- myasthenic patients. *Muscle Nerve* 2004;**30**:55–60.
- 5 **Caress JB**, Hunt CH, Batish SD. Anti-MuSK myasthenia gravis presenting with purely ocular findings. *Arch Neurol* 2005;**62**:1002–3.
 - 6 **McConville J**, Farrugia ME, Beeson D, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol* 2004;**55**:580–4.
 - 7 **Lindstrom J**. Is "seronegative" MG explained by autoantibodies to MuSK? *Neurology* 2004;**62**:1920–1.

Cognitive changes in Parkinson's disease during subthalamic stimulation: a clinicopathologic study

It is well established that patients with Parkinson's disease (PD) can develop cognitive, behavioural, and mood changes.¹ Cognitive decline has been reported to be present in up to 84% of patients who survive for 15 years after diagnosis.² Several mechanisms may underlie these clinical problems including cholinergic deficiency, dopaminergic dysfunction, prefrontal-caudate nucleus disconnection, and intrinsic limbic and cortical pathology (Lewy bodies, Alzheimer-like changes). Concerns have been raised about the possibility that subthalamic deep brain stimulation (STN-DBS) could also produce cognitive changes and mood and behavioural alterations.^{3,4} We report the clinical and neuropathological features of a patient with advanced PD who developed behavioural changes and dementia while on STN-DBS.

Case report

A 74 year old man suffering from PD for 11 years presented troublesome dyskinesias and unpredictable motor fluctuations that did not respond to multiple changes in medication. The Hoehn and Yahr stage was IV while "off" and III while "on" medication. The Schwab and England scale score was 40% in the "off" and 80% in the "on" condition. The UPDRS-III score was 56 while "off" and 21 while "on". No clinically evident signs of cognitive impairment were present. The Mini-Mental State Examination (MMSE) score was 28/30. Neuropsychological assessment was considered to be normal except for the presence of mild cognitive processing slowness and free recall impairment (table 1).

Dyskinesias and motor fluctuations had disappeared 3 months after STN-DBS. The Hoehn and Yahr stage was III and the Schwab and England score was 70%. Dopaminergic medication was initially

reduced to 20% but the patient later developed restless legs syndrome (attributed to the reduction in dopaminergic medication) and levodopa was reintroduced (400 mg/day). Motor performance remained stable during the following months. There were no significant changes in neuropsychological performance 6 months after STN-DBS (table 1). However, shortly afterwards the patient developed mood changes consisting of apathy, anhedonia without sadness, and diurnal hypersomnolence. Levodopa was then increased and antidepressants were started. Changing stimulation electrical parameters and stimulation poles did not change the patient's mood.

The patient developed fluctuating confusion, visual hallucinations, and paranoid ideations 1.5 years after surgery. The MMSE score was 22/30. He became violent with his relatives. Clozapine (100 mg/day) reduced aggression but confusion persisted. The possible role of STN-DBS on these cognitive and behavioural changes was assessed by switching off the stimulators for 1 week. Mental status remained unchanged but parkinsonism worsened until the stimulators were again switched on. Later in the course of the disease, the patient received galantamine which improved psychiatric symptoms and temporal-spatial orientation. The patient died from bronchopneumonia 3.5 years after surgery. The patient was a donor of the Bank of Neural Tissues of the University of Barcelona-Hospital Clinic.

Pathological examination

Macroscopic examination of the brain disclosed important loss of pigmentation in the substantia nigra pars compacta and locus coeruleus. The electrode tips were placed within the boundaries of the subthalamus on both sides. On microscopic examination moderate inflammatory infiltrates of T lymphocytes and mild astrocytic gliosis were observed surrounding the leads. Lewy bodies (LB) and Lewy neurites were found in the substantia nigra pars compacta, locus coeruleus, raphe nuclei, the dorsal nucleus of the vagus, and the hypoglossal nerve. Dystrophic neurites and cytoplasmic inclusions were found in the nucleus of Meynert and the subthalamus. Cortical type LB were observed in the gyrus cinguli, transentorhinal cortex, the amygdala, and the parietal and temporal cortex. The density of LB was maximal in the sub-cortical nuclei and the limbic areas. A few neurons showing neurofibrillar degeneration were found in the transentorhinal and entorhinal cortex, amygdalar complex, locus

coeruleus, and raphe nuclei. Neocortical senile plaques were scarce and signs of amyloid angiopathy were absent. The pathological diagnosis was diffuse Lewy body disease, transitional type.

Discussion

Recently, concerns have been raised in relation to the possible negative effects of STN-DBS on cognition and behaviour.^{3,4} We report a patient with advanced PD who developed cognitive impairment and behavioural changes while on STN-DBS. The patient was judged to be cognitively normal before surgery. After death from bronchopneumonia, post-mortem examination of the brain disclosed pathological changes typical of diffuse Lewy body disease.

The present report is the second clinicopathological description of a patient with PD, dementia, and STN-DBS. The first report by Jarraya *et al*⁵ described a parkinsonian patient who had some cognitive impairment before STN-DBS and whose mental condition worsened after surgery. Post-mortem examination confirmed the diagnosis of PD. The authors concluded that the bad outcome after surgery was due to the inadequate selection of a candidate who had cognitive deterioration before surgery, but the cause of the worsening mental status after STN-DBS remained unclear. In the case reported here, post-mortem examination disclosed changes typical of diffuse Lewy body disease. In addition, the cognitive and behavioural alterations were not thought to be related to STN-DBS since mental problems appeared late after STN-DBS and changes in stimulation parameters or even disconnection did not result in any mental or behavioural change. The clinical manifestations, the course of the disease, the presence of hallucinations, and the good response to cholinesterase inhibitors were also typical of so called Parkinson's disease-dementia in which the main pathological substrate is the presence of LB in limbic and neo-cortical areas.⁶ The development of neuropsychiatric symptoms is common in advanced PD and becomes more prevalent with disease progression.² STN-DBS has not been shown to cause progressive cognitive deterioration so far. The present case report supports the view that mental problems observed after STN-DBS in some patients are not related to STN-DBS and suggests alternative explanations. Several predictive factors for dementia in PD have been identified, such as older age at onset of symptoms, longer duration of motor symptoms, predominance of akinesia, rigidity, and gait disturbances, depression, early hallucinations, and impairment of memory and language function¹ but, in general, it is difficult to foresee which patients are more likely to develop behavioural and cognitive problems. A better understanding of the predictive factors for the development of dementia in PD will help to improve candidate selection for STN-DBS.

Acknowledgements

Dr O Morsi was granted a fellowship for specific training in movement disorders by the Spanish Neurological Society.

F Valdeoriola, E Tolosa, M Alegret

Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Suñer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

Table 1 Neuropsychological performance before and 6 months after STN-DBS

	Normal values	Before surgery	Performance	6 months after surgery	Performance
RAVLT total	≥24.3	31	Normal	34	Normal
RAVLT recall 20 min	≥4.7	5	Impaired	5	Impaired
Line Orientation	≥21	24	Normal	23	Normal
Trail Making A (s)	≤161	72	Normal	49	Normal
Trail Making B (s)	≤350	343	Normal	256	Normal
Stroop C	≥62	52	Impaired	59	Impaired
Stroop PC	≥37	38	Normal	41	Normal
Phonetic verbal fluency	≥10	15	Normal	14	Normal
Semantic verbal fluency	≥10	19	Normal	22	Normal
Boston Naming Test	≥42	58	Normal	57	Normal

RAVLT, Rey Auditory-Verbal Learning Test.

E Tolosa, M J Rey

Banco de Tejidos Neurológicos, Universitat de Barcelona-Hospital Clínic, Barcelona, Spain

O Morsi, M Pilleri

Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Suñer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

J Rumià

Department of Neurosurgery, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Correspondence to: Dr Francesc Valldeoriola, Neurology Department, Hospital Clínic, C/ Villarreal, 170, 08036-Barcelona, Spain; fvallde@clinic.ub.es

Patient details are published with consent

doi: 10.1136/jnnp.2005.077990

Competing interests: none declared

References

- 1 Aarsland D, Andersen K, Larsen JP, *et al.* Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 2003;**60**:387–92.
- 2 Hely MA, Morris JGL, Reid WGJ, *et al.* Sydney Multicenter Study of Parkinson's disease problems: non-L-dopa responsive problems dominate at 15 years. *Mov Disord* 2005;**20**:190–9.
- 3 Alegret M, Junqué C, Valldeoriola F, *et al.* Effects of bilateral subthalamic stimulation on cognitive function in Parkinson's disease. *Arch Neurol* 2001;**58**:1223–7.
- 4 Funkiewiez A, Ardouin C, Caputo E, *et al.* Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004;**75**:834–9.
- 5 Jarraya B, Bonnet A-M, Duyckaerts C, *et al.* Parkinson's disease, subthalamic stimulation and selection of candidates: a pathologic study. *Mov Disord* 2003;**18**:1517–20.
- 6 Cummings JL. Cholinesterase inhibitors for treatment of dementia associated with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2005;**76**:903–4.

Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases

Restless legs syndrome (RLS) is an awake phenomenon characterised by an intense, irresistible urge to move the legs, sensory complaints, and motor restlessness. RLS is usually associated with periodic limb movements in sleep (PLMS). Clinical evidence suggests that dopaminergic agents are the treatment of first choice. Dopaminergic treatment is usually effective, but many patients develop augmentation.¹ Augmentation is the worsening of RLS symptoms attributable to a specific therapeutic intervention; its primary feature is a shift of RLS symptoms to an earlier time than was typical at symptom onset during the initial course of beneficial stable treatment.² Augmentation requires the withdrawal of dopaminergic agents. Anticonvulsants may be used if the response to dopaminergic agents is not adequate or if augmentation occurs.¹

We describe two patients affected by RLS with PLMS who became unresponsive to the traditional dopaminergic agents and

Table 1 Results of clinical and instrumental evaluations

	Baseline	Pramipexole	Augmentation	Levetiracetam
Patient no. 1				
IRSSG scale score	34	21	35	22
Suggested immobilisation test				
PLM index (events/h)	39	26	40	11
Epworth sleepiness scale	14	10	13	10
Polysomnography				
Sleep latency (min)	165	34	172	27
Sleep efficiency index (%)	77.3	90.5	78.4	89.3
PLM index (events/h)	41.5	23.1	45.6	10.9
Patient no. 2				
IRSSG scale score	27	15	31	18
Suggested immobilisation test				
PLM index (events/h)	45	29	47	21
Epworth sleepiness scale	12	9	13	11
Polysomnography				
Sleep latency (min)	194	35	125	32
Sleep efficiency index (%)	71.2	85.6	79.5	89.9
PLM index (events/h)	64.2	31.5	45.6	12.6

IRSSG, International Restless Legs Syndrome Study Group; PLM, periodic limb movements; PLM index, number of events per hour of time in bed. Sleep efficiency index: percentage of time in bed spent asleep. Sleep latency: interval between lights off and the first epoch of stage II NREM.

developed augmentation. Both patients were treated with the antiepileptic drug levetiracetam and showed a clear and persistent clinical improvement of both RLS symptoms and PLMS. The clinical assessment and follow up included: subjective evaluation of symptoms and their impact on everyday life by means of the International Restless Legs Syndrome Study Group (IRLSSG) rating scale; evaluation of daytime sleepiness with the Epworth sleepiness scale; a suggested immobilisation test (SIT); and overnight, laboratory based polysomnography (PSG). Patients gave written informed consent to the use of levetiracetam. Results are given in table 1.

Patient no. 1

Patient no. 1, a 58 year old man, had been affected by rheumatoid arthritis since the age of 34. He presented the first symptoms of RLS at the age of 40, characterised by a creeping sensation at rest, prevalent in the left lower limb, and severe insomnia. He had no familial history of RLS. Initially, he was treated with clonazepam with partial benefit, then with carbamazepine (600 mg) without success. In the following years he reported progressive worsening. RLS interfered with his work, since he was a manager, and he became unable to sit in meetings. He came to our attention at the age of 53. He reported severe RLS with sleep latency >3 h. EMG, and brain and spine MRI were normal. Ferritin levels were low (50 ng/ml); iron supplementation normalised the blood levels of ferritin, but symptoms did not remit. RLS was associated with PLMS (table 1). The patient complained of severe daytime sleepiness and depressed mood. Pramipexole (0.18 mg at bedtime) was started, with immediate clinical improvement which persisted for about 6 months. However, the patient then developed drug resistance and augmentation. Pramipexole was progressively titrated up to 2.1 mg and cabergoline (4 mg) was added. Since no amelioration occurred, the patient switched to ropinirole (5 mg), then gabapentin (1800 mg), L-dopa (500 mg), and again clonazepam and carbamazepine, all of which proved ineffective. Therefore, levetiracetam was started

(1000 mg at bedtime). Immediately, the patient presented a clear subjective benefit, consisting of a reduction in the restless sensation, a reduction in the time spent walking before sleep onset, and a subjective improvement in sleep quality as well as in daytime sleepiness. PLM index was decreased both in PSG and SIT. After 26 months the patient is still taking levetiracetam (1000 mg) at bedtime with satisfactory control of RLS symptoms.

Patient no. 2

Patient no. 2 was a 44 year old woman. Her mother and sister were affected by RLS. RLS symptoms started at the age of 30 and consisted of a burning sensation in her lower limbs and severe insomnia. Traditional sleep inducing drugs and carbamazepine provided no benefit. In the following years she reported a progressive worsening of restlessness, which spread to the upper limbs, and insomnia. She developed a nocturnal eating and drinking syndrome, which led to a 10 kg weight gain. She came to our observation at the age of 39. At that time, she reported severe RLS, with a sleep latency >2 h, and related daytime sleepiness. PSG revealed PLMS. Brain and spine MRI were normal. Ferritin levels were normal. Treatment with pramipexole (0.36 mg at bedtime) was effective. Eight months later she started to complain of re-occurrence of severe RLS symptoms, and pramipexole was increased to 1.4 mg without benefit. Ropinirole (5 mg), cabergoline (2.5 mg), L-dopa (750 mg), and gabapentin (1200 mg) were ineffective. Levetiracetam (500 mg at bedtime) was started, and the patient reported an almost immediate improvement in sensory symptoms associated with reduced sleep latency, increased sleep efficiency, and reduced daytime sleepiness. Currently, the patient is taking levetiracetam (1000 mg) at bedtime, and after a 21 month follow up no relapse of RLS has occurred.

Discussion

The present report concerns two patients with severe RLS with PLMS, who became unresponsive to dopaminergic treatment,