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ORIGINAL COMMUNICATION

# Clinical course of patients with pantothenate kinase-associated neurodegeneration (PKAN) before and after DBS surgery

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## Abstract

**Introduction** Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disorder with a progressive clinical course. In addition to symptomatic therapy, DBS has been increasingly recognized as a potential therapeutic strategy, especially in severe cases. Therefore, we wanted to report our experience regarding benefits of DBS in five PKAN cases in 3-year follow-up study.

**Methods** Five genetically confirmed PKAN patients from Serbia underwent GPi-DBS. To assess clinical outcome, we reviewed medical charts and applied: Schwab and England Activities of Daily Living Scale (S&E), EQ-5D questionnaire for quality of life, Patient Global Impression of Improvement (GPI-I), Functional Independence Measure (FIM), Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), Barry Albright Dystonia Scale (BAD). Patients were evaluated in five visits: at the disease onset, 5 years after the onset, before surgery, 6 months and 14–36 months after the surgery. Improvement of 20% was accepted as significant.

**Results** Overall, dystonia significantly improved after GPi-DBS at 6 and 14–36 months postoperatively, when assessed by the BFMDRS and BAD. However, two patients failed to improve considerably. Four patients reported improvement on GPI-I, while one remained unchanged. Three patients reported significant improvement, when assessed with S&E and FIM. EQ-5D showed the most prominent improvement in the domains of mobility and pain/discomfort.

**Conclusion** Three out of our five patients experienced beneficial effects of the GPi-DBS, in up to 36 months follow-up. Two patients who had not reached significant improvement had longer disease duration; therefore, it might be reasonable to recommend GPi-DBS as soon as dystonia became disabling.

**Keywords** Deep brain stimulation · Dystonia · Globus pallidus internus · Pantothenate kinase-associated neurodegeneration

## Introduction

The most common form of the neurodegeneration with brain iron accumulation (NBIA), accounting for approximately 50% of cases, is pantothenate kinase-associated neurodegeneration (PKAN) [1]. This rare, recessively inherited disorder is caused by mutations in the *pantothenate kinase 2* (PANK2) gene, which encodes a mitochondrial pantothenate kinase, an essential regulatory enzyme in the biosynthesis of coenzyme A [2]. PKAN can be distinguished from other forms of the NBIA by the characteristic "eye of the tiger" sign on brain MRI [2].

Typical PKAN (presents at age < 6 years) has a progressive course (patient is wheelchair-bound within a few years), with dystonia as an early manifestation, with subsequent generalization and affection of cranial, limb and trunk muscles. Almost 90% of affected children are presented with gait difficulty, followed by generalized pyramidal and extrapyramidal features, neuropsychiatric involvement and visual disturbances [1, 3].

Atypical PKAN presents later and progresses more slowly, with less pronounced motor involvement including dystonia, while cognitive decline and psychiatric features may be prominent [4]. Majority of milestones which may significantly influence functional abilities and quality of life in these patients appeared in the first 5 years of the disease, followed by a long-lasting period of slower progression [4].

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Existing pharmacological treatments have not been satisfactory [2, 5, 6]. Several groups have recently applied deep brain stimulation (DBS) [7–14] in the treatment of PKAN patients, with heterogeneous responses [15, 16]. Still, DBS has been suggested in severe and resistant cases [17].

The aim of this study was to report five PKAN patients who underwent DBS and were followed for 3 years.

## Patients and methods

The study comprised five genetically proven patients with NBIA-PKAN recruited at the Movement Disorders Department, Clinic of Neurology (Belgrade, Serbia) from 1990 until 2017. In all of them, DBS was performed due to severe generalized, pharmacologically unresponsive dystonia. Before the surgery, they were regularly clinically screened (approximately every 6 months) from the initial stages of the disease (VSK, MS). They were clinically diagnosed based on the presence of (i) the progressive course; (ii) at least one of: dystonia, rigidity, tremor, bradykinesia, choreoathetosis; and (iii) the presence of abnormal MRI with hyperintensity of the pallidum on T1 images and hypointensity on T2 images ("eye of the tiger" sign) [18]. The diagnosis was finally confirmed by genetic testing of the PANK2 gene mutation (Table 1) [2].

The study was approved by the Institutional Review Board of the Clinic of Neurology and all patients gave informed consent.

Upon recruitment, medical charts were reviewed and detailed interview was obtained on demographic and clinical features in each patient. Clinical data were acquired in five consecutive visits: (V1) initial examination at the onset of symptoms (V2) 5 years after disease onset (V3) preoperative examination (V4) 6 months, and (V5) 14–36 months after the surgery. The following scales were used: (1) the Schwab and England Activities of Daily Living Scale (S&E) [19]; (2) quality of life was assessed by the five-dimensional EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) [20] (3) the Patient Global Impression of Improvement (GPI-I); ranged from one, as the highest possible level of satisfaction with an intervention, to seven for the highest level of deterioration [21]; and (4) the Functional Independence Measure (18 items arranged in domains: self-care, sphincter control, transfers, locomotion, communication and social cognition) defined the patient's

**Table 1** Clinical and demographic data of five PKAN patients

| Patient | ZĆ | UP | VK | NP | DB |
|---|---|---|---|---|---|
| Gender | F | M | F | M | F |
| Age (years) | 26 | 22 | 41 | 35 | 44 |
| Age at onset (years) | 10 | 7 | 13 | 18 | 20 |
| Age at diagnosis (years) | 15 | 10 | 13 | 18 | 20 |
| Disease duration (years) | 16 | 15 | 28 | 17 | 24 |
| Age at surgery (years) | 24 | 20 | 40 | 33 | 43 |
| Mutation | c.1583C > T, p.T528M/ c.1418_1424 del, p.N474X | c.1583C > T, p.T528M/ c.1418_1424 del,p. N474X | c.1583C > T, p.T528M/ c.1418_1424 del,p. N474X | c.1583C > T, p.T528M homozygous | c.1583C > T, p.T528M homozygous |
| Initial symptoms | Dystonia (arms) | OMD | OMD, dystonia (arms) | OMD | Dystonia (legs) |
| Left electrode (position of contact 0) | Sl = 18.3<br>Fa = 1.6<br>Hv = 4.0 | Sl = 18.8<br>Fa = 1.5<br>Hv = 3.5 | Sl = 19.6<br>Fa = 2.7<br>Hv = 3.1 | | Sl = 19.6<br>Fa = 3.4<br>Hv = 3.4 |
| Left DBS parameters (Active contacts, current stimulation (mA), pulse width (μs), frequency (Hz) | 0 −,C +<br>6.7 mA<br>210 μs<br>130 Hz | 0 −, C +<br>6.2 mA<br>210 μs<br>130 Hz | 0 −, C +<br>5.6 mA<br>120 μs<br>130 Hz | 0 −, C + 7<br>8.5 mA<br>125 μs<br>130 Hz | 0 −, C +<br>6.1 mA |
| Right electrode (position of contact 0) | Sl = 19.0<br>Fa = 1.7<br>Hv = 4.7 | Sl = 21.0<br>Fa = 2.5<br>Hv = 4.2 | Sl = 19.6<br>Fa = 2.3<br>Hv = 5.2 | | Sl = 19.0<br>Fa = 3.2<br>Hv = 3.2 |
| Right DBS parameters (Active contacts, current stimulation (mA), pulse width (μs), frequency (Hz) | 8 −, C +<br>6.7 mA<br>210 μs<br>130 Hz | 9 −, C +<br>6.0 mA<br>210 μs<br>130 Hz | 10 −, C +<br>5.3 mA<br>120 μs<br>130 Hz | 8 −, C +<br>5.2 mA<br>125 μs<br>130 Hz | 8 −, C +<br>6.0 mA |

OMD oromandibular dystonia, Sl distance (mm) from midline, Fa distance (mm) anterior to midpoint (midpoint = 1/2 of AC-PC line), Hv distance (mm) below AC-PC line

physical, psychological and social functional status according to the categories ranging from total independence to total assistance [22].

Dystonic features in all pointed testings have been assessed by the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), composed of two subscales [Burke–Fahn–Marsden Movement Scale (BFMDRS-M) and Burke–Fahn–Marsden Disability Scale (BFMDRS-D)] [23], and Barry Albright Dystonia Scale (BAD) [24] that evaluated eight body regions separately (total score ranging from 0 to 30). Improvement of 20% was accepted as significant according to previous recommendation [25].

## Individual patient characteristics

### Patient ZĆ

Generalized dystonia (GD) with prominent oromandibular dystonia (OMD) (progression in the first 5 years after onset), postural instability; anxiety and obsessive–compulsive disorders (OCD); gradual worsening: wheelchair bound at the age of 20.

### Patient UP

GD (extremities, trunk, neck—in the first 5 years after onset) particularly affecting gait (left leg); speech and swallowing slightly compromised; wheelchair-bound at the age of 15 and bedridden 2 years later with dystonic contractures and deformities, prolonged blepharospasm (BF) and global hypotrophy; dystonic storm which required hospitalization and coma induction prior surgery; sporadic compulsive actions progressed to OCD.

### Patient VK

During a course of 20 years, GD (arms, legs, trunk, OMD) completely disabled gait and speech; completely dependent in daily activities; depression.

### Patient NP

OMD progressed to generalized (neck, trunk, legs, arms), with BF, involuntary tongue protrusions, speech difficulties and occasional chocking (progression in the first 5 years after onset); in the following 10 years unable to walk, prolonged tonic BF; dystonic storm with opisthotonus; depression.

### Patient DB

In the first 5 years dystonia extended to her trunk and neck (extreme retrocollis) and caused grave posture instability with frequent falls; OMD with still comprehensible speech and dysphagia; anxiety and aggressivity; completely dependent in ADLs and unable to walk unattended.

## Surgical procedure

Implantation of the DBS system in four patients (ZC, UP, VK, DB) was performed at the Na Homolce Hospital in Prague, Czech Republic during one surgery under propofol anesthesia without muscle relaxants. Leksell frame and SurgiPlan Software system (Elekta, Stockholm, Sweden) were employed in stereotactic procedure and pre-surgical planning was based on 1.5 T MRI using previously published targeting procedure [26]. Microrecording with three tungsten microelectrodes spaced 2-mm apart in medio-lateral direction with the central microelectrode intentionally targeted to the posteroventral part of the globus pallidus internus (GPi) was used to improve navigation. Perioperative stimulation was then carried out to confirm that no tetanic cramps or dystonia was induced with common stimulation parameters. Exploratory electrode was subsequently replaced by a permanent electrode (type 3389, Medtronic, Minneapolis, MN). Immediately after the procedure, the position of the permanent electrode of each hemisphere was verified by two orthogonal X-ray images co-registered with presurgical MRI plan. Final positions are given in Table 1. No dislocation higher than 1 mm was found in any patient. Finally, implantation of extension cables and rechargeable internal pulse generator Activa RC (Medtronic, Minneapolis, MN) was implanted to subclavial region. The bilateral GPi-DBS using the current mode was initiated within one week after surgery starting with the distalmost contact of the quadripolar electrode.

Patient NP, who was regularly followed by our group, was operated in Vienna (his parents decided to organize the surgery by their own) and we do not have precise details regarding his surgical procedure.

## Statistical analysis

Descriptive statistics were used for demographic and clinical variables. The relative frequency was calculated by dividing the absolute frequency by the total number of values for the variable and expressed as a proportion and/or percentage.

## Results

### Clinical symptoms of individual patients after surgery

#### Patient ZĆ

General decrease of dystonia (except OMD) which allowed unaided walk and more independence in daily activities; relief of OCD.

#### Patient UP

Decrease of dystonic symptoms (incl. swallowing), except for fixed deformities disabling gait or standing; enabled to sit in a specially designed wheelchair; alleviated symptoms of OCD.

#### Patient VK

The least benefit after DBS in this series, with only slight decrease in arms dystonia.

#### Patient NP

Major improvements were unaided gait and more independence in activities of daily living (ADLs), due to decrease in dystonia; transient and slight speech improvement in the first 6 months after DBS later returned to the baseline; improvement in depressive symptoms.

#### Patient DB

Decrease of dystonic symptoms (particularly cervical dystonia (CD), but with no improvement of OMD) in the first 6 months after DBS, with reaggravation in the subsequent year, destabilizing gait (required aid).

### Objective measurement of symptoms after the surgery

Both the severity of dystonia and dystonia-related disability, assessed by the BFMDRS-M and BFMDRS-D, respectively, significantly improved after GPi-DBS at 6 and 14–36 months postoperatively compared to the state before surgery (Fig. 1a and b). None of our patients experienced significant surgical, stimulation- and device-related adverse events. Patient NP had an improvement of 55% in the movement score and 43% in the disability score 6 months postoperatively. During the next 30 months, the movement score declined to 47%, while the disability score lowered to 37%. Response in Patient ZĆ was even better, with both the BFMDRS-M and BFMDRS-D scores improvement of 60% after 6 months and remained stable (59%) after 36 months. Patient DB had a notable improvement of 21% 6 months after surgery but returned to the baseline conditions 14 months later (3%). The other two patients, UP and VK, also showed slight changes in both the BFMDRS-M and BFMDRS-D scores after GPi-DBS (bellow 20%) (Fig. 1a and b).

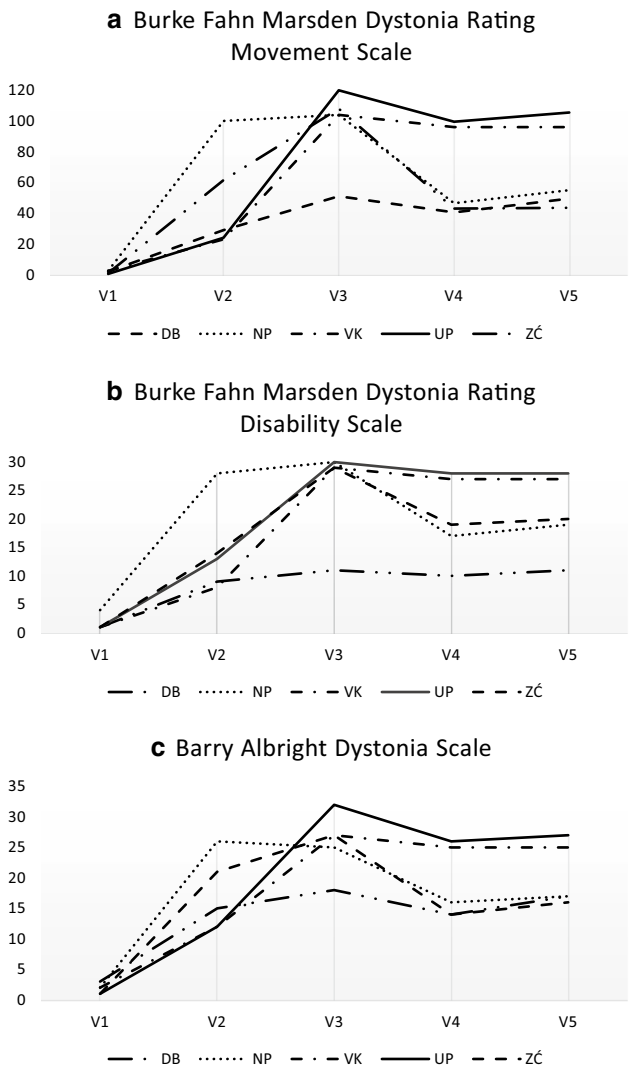


**Fig. 1** Burke–Fahn–Marsden Dystonia Rating Movement Scale (a), Burke–Fahn–Marsden Dystonia Rating Disability Scale (b), Barry Albright Dystonia Scale initially (c), at disease onset (V1) 5 years after disease onset (V2), before surgery (V3), 6 and 14–36 months after the surgery (V4 and V5, respectively)

The results obtained from the Barry Albright Dystonia Scale showed comparable results with a significant improvement in severity of dystonia both at 6 months and at 36 months (Fig. 1c).

With regard to GPI-I, patient ZĆ had the highest impression of improvement (score 1: very much better) at 6 months

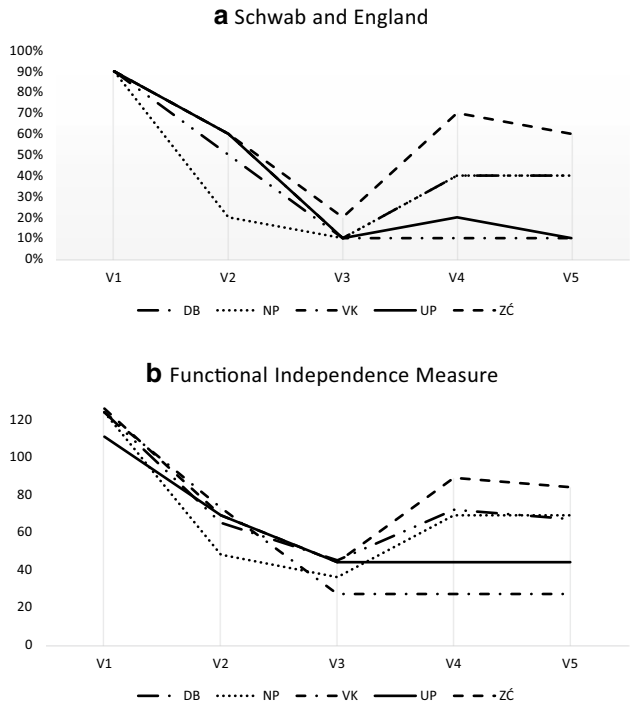


**Fig. 2** Schwab and England (a) and functional independence measure (b) at disease onset (V1), 5 years after disease onset (V2), before surgery (V3), 6 and 14–36 months after the surgery (V4 and V5, respectively)

that decreased to score 2 (much better) 36 months later. Patients DB, NP and UP had GPI-I score 2 after 6 months, followed with slight worsening to the score 3 (a little better) 36 months later. Patient VK did not observe any change in the postoperative course. None of our patients reported an impression of worsening.

On the S&E Scale (Fig. 2a), patients NP and DB showed the same pattern of improvement. They both had an increase from 10% before to 40% 6 months after, which remained the same at 36 months. Patient ZĆ had the most prominent benefits in functionality from the baseline 10% to 70% and 60% 6 and 36 months, respectively. Similar results were obtained on the functional independence measure (Fig. 2b). Patients with an improvement at both six and 36 months after surgery were NP (48% at both time points), DB (37% 6 months and slightly lower, 33%, 14 months after the procedure), and ZĆ (51% and 48% at 6 and 36 months, respectively). For these three patients, the biggest improvement was in the locomotion, while patients ZĆ and DB also gained significantly more functionality of upper extremities, allowing them to be more independent in dressing and taking care of their hygiene.

Regarding the health-related quality of life (HR-QoL) assessed by the EQ-5D scale (Table 2), the most prominent changes occurred in the domains of mobility and pain/

**Table 2** Health-related quality of life (HR-QoL) of five PKAN patients assessed by the EQ-5D scale

| Level | Mobility | | | Self-care | | | Usual activities | | | Pain/discomfort | | | Anxiety/depression | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BS | 6 m | 36 m | BS | 6 m | 36 m | BS | 6 m | 36 m | BS | 6 m | 36 m | BS | 6 m | 36 m |
| 1 | 0 | 20% (1) | 20% (1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60% (3) | 60% (3) | 0 | 60% (3) | 60% (3) |
| 2 | 0 | 40% (2) | 40% (2) | 0 | 40% (2) | 20% (1) | 0 | 20% (1) | 20% (1) | 20% (1) | 20% (1) | 20% (1) | 40% (2) | 20% (1) | 20% (1) |
| 3 | 100% (5) | 40% (2) | 40% (2) | 100% (5) | 60% (3) | 80% (4) | 100% (5) | 80% (4) | 80% (4) | 80% (4) | 20% (1) | 20% (1) | 60% (3) | 20% (1) | 20% (1) |
| Number reporting extreme problems | 100% (5) | 40% (2) | 40% (2) | 100% (5) | 60% (3) | 80% (4) | 100% (5) | 80% (4) | 80% (4) | 80% (4) | 20% (1) | 20% (1) | 60% (3) | 20% (1) | 20% (1) |
| Change in number (%) reporting extreme problems | 3 (60%) | | | 2/1 (40%/20%) | | | 1 (20%) | | | 3 (60%) | | | 2 (40%) | | |

Values presented as percentage of patients with number of patients in brackets

BS before surgery, m months after surgery

discomfort. All patients reported extreme difficulties in mobility and four of them reported having extreme pain/discomfort before surgery. After the procedure, only two patients still reported extreme difficulties in mobility, two stated having some difficulties and one reported no difficulties. Considering pain/discomfort, three patients stated feeling no more pain after the procedure, one remained at the extreme level and one lowered to a milder level (Table 2). All the patients reported anxiety/depression (three at the extreme level, two at the milder level) before the procedure, while three of them testified having no more symptoms after GPi-DBS.

The least improvement of the HR-QoL was in the domains of self-care and usual activities; only one patient reported improvement, while the others remained at the highest level of difficulty even 36 months after surgery. One more patient had an improvement in the first 6 months after GPi-DBS regarding the self-care activities, but it diminished in the subsequent period.

## Discussion

Three out of our five patients experienced beneficial effects 6 months after the GPi-DBS, which despite slight gradual worsening was still present in a course of the subsequent 30 months, particularly regarding severity of dystonia, disability, activities of daily living (ADLs), functional independence and HR-QoL in comparison to their state before the surgery. We witnessed a situation when battery in one of our patients was accidentally turned off and he urgently visited our department due to reappearance of generalized twisting movements. After checking and turning on his battery with a gradual increase of stimulation, dystonic movements decreased. Two patients (patient VK and UP) were considered non-responders. Patient VK, one of the two oldest patients at the time of surgery (40 years), had also the longest duration of symptoms prior to DBS (27 years) (Table 1). GPi-DBS induced a slight decrease of dystonic symptoms in arms, but otherwise she remained bedridden and functionally incapable in any of the daily activities. The second one, patient UP, experienced improvement of swallowing and psychiatric status (obsessive–compulsive disorder), but, although the S&E scale suggested some benefits, severe contractures prevented his improvement to reach clinically relevant level. In line with this observation, Dupre et al. [27] recommended that DBS in primary dystonia should be performed before the onset of permanent musculoskeletal deficits. Also, Timmermann et al. [9] suggested bilateral GPi-DBS in NBIA patients as soon as dystonia became disabling and before any possible secondary skeletal deformities.

Three "responders" in our study had a similar presentation with severe, disabling generalized dystonia before the procedure. The same symptom responded the best postoperatively, allowing them unaided gait and more independency in ADLs. Timmermann et al. [9] observed significant improvement with bilateral GPi-DBS in severely affected NBIA patients, particularly those with disabling dystonia. Umemura et al. [8] also reported that such treatment was effective and safe for intractable generalized dystonia in PKAN patients. Vloo et al. in meta-analysis provide level 4 evidence that GPi-DBS for pantothenate kinase-associated neurodegeneration may improve dystonia movement scores in classic type and atypical type and disability scores in atypical type 1 year postoperatively [28]. In this large meta-analysis that used independent participant data from 38 articles, primary outcome was changed in movement and disability scores of the Burke–Fahn–Marsden Dystonia Rating Scale 1 year postoperatively [28].

The target nucleus for bilateral DBS in all our patients was GPi, in accordance with the previous experiences with positive results of pallidal DBS in isolated generalized and segmental dystonia [29]. However, in general, improvements in our patients were lower in comparison to patients with isolated generalized dystonia [9]. It was difficult to make clear conclusions on GPi-DBS efficacy in other forms of secondary dystonias (with exception of tardive dystonia) due to a small number of patients included or only sporadic analyzed cases [30]. In continuation with the previous findings [10], Timmermann et al. [9] in a large multicenter study with NBIA patients reported beneficial and persistent effects of GPi-DBS on severity of dystonia which slowly abated in the course of 9–15 months. The authors observed a discrepancy between a rather small effect on disability and substantial improvement in the HR-QoL (a median improvement of 83% at 9–15 months). This was explained by the fact that the QoL in patients with dystonia reflected numerous factors beyond disability, such as dystonia-related pain, stigma, and fatigue due to medication that were not assessed by the BFMDRS-D. Recently, Liu et al. [31] suggested that the STN could also be a candidate target for DBS treatment of PKAN, especially in patients with prominent appendicular symptoms.

Swallowing was markedly improved by GPi-DBS, with subsequent increase in the body weight, but the effects on speech were disappointing; since in almost all our patents, it remained incomprehensible (one of them had slightly more comprehensive speech 6 months after surgery, but it slowly returned to baseline level).

Although our study included small number of PKAN patients, particular strengths of our report include comprehensive evaluation of QoL, and longer follow-up in genetically confirmed PANK2 mutation cases. Even in largest meta-analysis, which has been recently published, there is a lack of genetic confirmation of PANK2 mutations (in 56%

of cases), and some follow-up data were based on linear interpolation [28].

We find out that obtained data might still valuable for the limited experience on DBS treatment of patients with this rare disease.

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## Compliance with ethical standards

**Conflicts of interest** Marina Svetel has received speaker's honoraria from Actavis. Robert Jech is Consultant to Ipsen, Cardion; Advisory Board of Ipsen. Vladimir Kostić has received research grants from the Ministry of Education, Science, and Technological Development, Republic of Serbia and the Serbian Academy of Science and Arts; and speaker honoraria from Actavis and Salveo. Aleksandra Tomić, Nataša Dragašević, Igor Petrović, Nikola Kresojević, Isidora Banjac, Jelena Vitković, Ivana Novaković and Dušan Urgošik declare no conflict of interest.

**Ethical standards** The study was approved by the Institutional Review Board of the Clinic of Neurology and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** All patients gave informed consent.

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