **MDS-UPDRS II. M-EDL** = Motor Experiences of Daily Living (Part II of MDS-UPDRS); **MDS-UPDRS III. ME** = Motor Examination (Part III of MDS-UPDRS); **MDS-UPDRS IV. MC** = Motor Complication (Part IV of MDS-UPDRS); **AI** = asymmetry index; PIGD = postural instability and gait difficulty; **LARS** = Lille Apathy Rating Scale; **MADRS** = Montgomery-Asberg Depression Rating Scale; **PAS** = Parkinson Anxiety Scale; **MoCA** = Montreal Cognitive Assessment; **PDQ-39** = 39-item Parkinson's Disease Questionnaire; **ADL** = activities of daily living; **SI** = summary index; **NMSS** = Non-Motor Symptoms Scale.

Despite the warnings about the parkinsonism-inducing effect of TMZ given by previous studies, TMZ-induced parkinsonism is unfortunately a highly neglected yet probably frequent condition. In 2005, Marti Masso et al. identified 56 patients with movement disorders taking TMZ between 1990 and 2003. Of them, 10 patients (18%) had drug-induced parkinsonism associated with TMZ alone [5]. In the present study, this portion was higher. Between 2013 and 2016, we identified 11 patients (33%) with reversible TMZ-induced parkinsonism of 33 subjects presenting parkinsonian symptoms that developed during TMZ treatment. This phenomenon highlights the need for large-scale studies evaluating the prevalence of TMZ-induced neurological side effects more reliably.

In the present study, the cases of nonreversible parkinsonism might indicate that TMZ can also unmask or worsen incipient parkinsonism. Symptoms of these patients were more severe and occurred asymmetrically. Resting tremor was the main feature, and the symptoms showed some improvement after TMZ discontinuation. Further improvement of symptoms could only be achieved by antiparkinsonian therapy. As TMZ-induced parkinsonism has been found to be resistant to antiparkinson therapy [10,29], a good response to dopaminergic treatment may be another indicator for neurodegenerative parkinsonism. In addition, the DaTSCAN examination may also be a promising approach for differentiating cases with TMZ-induced parkinsonism from those patients with subclinical neurodegenerative parkinsonism aggravated by TMZ treatment.

The strength of the present study partly lies in its longitudinal design. Follow-up is an important part of our approach because it provides a good opportunity for the more careful evaluation of remission of the parkinsonian symptoms and the need for antiparkinsonian medication. Another strength of the study can be the application of numerous validated scales measuring objectively reversible TMZ-induced parkinsonism from several aspects and allowing the reliable judgment of previous findings and the investigation of new aspects of this drug-induced neurological side effects. To the best of our knowledge, it is the first study using DaTSCAN examination during the investigation of parkinsonism associated with TMZ. However, the authors are aware that the study may have some limitations. First, some of the enrolled patients had no DaTSCAN examinations due to patient preference. Therefore, data of only seven patients with RP and 13 patients with NRP could be utilized for judging the clinical relevance of this novel approach in diagnosing TMZ-induced parkinsonism. Future studies investigating TMZ-induced parkinsonism should also include DaTSCAN examination in their methods to confirm or disprove that a normal DaTSCAN exam is characteristic for TMZ-induced parkinsonism. Another limitation may be the relatively small number of patients with TMZ-induced parkinsonism. This small number may have prevented the authors from identifying some features of TMZ-induced parkinsonism. To clarify this possible issue, systematic investigations of larger cohorts of patients with TMZ-induced parkinsonism should be performed by future studies.

To the best of our knowledge, this is the first study that systematically analyzed parkinsonism related to TMZ use during long-term follow-up and provided detailed phenomenological and neuropsychological descriptions. To conclude, TMZ-induced parkinsonism is characterized by rigidity, akinesia, postural instability and gait disturbances rather than tremors. Furthermore, a normal DaTSCAN exam can also support a diagnosis of reversible TMZ-induced parkinsonism. Although the motor symptoms are mild, symmetrical, and generally completely disappear after TMZ discontinuation, they have serious consequences on the health-related quality of life. Further large-scale prospective studies are warranted to estimate the prevalence of TMZ-induced parkinsonism in real life.

Conflicts of interest

None is declared. This study was supported by the Hungarian Brain Research Program (2017-1.2.1-NKP-2017-00002), NKFIH EFOP-3.6.2-16-2017-00008, NKFIH SNN125143, and ÚNKP-17- 4 -I.- PTE-311 government-based funds. Our research was partly financed by the Higher Education Institutional Excellence Program of the Ministry of Human Capacities in Hungary, within the framework of the 5th thematic program of the University of Pécs, Hungary (20765/3/2018/FEKUSTRAT).

Author roles

1. Research project:	A. Conception,	B. Organization,	C. Execution;
2. Statistical Analysis:	A. Design,	B. Execution,	C. Review and Critique;
3. Manuscript:	A. Writing of the first draft,	B. Review and Critique	

DP 1, 2, 3
MK 1B, 2C, 3B
MH 1B, 2C, 3B
AJ 1B, 2C, 3B
JJ 1A, 2C, 3B
NK 1, 2, 3

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DP reported no financial disclosure.
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JJ received < 1000 EUR consultation fees from Hungarian subsidiaries of UCB, Valeant and Eisai. Regarding this pilot study, the author did not receive any corporate funding.
NK received < 1000 EUR consultation fees from Hungarian subsidiaries of Medtronic. Boehringer Ingelheim. Novartis. GlaxoSmithKline. UCB, Krka and Abbvie. Regarding this study, the author did not receive any corporate funding.

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