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SHORT COMMUNICATION

Cardiac sympathetic denervation precedes nigrostriatal loss in the E46K mutation of the α-synuclein gene (*SNCA*)

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Abstract
Introduction Here we report the case of an asymptomatic carrier of the E46K substitution in α-synuclein gene where we have documented that cardiac sympathetic denervation precedes nigrostriatal dopaminergic loss.
Material and methods She has been followed up regularly with standard neurological examination, UPDRS, neuropsychological formal testing, parkinson disease sleep scale-PDSS, Epworth scale, Hamilton-D scale, SCOPA Aut, orthostatic hypotension test, brief smell identification test, polysomnography, cerebral 123-I-FP-CIT SPECT, and, 123I-MIBG cardiac scintigraphy.
Results She shows no presence of orthostatic hypotension. Olfactory test results demonstrate normal limits. In the PSG the nocturnal sleep shows mild abnormalities although the sleep efficiency and stage proportion remain under normal limits. The 123-I-FP-CIT SPECT is normal; in contrast, the 123I-MIBG cardiac scintigraphy shows a complete lack of isotopic uptake compatible with a severe sympathetic myocardial denervation.
Conclusion This example of monogenic autosomal dominant parkinsonism due to an α-synuclein mutation favours the hypothesis that peripheral autonomous nervous system involvement occurs earlier than the CNS degeneration.

Keywords Parkinson disease · Autonomic failure · 123I-MIBG cardiac scintigraphy

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Introduction

In 2004, we reported the third known point mutation in the *SNCA* gene (E46K substitution in α-synuclein) in a family with autosomal dominant Parkinson disease (PD) and Lewy body dementia (LBD) [9]. Thereafter, we reported that the carriers of the mutation have an abnormal sleep architecture that precedes in some of them the beginning of motor symptoms [10].

Several lines of evidence support the notion that in sporadic PD, abnormalities in sleep, hyposmia and dysautonomia may antedate the classic parkinsonian motor symptoms and signs [5]. These data are in agreement with the Braak et al. [2] hypothesis of an orderly spreading of neuropathologic lesions in the brains of patients with PD from the olfactory bulb and lower medulla to the upper brainstem and cerebral cortex. However, other evidence

suggests that in a significant proportion of PD brains [4], the Lewy body neuropathologic burden does not follow the course suggested by Braak et al.

The involvement of peripheral autonomic neurons in PD was demonstrated by reduced MIBG uptake in >80% of parkinsonian patients with and without neurocirculatory failure [7, 8]. In a series of non-selected abdominal surgical specimens [6], α-synuclein was detected in the autonomic abdominal plexuses in 9% of the patients. In all of them, the MIBG scintigraphy was reduced suggesting that these structures may the earliest to be involved in PD. As a matter of fact, Kaufmann et al. [5] reported the neuropathological findings of two patients, in whom dysautonomia antedated the parkinsonian clinical features.

Here, we add further evidence in favour of early involvement of the autonomic nervous system in patients with PD by showing that in an asymptomatic carrier of the E46K substitution in the α-synuclein gene; the 123I-MIBG cardiac scintigraphy was abnormally low while the brain 123-I-FP-CIT SPECT and olfaction test were still within normal limits.

Patient and methods

We refer the reader to the original paper [9] for details about the pedigree. Two out of the three offspring from the index patient volunteered to be genetically tested, one of them turn out to be a carrier of the mutation. She has been monitored regularly with standard neurological examination, Unified Parkinson Disease Rating Scale (UPDRS), neuropsychological testing, validated sleep scales (Parkinson Disease Sleep Scale-PDSS, Epworth), depression (Hamilton-D) and dysautonomia scales (SCOPA-AUT), orthostatic blood pressure tests, Olfactory test (Brief Smell Identification Test- BSIT Sensonic®), polysomnography, cerebral 123-I-FP-CIT SPECT, and, recently, 123I-MIBG cardiac scintigraphy. All procedures were approved by the Hospital Ethics committee.

The patient was a 49-year-old woman with no medical history. She was married, had two children and was a manual worker in a paper factory. She was taking no drugs and had no risk factors for cardiovascular disease. She did not refer motor symptom or complained of memory or sleep difficulties. Her neurological examination was normal. She scored 5 in the UPDRS III, 6 in the SCOPA-AUT scale, 0 in depression (Hamilton-D scale), 120 in PDSS and 6 in Epworth scale. In the supine position, her blood pressure was 140/71 mmHg and heart rate was 80 beats/min, while standing blood pressure was 146/99 mmHg and heart rate 84 beats/min. Olfactory test was within normal limits (10 out of 12 odours). In the

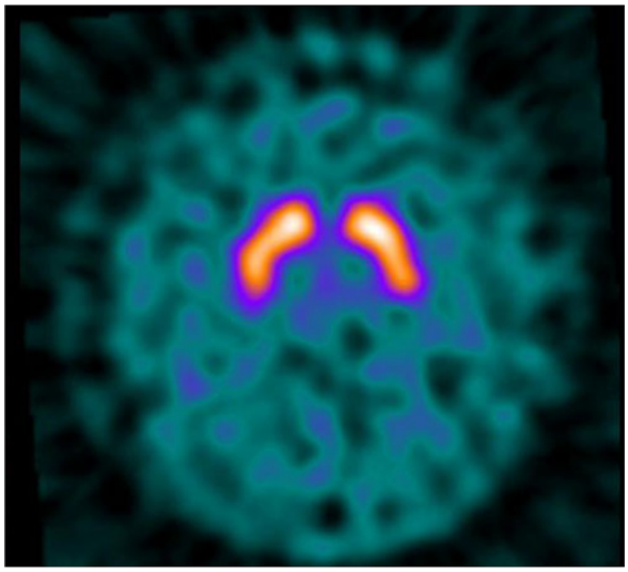

Fig. 1 Axial brain CT scan done 3 h after administration of 123-I-FP-CIT. Normal uptake is seen in the basal ganglia without any appreciable changes in morphology

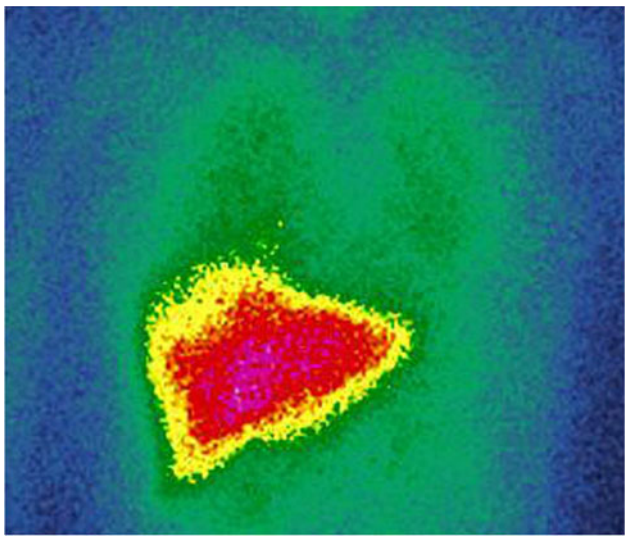

Fig. 2 The 123I-MIBG cardiac scintigraphy show a complete lack of isotopic uptake compatible with severe sympathetic myocardial denervation

PSG, the nocturnal sleep showed mild abnormalities (long latency to sleep, sleep fragmentation, increased number of stage transitions) although the sleep efficiency and stage proportion were within normal limits. REM abnormalities were not observed.

The 123-I-FP-CIT SPECT was normal and showed no difference to the one performed on 2005 (Fig. 1).

In contrast, the 123I-MIBG cardiac scintigraphy showed a complete lack of uptake indicating severe sympathetic myocardial denervation (Fig. 2).

Comments

Studying the rare autosomal dominant varieties of PD may contribute to a better understanding of the much more frequent sporadic cases of the disease. The E46K substitution in the alpha-synuclein gene is relevant in several ways. It is a highly pathogenic mutation as proved by its complete clinical penetrance and by the studies in vitro [3] showing a remarkable tendency to form α-synuclein fibrillary structures.

This mutation supports the concept that PD and LBD are the result of the same pathogenetic basic process [1], because all affected patients eventually develop dementia and in some of them cognitive decline was the first symptom.

In addition, this family provide evidence that sleep disorganization [10] and cardiac sympathetic denervation precede the parkinsonian motor syndrome and the dopaminergic loss in the brain. It is interesting to note that in agreement with others studies [8], in the present case, the 123I-MIBG cardiac scintigraphy detected sympathetic denervation in the absence of symptoms or signs of neurocirculatory failure. However, the olfactory test was normal suggesting that the peripheral sympathetic ganglia are affected earlier than the olfactory bulb, although a subclinical pathologic involvement of the olfactory system cannot be ruled out.

In summary, our case emphasize the importance of investigating the autonomic nervous system in patients at risk of suffering PD so that abnormalities could be detected as early as possible and neuroprotective therapy when available be instituted.

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