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Outcome of deep brain stimulation in slowly progressive multiple system atrophy: A clinico-pathological series and review of the literature

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ABSTRACT

Objectives: To highlight the risk of clinical worsening after deep brain stimulation in histologically proven multiple system atrophy (MSA) patients presenting slow and relatively benign disease progression mimicking Parkinson's disease (PD). In such cases but also in more typical MSA patients, the results of deep brain stimulation have been mostly reported as case reports and small patient series.
Methods: The present study describes the outcome of the largest series of histologically proven MSA patients who underwent deep brain stimulation (DBS) of the subthalamic nucleus because they were considered as having PD at the time of surgery.
Results: Three patients showed significant improvement of motor signs after surgery while two did not. Clinical improvement was short-lasting and rapidly followed by the occurrence of disabling manifestations of MSA that counteracted DBS benefits.
Conclusions: Together with previous reports, our study demonstrates that DBS should not be recommended for MSA patients. It also underlines that detecting subtle red flags is crucial to avoid DBS surgery in this population.

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1. Introduction

Multiple system atrophy (MSA) is a relentlessly progressing fatal neurodegenerative disease characterized by a variable combination of poorly levodopa responsive parkinsonism, autonomic failure, cerebellar signs and pyramidal tract involvement [1]. Two clinical phenotypes exist, i.e. MSA-P with predominant parkinsonism and MSA-C with prevailing cerebellar manifestations [2]. The prognosis of MSA is generally poor with a mean survival of 6–10 years [1,3,4]. It is noteworthy that some patients with histologically proven MSA may present slower and more benign disease progression [5]. These patients may have prolonged levodopa responsiveness in contrast to the only initial and transient efficacy of this treatment in 20–30% of MSA patients. Dyskinesia may further extend beyond classical oro-facial dystonia and mimic generalized peak-dose dyskinesia as observed in Parkinson's disease (PD) [4–6]. A few case reports and small patient series have mostly reported a poor outcome after deep brain stimulation (DBS) in MSA patients, contrasting with the high effectiveness of this treatment in PD patients with motor complications [7–20].

The aim of the present study is to describe the largest series of histologically proven MSA patients who underwent DBS because they were considered as having PD at the time of surgery. We also provide some considerations to better identify these patients prior to surgery.

2. Methods

Five histologically proven MSA patients who underwent DBS and experienced severe worsening of their condition after DBS surgery were identified retrospectively by the investigators of the French MSA network. These patients were followed in Lyon, Marseille, Bordeaux, Strasbourg, Aix-en-Provence and Paris.

3. Results

3.1. Patient 1

This 55 year-old woman developed in 1992 levodopa-responsive left-sided akinetic-rigid and tremulous parkinsonism. No pyramidal or cerebellar signs were observed at initial examination and during follow-up. Unexplained dyspnea with slight hypoxemia occurred several years after symptom onset and was retrospectively interpreted as first manifestation of autonomic failure. Motor fluctuations and peak-dose dyskinesias appeared two years after the initiation of levodopa. Subthalamic nucleus (STN) DBS leads were finally implanted in 2000, while she was considered as having PD at this time. Prior to surgery, brain magnetic resonance imaging (MRI) was normal and an acute levodopa challenge decreased the Unified PD Rating Scale (UPDRS) motor score by 59% (56 points in Off vs. 23 in On). Motor benefit in On stimulation/Off medication condition one year after surgery was moderate with a 31% decrease of the UPDRS motor score compared to Off stimulation/Off medication (32 points vs. 22). She received bilateral double monopolar DBS with the following parameters: 2.1/3.0 V; 90 130 Hz. During the second year after surgery the patient's clinical condition rapidly worsened with daily falls and the onset of urinary incontinence. Other DBS parameters were tested without additional improvement. Five years after surgery she was bedridden and finally died in 2007. Autopsy revealed typical MSA lesions with neuronal loss and gliosis in putamen, mesencephalon, pons, medulla oblongata, dentate nucleus and cerebellum. Abundant alpha-synuclein positive glial cytoplasmic inclusions (GCIs) were found in these regions proving the diagnosis of MSA. No Lewy bodies were observed. Total disease duration was 15 years.

3.2. Patient 2

This 54-year-old woman presented right-sided hemiparkinsonism in 1991. She did not show dysautonomia, pyramidal or cerebellar signs at initial examination and during follow-up. Because of severe motor fluctuations and peak-dose dyskinesia she was operated on with bilateral STN DBS in 1998. Prior to surgery, an excellent responsiveness to levodopa was observed with a 80% reduction of the UPDRS motor score (60 points in Off vs. 12 in On). Preoperative brain MRI was normal. She received bilateral monopolar DBS with the following parameters: 1.7/3.2 V; 60 μsec; 130 Hz. Motor benefit in On stimulation/Off medication condition 6 months after surgery was excellent with a 84% decrease of the UPDRS motor score compared to Off stimulation/Off medication condition (46 points vs. 7). However, one year after DBS, clinical symptoms rapidly worsened with the onset of severe end-of-dose dystonic and dyskinetic episodes and postural instability. Several DBS parameter adjustments were tried without any efficacy. She died suddenly when washing herself 4 years after DBS surgery. At that time, she also presented facial dystonia treated by botulinum toxin injections and UPDRS motor score in On stimulation/off medication condition had raised at 65/108. Autopsy revealed typical MSA lesions with neuronal loss and gliosis in striatum, substantia nigra, locus coeruleus, pons, mesencephalon, medulla oblongata and cerebellum. Abundant GCIs containing alpha-synuclein were found in these regions proving the diagnosis of MSA. No Lewy bodies were found. Total disease duration was 11 years.

3.3. Patient 3

This 56-year-old man was diagnosed with PD in 1995 following the onset of a left akineto-rigid syndrome and hypophonia. His familial history was marked by the notion of parkinsonism in his mother. He complained about urinary urgency in 1998 but did not present pyramidal or cerebellar signs at initial examination and during follow-up. Because of severe motor and non-motor fluctuations he underwent bilateral STN DBS in 2001. Preoperative brain MRI was normal. Prior to surgery, a levodopa test was performed confirming the responsiveness with an improvement of the UPDRS motor score by 49% (49 points in Off vs. 25 in On). After surgery, he showed a significant clinical improvement with, 2 years after surgery, a 50% reduction of UPDRS motor scores in On stimulation/Off medication condition compared to Off stimulation/Off medication condition (36 points vs. 18). He received bilateral monopolar DBS with the following parameters: 3.0/3.5 V; 60 μsec; 130 Hz. However, 18 months after surgery, his neurological status worsened with the onset of gait instability and falls. Trying to adjust DBS parameters did not lead to any improvement. The patient died in 2003 after a prostatic surgery unrelated to PD. Autopsy revealed no Lewy bodies but numerous alpha-synuclein positive GCIs in the substantia nigra, putamen, globus pallidus, pontine nuclei and cerebellar white matter, proving the diagnosis of MSA. Total disease duration was 7 years.

3.4. Patient 4

This man presented micrographia and fatigue at age 47 in 1996. Neurological examination did not reveal any pyramidal or cerebellar signs at initial examination and during follow-up. Motor symptoms were levodopa responsive. In 1999, he developed generalized peak-dose dyskinesia (without facial involvement). At that time, he started to complain about urinary urgency and erectile dysfunction. Brain MRI before surgery was considered as normal but reassessment for the purpose of the present study revealed