causative organism, for decompressing large lesions, and when the patient is deteriorating despite antibiotic therapy.[5] The duration of antibiotic treatment is to an extent empirical. In previous reports of brainstem abscesses treated with antibiotics, the treatment was usually continued for 6–8 weeks. In our case, antibiotics were continued for 10 months because of the coexistent cervical osteomyelitis.

This case illustrates a devastating complication arising from endotrachracheal intubation and the possibility of conservative management in the management of medulla abscesses owing to the obvious risks of surgical intervention.

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Anti-MuSK antibodies in a case of ocular myasthenia gravis

In 10–20% of patients with generalised myasthenia gravis and in up to 50% of patients with ocular myasthenia gravis there are no detectable antibodies to the acetylcholine receptor (AChR). In such cases the disease is commonly referred to as seronegative myasthenia gravis. Seronegative myasthenia gravis has been recognised as an antibody mediated disease, and recently antibodies to muscle specific kinase (MuSK) were demonstrated in the sera of patients with generalised seronegative myasthenia gravis.[1] Anti-MuSK antibodies were not found in seropositive myasthenia gravis. Myasthenia gravis patients with these antibodies have been described as having more prominent bulbar and neck weakness and more respiratory crises.[2–4] These studies differ in the degree of ocular involvement reported, however, only one previous case of anti-MuSK antibodies being found in purely ocular myasthenia gravis has been described.[5] We would like to describe a further case of seronegative ocular myasthenia gravis associated with anti-MuSK antibodies.

Case report

A 21 year old male student presented with a four month history of variable diplopia and bilateral ptosis. He did not complain of any limb weakness or speech, swallowing, or respiratory problems. He had no past medical history of note and was not taking any regular medication. He is the youngest of eight siblings and there is no family history of neuromuscular disease.

On examination he had bilateral ptosis with fatigue and Cogan's lid twitch sign was positive. Extraocular movements were limited in all directions, and particularly pronounced on eye abduction bilaterally. The ptosis and ophthalmoplegia varied between clinical assessments. He had no facial or neck weakness, and bulbar function and limb power was normal with no evidence of fatigability.

Anti-AChR antibodies were negative as measured by a standard radioimmunoprecipitation assay using human adult-type AChR as antigen. Repetitive nerve stimulation revealed no decrementing response in abductor digiti minimi but stimulated single fibre electromyography of orbicularis oculi demonstrated enhanced jitter (mean of 10 single fibres 31 ms; normal range >23 ms) consistent with a defect in neuromuscular transmission. A computed tomography (CT) scan of the head and orbits was normal, and a magnetic resonance scan of the brain was also normal. CT thorax showed normal residual thymic tissue in the anterior mediastinum.

A provisional diagnosis of seronegative ocular myasthenia gravis was made and he was treated with pyridostigmine up to 60 mg four times daily, which had no benefit. Treatment with 3,4-diaminopyridine (20 mg three times daily) was also ineffective. An edrophonium test was then performed which was negative. A quadriceps muscle biopsy showed mild variation in fibre size with some atrophic fibres (predominantly type II). He was subsequently found to have anti-MuSK antibodies as detected by immunoprecipitation of ^{125}I-recombinant MuSK extracellular domains.[6] He was started on treatment with prednisolone 10 mg once daily which resulted in a marked symptomatic improvement.

Discussion

It could be argued that this patient will go on to develop generalised myasthenia gravis since this progression occurs in up to 85% of patients with ocular myasthenia gravis. His symptoms and signs, however, have now remained purely ocular for over a year whereas in the majority of patients the progression of ocular to generalised myasthenia gravis occurs in the first year. The frequency of anti-MuSK antibodies in generalised but seronegative myasthenia gravis has been reported as between 40% and 70% in Caucasian populations.[1–4 6] The frequency of these antibodies in purely ocular myasthenia gravis is likely to be much lower. One recent report has described positive anti-MuSK antibodies in purely ocular myasthenia gravis.[5] In other reports anti-MuSK antibodies were tested in 38 patients with purely ocular seronegative MG with all being negative.[2 4 6]

Interestingly, our patient did not respond to treatment with acetylcholinesterase inhibitors and an edrophonium test was negative. Both of these findings have previously been described in the context of MuSK positive generalised myasthenia gravis.[2 3] In one study the edrophonium test was unhelpful in 30% of patients with anti-MuSK antibody positive generalised myasthenia gravis.[3] Although our patient did not find treatment with acetylcholinesterase inhibitors beneficial he responded well to a low dose of prednisolone.

MuSK is a tyrosine kinase receptor predominantly located on the postsynaptic membrane of the neuromuscular junction. It is activated upon binding of nerve released agrin and then mediates AChR clustering and formation of the neuromuscular junction. Anti-MuSK antibodies interfere with agrin induced clustering of AChRs in cultured muscle cell lines.[1] It is unclear what effect anti-MuSK antibodies will have on the more stable adult neuromuscular junction, and indeed there is some controversy over the pathogenicity of anti-MuSK antibodies.[7] In patients with these antibodies there was no substantial loss of AChRs or MuSK on muscle biopsy. Recent studies suggest that sera from seronegative myasthenia gravis patients may have an inhibitory effect on AChRs that is independent of the IgG fraction or the MuSK antibody itself. Despite these uncertainties the presence of anti-MuSK antibodies is a useful diagnostic marker of myasthenia gravis. Their frequency appears to be low in purely ocular myasthenia gravis. Finding anti-MuSK antibodies in a patient with purely ocular seronegative myasthenia gravis, however, may be extremely helpful. This report demonstrates their use in particularly challenging diagnostic cases where the edrophonium test is negative and there is no response to acetylcholinesterase inhibitors.

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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 cytoplasmatic 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 neurofibrilar 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.

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.

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 function[1] 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.

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