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Short communication

Non-motor symptoms and cardiac innervation in SYNJ1-related parkinsonism

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ABSTRACT

Introduction: PARK20 is a rare autosomal recessive parkinsonism related to the *SYNJ1* gene and characterized by early-onset of disease and atypical signs such as supranuclear vertical gaze palsy, dementia, dystonia, and generalized tonic-clonic seizures.
Objective: Non-motor features and cardiac sympathetic innervation were assessed in two siblings affected by parkinsonism who harboured the homozygous Arg258Gln mutation in the *SYNJ1* gene.
Methods: The Non-Motor Symptoms, the SCOPA-AUT, the Mayo Sleep Questionnaires and polysomnography were used to investigate non-motor signs (NMS), autonomic dysfunction and REM Behavioural Disorder (RBD). Cognitive functions were examined by an extensive battery of neuropsychological tests. In addition, motor and sensory nerve conduction studies and evoked laser potentials were performed. Cardiac sympathetic innervation was assessed in the two patients by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, computing early and late heart-to-mediastinum (H/M) ratios and myocardial washout rates (WR).
Results: Among the non-motor symptoms and autonomic signs, case 1 had cold intolerance, drooling and dysphagia, while case 2 had pain and urinary dysfunction. Both cases showed mood and behavioural disorders. RBD were not found, whereas the neuropsychological assessment revealed a progressive cognitive impairment. Neurophysiological studies revealed no abnormalities. Indexes of cardiac sympathetic innervation in the two patients did not differ from those of control subjects.
Conclusions: Our findings expand the phenotypic profile of *SYNJ1*-related parkinsonism. Preserved cardiac sympathetic function and absence of RBD suggest that PARK20 should be explained by a pathogenic mechanism different from Lewy Body pathology, or that the latter is not as widespread as idiopathic Parkinson's disease.

1. Introduction

SYNJ1 gene mutations have recently been identified as the cause of an atypical autosomal recessive parkinsonism designated as PARK20 [1,2]. To date, one homozygous mutation (p. Arg258Gln) has been described in two unrelated Southern Italian families [3,4] and one Iranian family [2]. A heterozygous variant (pSer1422Arg) has been reported in a Brazilian patient who also carried a heterozygous truncating *PINK1* mutation (p. Trp437Stop) [3].

The *SYNJ1* gene encodes a phosphoinositide phosphatase protein designated as synaptojanin 1 (Synj1), and seems to be involved in the clathrin-mediated endocytosis. The main isoforms, derived from alternative splicing, are ubiquitous, but the 145 kDa isoform is preeminently expressed in the brain presynaptic terminals.

PARK20 is characterized by early-onset parkinsonism and may also present supranuclear vertical gaze palsy, cognitive decline, dystonic signs, and generalized tonic–clonic seizures [2–4]. The

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response to L-dopa treatment is dramatic but the appearance of severe low dose effects, such as dyskinesias, oromandibular or limb dystonia, and hypotension limit its use [2,3]. Brain MRI findings were variable, with cortical and quadrigeminal plate atrophy, T2 hyperintensity in the posterior white matter and hippocampi, and T2 hypointensity of the cerebellar dentate nuclei [2–4]. ^{123}I-FP-CIT SPECT studies showed nigrostriatal dopaminergic dysfunction [3,4].

We investigated non-motor symptoms (NMS), peripheral nervous system function and cardiac sympathetic innervation (PD) by ^{123}I-metaiodobenzylguanidine (MIBG) in two siblings with *SYNJ1* gene mutations.

2. Patients and methods

We previously reported two siblings originating from Southern Italy with early-onset parkinsonism associated with the homozygous Arg258Gln mutation in the *SYNJ1* gene [4].

A detailed neurological evaluation, including the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS-III), was performed. The stage of the disease was set by the Hoehn and Yahr scale. The local Ethics Committee approved the study. After giving written informed consent, the patients underwent the Non-Motor Symptoms Questionnaire (NMSQuest) [5], the Mayo Sleep Questionnaire [6] and polisomnographic study with video recording overnight in a sleep laboratory to assess the presence of REM Behaviour Disorder (RBD), and the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) Questionnaire [7], to investigate autonomic dysfunction. Neuropsychological evaluation comprised: Mini Mental State Examination (MMSE); Raven's Coloured Progressive Matrices for assessment of visuospatial abilities and general intelligence; Spatial Span for spatial short-term memory; Verbal Span for verbal short-term memory; Rey's 15-word Immediate and Delayed Recall and Story Recall for verbal long-term memory; Arrigoni – De Renzi Test for constructional skills; Frontal Assessment Battery, Attentive Matrices, Phonemic Verbal Fluency test for attention and executive-frontal functions.

Motor conduction was assessed in median, ulnar, tibial and peroneal nerves, and sensory conduction in median, ulnar, and sural nerves, using standard techniques. We measured nerve conduction velocity, and the amplitude of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). To activate A δ nociceptors, laser evoked potentials (LEPs) were performed delivering brief radiant heat pulses using a CO2 laser stimulator (1–15 W, wave-length 10.6 mm) on the skin of the foot. Signals were recorded from the vertex.

At the time of enrolment, both patients were treated with SSRIs and MAO-B inhibitors, which were gradually reduced and discontinued at least two weeks before the MIBG study, to avoid any interference with the tracer uptake. Ten subjects (five men, mean age 41 ± 14 years), studied to exclude medullary adrenal disease, served as the control group. Patients underwent ^{123}I-MIBG cardiac imaging according to the recommendations of the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. An activity of 111 MBq ^{123}I-MIBG (Mallinckrodt) was intravenously administered over 1–2 min after thyroid blockade by oral administration of 300 mg of potassium perchlorate. Ten-minute planar images of the thorax in standard anterior view were performed 15 min ("early" image) and 3 h 50 min ("late" image) after tracer administration, as previously described in detail [8]. The heart to mediastinum (H/M) ratio was computed, for early and late planar imaging, by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. The MIBG washout rate (WR) was also calculated using the following formula: [early H/M ratio − late H/M ratio]/early H/M ratio × 100.

The data of control subjects were expressed as means ± standard deviation. Individual values of early and late H/M ratios and of washout rate in patients were compared with the corresponding 95% individual prediction limits determined in the controls using appropriate *t* values.

3. Results

Both patients had presented mild developmental delay and parkinsonism in their thirties. We previously reported a detailed description of the onset and the neurological examination at our first visit [4]. After a six year-follow up, the motor progression per year was similar to that usually observed in idiopathic PD. The main clinical features relative to the present study are summarized in Table 1.

The neurological examination in case 1 showed masked face, monotone and slurred speech, moderately stooped posture, mild upward vertical gaze limitation, short steps and reduced arm swings during walking, start hesitation of the gait initiation, retropulsion but with recovery at pull test, oromandibular tremor, bradykinesia. Compared to the previous report [4], UPDRS-III score and the truncal dystonia leaning to left side had worsened. The treatment with pramipexole 3 mg once a day and rasagiline 1 mg once a day resulted in moderate improvement of the extrapyramidal signs. The patient's depression, restlessness and irritability benefited from citalopram 20 mg once a day. He reported dysphagia, drooling, sadness, anxiety, daytime sleepiness, and trouble tolerating cold (Tables 2 and 3 in Supplementary Data). Furthermore, he presented severe and constant hand acrocyanosis. RBD was not reported by questionnaire (Table 1). Compared to the previous assessment [4], neuropsychological examination showed a worsening of MMSE, whereas the deficit of verbal and spatial short-term memory, and verbal long-term memory was stable.

At the time of the study, the clinical picture in case 2 was characterized by facial hypomimia, hypophonia, normal eye movements, slightly stooped posture, slow gait with reduced arm swings, retropulsion but recovery at pull-test, resting tremor in lower limbs, mild rigidity and moderate bradykinesia prevalent in right limbs. Knee tendon reflexes were brisk. Compared to the previous assessment, we observed a downward gaze limitation and a worsening of bradykinesia. UPDRS-III score was increased. The

Table 1
Demographic, clinical and MIBG study features of the patients.

	Case 1	Case 2
Clinical data		
Age	35	31
Disease Duration	7	4
UPDRS-III	47/108	39/108
HY stage	2.5/5	2.5/5
MMSE	24/30	21/30
MAYO SLEEP quest	–*	–*
NMSQUEST	6^	6^
SCOPA-AUTquest	3/69	4/69
MIBG study		
early H/M	2.1	2.3
late H/M	2	2
WR	3.6%	13%
Neurophysiologic study		
Peripheral nerve sensory/motor conduction	normal	normal
Laser evoked potentials	normal	normal

UPDRS-III: Unified Parkinson's Disease Rating Scale, Section III; HY: Hoehn & Yahr scale; MMSE: MiniMental State Examination; MAYO SLEEP quest: MAYO SLEEP questionnaire (*: no sleep disorders); NMSQUEST: Non-Motor Symptoms Questionnaire (^: number of NMS); SCOPA-AUTquest: SCOPA-AUT Questionnaire (items score ranges from 0 = never to 3 = often); H/M ratio: heart-to-mediastinum ratio; WR: washout rate.