A53T IN A PARKINSONIAN FAMILY: A CLINICAL UPDATE OF THE SNCA PHENOTYPES

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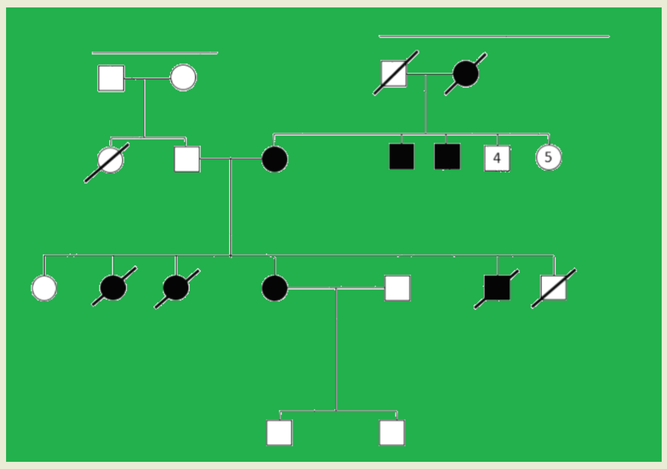
Sin XLVII CONGRESSO

INTRODUCTION

Monogenic forms of PD have always been an intriguing field on which to search for PD pathophysiology [1]. The first mutation associated with familial Parkinson disease was found in SNCA gene in 1997 [2]. Since then, intensive research efforts have established a total of seven genes and 18 loci containing causal mutations for parkinsonism clinically resembling PD.

CASE REPORT

The proband is a 60-year-old woman with a family history of PD. At our first ambulatory assessment (1 year after symptoms onset), neurological examinations revealed decreased facial expression, hypophonic speech, mild rigidity of right limbs, mild bradykinesia that appeared to be more severe in the right side, slightly stooped posture and slow walking, no tremor and preserved postural reflexes (OFF: UPDRS part III: 21, H&Y: 2). Levodopa challenge test (300 mg): UPDRS III: off 21 - on 8. Olfaction impairment (IOIT 26/33 errors) was detected as well as symptomatic orthostatic hypotension (PA 130/90→ 100/80). Vivid dreaming, periods of sadness greater than normal, loss of initiative, fatigue were referred (NMSS total score: 59). No cognitive impairment was evidenced. Family history showed that the mother of the proband developed parkinsonism at the age of 63 years and died for pneumonia at the age of 66. Her maternal grandmother suffered from parkinsonism. Details about affected uncles are not available. Additionally, she had three affected (brother dead at the age of 38 years, two sisters dead respectively at the age of 50 and 70 years) and two unaffected siblings. Many details of the family history were missing. Levodopa therapy was introduced (levodopa/carbidopa 100/25 mg tid) and the patient had an excellent response for 1 year without motor complications. Sequencing of intron-exon boundaries and coding region of LRRK2 and SNCA genes were performed in the proband, after obtaining informed consent, and reveled a heterozygous A53T mutation in the SNCA gene.



PEDIGREE

MATERIALS AND METHODS

We accurately illustrate the case of a 60 years old woman with A53T point mutation derived PD and review SNCA mutations phenotype, focusing on non-motor features. A literature search was performed using the terms "SNCA", "Parkinson's disease", "PD", "alpha-synuclein mutations", "alpha synuclein", "monogenic", "duplication", "triplication" and "point mutations". All works lacking of accurate clinical data were discarded. We found 136 cases that described SNCA mutations phenotype in PD.

	N°	n	asymptomatic carriers at the time of DNA collection	Age at onset	Age at examination	Time from motor onset to death	Tremor	Depression	Anxiety	SD	CI	Psychosis	GID	Urinary	SeD	OH	Falls	Hyposmia	WR	Myo	RB	Died for pneumonia
H50Q	3	2 1	0 0	62.3 ± 7.7	64 ± 6.1	9.6 ± 4.0	3 (100)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E46K	9	1 8	0 1 2	52.4 ± 12.5	53.8 ± 18.5	7 ± 1.4	1 (11.1)	3 (33.3)	0 (0)	6 (66.7)	4 (44.4)	0 (0)	2 (22.2)	3 (33.3)	0 (0)	4 (44.4)	2 (22.2)	2 (22.2)	0 (0)	0 (0)	0 (0)	0 (0)
A30P	5	5	2	59.7 ± 4.3	/	5.2 ± 4.3	/	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
A53T	41	1 8 9 2 3 15 2 1	0 0 2 1 0 0 1 0	45.6 ± 11.4	52.1 ± 12.0	9.2 ± 5.0	4 (9.8)	2 (4.9)	0 (0)	1 (2.4)	5 (12.2)	0 (0)	3 (7.3)	4 (9.8)	0 (0)	4 (9.8)	4 (9.8)	3 (7.3)	0 (0)	5 (12.2)	3 (7.3)	0 (0)
G51D	8	3 4 1	0 0 0	36.0 ± 12.8	40.7 ± 14.7	21.0 ± 13.7	1 (12.5)	3 (37.5)	3 (37.5)	0 (0)	3 (37.5)	5 (62.5)	0 (0)	1 (12.5)	0 (0)	3 (37.5)	2 (25.0)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)
A29S*	1	1	0	60	67	7	/	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
A18T*	1	1	0	50	61	/	/	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All point mutations	68			47.6 ± 12.9	51.7 ± 14.2	11.6 ± 8.9	9 (13.2)	9 (13.2)	4 (5.9)	7 (10.3)	17 (25.0)	5 (7.3)	7 (10.3)	8 (11.8)	0 (0)	12 (17.6)	8 (11.8)	5 (7.3)	0 (0)	5 (7.3)	3 (4.4)	0 (0)
Duplication	40	5 3 11 2 1 4 4 2 2 4 1 1	0 8 14 0 2 6 0 0 0 4 0 0	46.8 ± 10.3	56.9 ± 11.8	16.5 ± 6.0	13 (32.5)	14 (35.0)	2 (5.0)	7 (17.5)	17 (42.5)	16 (40.0)	5 (12.5)	4 (10.0)	2 (5.0)	10 (25.0)	2 (5.0)	6 (15.0)	0 (0)	0 (0)	0 (0)	5 (12.5)
Triplications or homozygotic duplication	29	13 1 3 1 3 4 2 2	0 0 0 0 0 0 0 0	36.6 ± 7.6	40.3 ± 7.2	10.9 ± 6.5	21 (72,4)	20 (69,0)	1 (3.4)	6 (20.7)	20 (69.0)	20 (69.0)	7 (24.1)	8 (27.6)	2 (6.9)	11 (37.9)	4 (13.8)	2 (6.9)	4 (13,79)	4 (13,79)	0 (0)	4 (13,79)
Overall	137			45.4 ± 12.0	49.0 ± 13.8	16.5 ± 15.7	43 (31.4)	43 (31.4)	7 (5.1)	20 (14.6)	54 (39.4)	41 (29.9)	19 (13.9)	20 (14.6)	4 (2.9)	33 (24.1)	14 (10.2)	13 (9.5)	4 (2.9)	9 (6.6)	3 (2.2)	9 (6.6)

RESULTS

136 cases with SNCA related-PD were found in English literature. According to Kasten [3], cases were organized into three groups: point mutations (PMc), duplication (Dc) and triplication (Tc). No difference was noted for gender. Patients with Tc showed an early onset (36.6 ± 7.6 years) than those with Dc (46.8 ± 10.3 years) and PMc (47.6 ± 12.9 years). The mean time from motor onset to death was 16.5 years, decreasing when moving from Dc (16.5 ± 6.0) to PMc (11.6 ± 8.9 years) and to Tc (10.9 ± 6.5 years).

Regarding motor symptoms, 31,4% of all patients presented tremor at rest with the highest frequency (72,4%) in triplication group. The frequency of non motor symptoms is described in Table 1. The frequency of cognitive impairment was 25% of PMc, 42.5% of Dc and 69% of Tc. Psychosis and postural hypotension were more frequently observed in Tc. Among point mutations, postural hypotension and falls were very frequent in E46K and G51D groups, with respectively 44.44% and 37.5% of patients experiencing the first, and respectively 22.22% and 25% of cases reporting recurrent falls. Hyposmia was more common in Dc.

DISCUSSION

Among monogenic PD, the SNCA gene exhibits the most pronounced mutation-specific effects on clinical phenotype including the non-motor spectrum. These findings above suggest a specific speed and a spread of neuropathological involvement in patients with SNCA mutations. Moreover, a correlation emerged between the incidence of non-motor symptoms and disease severity. Here we report on a patient with the A53T mutation, whose maternal grandmother was of Greek origin, further suggesting a possible founder effect for this mutation in this country. Our case presented a wide range of non-motor symptoms including postural hypotension, severe Rem Behavior Disorders (RBD) and hyposmia. Generally, in RBD, α-synuclein abnormalities in the brainstem disinhibit rapid eye movement sleep motor activity, leading to dream enactment. RBD as a non-motor biomarker of α-synuclein disorder (Howell and Schenck 2015) was confirmed by its high frequency among SNCA mutation carriers, especially in those with Dc. Hyposmia is an early and severe presenting feature of PD. However, since most SNCA-derived PD cases date back before 2005, an accurate evaluation of hyposmia was not often performed making it difficult to determine its incidence. However, being that the few reported cases were positive for hyposmia, IOIT or similar tests, should be considered. Finally, future investigations are needed into phenotype characterization having the aim of identifying patients at particular risk for specific clinical features and of better understanding the underlying pathogenetic mechanisms of genetic mutations in PD.

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