Clinical phenotype in patients with α -synuclein Parkinson's disease living in Greece in comparison with patients with sporadic Parkinson's disease

S Papapetropoulos, C Paschalis, A Athanassiadou, A Papadimitriou, J Ellul, M H Polymeropoulos, Th Papapetropoulos

Abstract

Objective—An Ala53Thr mutation of the α -synuclein gene has been recently identified as a rare cause of autosomal Parkinson's disease (PD). The clinical characteristics of 15 patients with PD living in Greece with the Ala53Thr α -synuclein mutation (α -synPD) were compared with patients with sporadic Parkinson's disease (sPD).

Methods—An investigator, blind to the results of the genetic analysis, examined 15 patients with α -synPD and 52 consecutive patients with sPD. Demographic data, age at onset of the illness, modality of presentation, and duration of PD were collected. The unified Parkinson's disease rating scale, the Hoehn and Yahr scale, and the Schwab-England scale were completed. The patients with α -synPD were matched for duration of disease with 32 of the 52 patients with sporadic PD (MsPD group).

Results—Patients with the α -synuclein mutation were significantly younger (mean 7.6 years), showed the first sign of the disease significantly earlier in life (mean 10.8 years), and had significantly longer duration of the disease compared with patients with sPD. Tremor at onset of the disease was present in only one (6.7%) of the patients with α -synPD, whereas it was present in 32 (61.5%) of the patients with sPD ($p=0.0006$). During the course of the disease one patient in the α -synPD group went on to develop tremor compared with six patients in the sPD group. Rigidity, bradykinesia, postural instability, orthostatic hypotension, intellectual impairment, depression, complications of therapy, and clinical severity of the disease at the time of examination did not differ significantly between patients with α -synPD and those with sPD, or between patients with α -synPD and the MsPD group.

Conclusion—The younger age at onset of the illness, the much lower prevalence of tremor, and the longer duration of the disease characterise the clinical phenotype in this sample of patients with α -synPD. The other symptoms and signs of the illness did not seem to differentiate the patients with α -synPD from those with sPD.

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Keywords: α -synuclein Parkinson's disease; sporadic Parkinson's disease; familial Parkinson's disease

Recently two missense mutations in the α -synuclein gene situated in chromosome 4, were reported as a rare cause of familial Parkinson's disease (PD) with autosomal dominant inheritance. The first mutation was a G209A substitution in the exon 4 of the gene resulting in Ala53Thr mutation of α -synuclein. This mutation was first identified in a large Italian kindred and in three unrelated Greek families.¹ Later it was reported in seven more Greek families²⁻⁴ and in one Greek-American kindred.^{5,6} The second mutation was a G88C substitution in exon 3 of α -synuclein gene resulting in an Ala30Pro mutation and it was detected in one affected member of a family of German origin.⁷

We set out to study the clinical characteristics of 15 patients with PD with an Ala53Thr α -synuclein mutation (α -synPD), living in Greece, and to compare them with patients with sporadic PD (sPD).

Patients and methods

During the period between February 1997 and July 1999 we studied 15 patients affected by α -synPD, recruited from 10 Greek families. The molecular genetic analysis of these patients was carried out according to the procedures described by Athanassiadou *et al.*³ All 10 families were apparently unrelated²⁻⁴; however, a founder effect (coancestry) could not be excluded. Seven of these families originated from three different counties of northern Peloponnese in Greece. One family originated from south west Peloponnese and the remaining two families from different villages of north west Greece.

During the same period 52 consecutive patients with sPD were recruited from our outpatient clinic. All patients with PD were diagnosed through self presentation to senior neurologists using the Parkinson's Disease Society brain bank diagnostic criteria.⁸ Brain imaging and biochemical blood testing were used to exclude other causes of parkinsonism. None of the patients with sPD were found to carry the Ala53Thr mutation.

An informal interview was carried out in all patients and their families by one of the authors (SP), who was blind to the results of the genetic analysis. Demographic data, age at onset of the illness, modality of presentation, and duration of PD were collected. The unified Parkinson's disease rating scale (UPDRS),⁹ and the Hoehn and Yahr¹⁰ and Schwab-England¹¹ scales were completed during the clinical examination. At

Department of
Neurology, Medical
School of Patras,
Greece

S Papapetropoulos
C Paschalis
J Ellul
Th Papapetropoulos

Department of
Biology, Medical
School of Patras,
University Hospital of
Patras, PO Box 1045,
26500 Rion, Greece
A Athanassiadou

Department of
Neurology, Medical
School of Larissa,
Greece
A Papadimitriou

Novartis
Pharmaceutical
Corporation,
Pharmacogenetics,
Gaithersburg, USA
M H Polymeropoulos

Correspondence to:
Dr Th Papapetropoulos
paschalis@med.upatras.gr

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Table 1 Clinical characteristics of subjects carrying the α -synuclein mutation, the total number of affected members in each family, and the number of the recalled generation in each family

Greek family	Age of onset (y)	Duration of disease (y)	Presenting complaint	Dyskinesias on examination	Total affected members in each family (n)	Recalled generations (n)
PDGR1	53	7	Bradykinesia	Present	6	4
PDGR2	51	2	Bradykinesia	Present	4	4
PDGR5	35	6	Bradykinesia	Present	9	5
PDGR5	62	9	Rigidity	Absent		
PDGR8	53	3	Rigidity	Absent	7	5
PDGR8	43	7	Rigidity	Present		
PDGR11	51	8	Rigidity	Present	10	4
PDGR11	49	11	Rigidity	Present		
PDGR15	62	16	Rigidity	Present	3	3
PDGR18	58	4	Rigidity	Present	4	4
PDGR27	43	19	Rigidity	Absent	8	4
PDGR27	42	16	Bradykinesia	Absent		
PDGR29	64	19	Tremor	Absent	4	3
PDGR30	25	17	Rigidity	Absent	7	3
PDGR30	27	17	Rigidity	Absent		

the time of the clinical examination patients were following the best medical treatment (all patients were taking levodopa, and were responding satisfactorily).

Comparisons were made between the patients with α -synPD and all patients with sPD using the above mentioned rating scales. The difference in the duration of the disease between the patients with α -synPD and those with sPD would have not allowed meaningful comparisons of clinical severity; therefore, the 15 patients with α -synPD were matched (± 2 years) for duration of disease with 32 of the 52 patients with sPD (the MsPD group). The duration of the disease of the patients with α -synPD was also compared with the duration of the disease of the 37 patients with younger onset sPD (YsPD group). The scores taken during on periods have been used in the comparisons for those patients who were known to have on-off episodes.

A Mann-Whitney U test for two samples was used in non-parametric comparisons, and χ^2 tests with Yates' corrected p value and two tailed Fischer exact p values in the comparison of proportions. The ethics committee of the University Hospital of Patras approved this study.

Results

The clinical characteristics of those carrying the α -synuclein mutation are shown in table 1. Table 2 shows that the patients with α -synPD were significantly younger (mean 57.8 (SD 12) years), showed the first sign of the disease significantly earlier in life (mean 47.9 (SD 12.1) years), and had significantly longer disease duration (mean 10.7 (SD 6.1) years) compared with patients with sPD (mean 65.4 (SD 12) years, mean 58.7 (SD 13.3) years, and mean 6.1 (SD 5.5) years respectively). The sex ratio

Table 2 Sex, age, age at onset, and duration of disease in α -synPD, sPD, MsPD, and YsPD groups

	α -synPD (n=15)	sPD (n=52)	p_1	Ms PD (n=32)	p_2	Ys PD (n=37)	p_3
Mean age (SD)	57.8 (12.0)	65.4 (12.5)	0.02*	63.1 (11.6)	0.07*	60.2 (10.5)	0.21*
Sex: number of females (%)	6 (40%)	25 (48%)	0.8†	14 (43.8%)	0.9†	20 (54.1%)	0.54†
Mean age at onset (y (SD))	47.9 (12.1)	58.7 (13.3)	0.010*	54.3 (11.0)	0.1*	52.4 (9.5)	0.24*
Mean duration of PD (y (SD))	10.7 (6.1)	6.1 (5.5)	0.008*	9.0 (5.1)	0.45*	7.0 (5.8)	0.046*

α -synPD=Parkinson's disease (PD) patients with the α -synuclein gene mutation; sPD=sporadic Parkinson's disease; MsPD=matched sporadic PD patients to α -synPD patients for duration of disease; YsPD=younger onset sporadic PD patients; p_1 =comparison between α -synPD and sPD; p_2 =comparison between α -synPD and MsPD; p_3 =comparison between α -synPD and YsPD.

*Mann-Whitney test; †Yates' corrected p value.

Table 3 Symptoms and signs at onset of disease and on examination in α -synPD, sPD, and MsPD patients

	α -synPD (n=15)	sPD (n=52)	p_1	Ms PD (n=32)	p_2
Symptoms and signs at onset of disease:					
Tremor	1 (6.7)	32 (61.5)		17 (53.1)	
Rigidity	10 (66.7)	16 (30.8)	0.0006†*	12 (37.5)	0.0063†*
Bradykinesia	4 (26.7)	4 (7.7)		3 (9.4)	
Symptoms and signs on examination:					
Tremor	2 (13.3)	38 (73.5)	0.0001*	22 (68.8)	0.001*
Rigidity	14 (93.3)	45 (86.5)	0.67‡	27 (84.4)	0.65‡
Bradykinesia	11 (73.3)	23 (44.2)	0.09*	17 (53.1)	0.3*
Postural instability	8 (53.3)	23 (44.2)	0.74 *	17 (53.1)	0.76 *
Orthostatic hypotension	3 (20.0)	5 (9.6)	0.36‡	3 (9.4)	0.37‡
Intellectual impairment	4 (26.6)	10 (19.2)	0.50‡	8 (25.0)	1.0‡
Depression	8 (53.3)	24 (46.2)	0.84*	15 (46.9)	0.92**

Values are No of patients (%). α -synPD=Parkinson's disease (PD) patients with the α -synuclein gene mutation; sPD=sporadic Parkinson's disease; MsPD=matched sporadic PD patients to α -synPD patients for duration of disease; p_1 = comparison between α -synPD and sPD; p_2 =comparison between α -synPD and MsPD.

*Yates' corrected p value.

†Rigidity and bradykinesia were combined in the rigid-akinetic variable for the comparison between groups.

‡2-tailed Fisher's exact test.

Table 4 Mean scores (SD) of the unified Parkinson's disease rating scale (UPDRS), Hoehn and Yahr, and Schwab-England scales in α -synPD, sPD, and MsPD patients

	α -synPD (n=15)	sPD (n=52)	p_1	Ms PD (n=32)	p_2
Four sections of UPDRS:					
Mentation, behaviour, mood (UPDRS I) (maximum score 16)	2.8 (3.9)	2.1 (3.3)	0.7	2.8 (3.8)	0.97
Activities of daily living (UPDRS II) (maximum score 52)	21.5 (14.7)	13.3 (9.6)	0.075	16.7 (10.3)	0.38
Motor examination (UPDRS III) (maximum score 56)	38.5 (27.1)	26.3 (18.4)	0.16	32.2 (20.4)	0.63
Complications of therapy (UPDRS IV) (maximum score 23)	4.5 (4.8)	3.1 (4.1)	0.068	4.6 (4.6)	0.82
Total UPDRS score (maximum score 147)	67.3 (45.7)	44.7 (31.2)	0.093	56.2 (33.4)	0.52
Hoehn and Yahr (staging 0-5)	3.1 (1.2)	2.4 (1.1)	0.024	2.8 (1.1)	0.30
Schwab-England (0-100% score)	0.53 (0.3)	0.70 (0.2)	0.017	0.70 (0.3)	0.18

α -synPD=Parkinson's disease (PD) patients with the α -synuclein gene mutation; MsPD=matched sporadic PD patients to α -synPD patients for duration of disease; p_1 =comparison between α -synPD and sPD; p_2 =comparison between α -synPD and MsPD (Mann-Whitney test).

did not differ significantly between the patients with α -synPD and patients with sPD (table 2).

The clinical characteristics at the onset of the disease and at the time of clinical examination are shown in table 3. Tremor at onset of the disease was present in only one (6.7%) of the patients with α -synPD, whereas it was present in 32 (61.5%) of those with sPD. After matching for duration of the disease the difference in the proportion of patients with tremor at the time of the clinical examination between the patients with α -synPD and the MsPD group remained significant. Table 3 also shows the significantly higher incidence of rigidity at disease onset in the α -synPD group (66.7%) compared with the sPD group (30.8%).

The scores for the four sections of the UPDRS scale, as well as the scores of the overall assessment of clinical severity for α -synPD, MsPD, and YsPD are shown in table 4.

Discussion

This study has shown that patients with α -synPD were significantly younger and that their disease started significantly earlier in life compared with the patients with sPD. Early onset of the disease in other affected persons carrying the α -synuclein mutation has previously been reported.^{6, 12} In the current study, the duration of the disease in the patients with α -synPD was significantly longer than the duration of the disease of both sPD and YsPD groups. Longer duration of the disease was also found in the patients of the families reported by Golbe *et al*¹² and Markopoulou *et al*.⁶ Although all patients with PD in the present study were diagnosed through self presentation, the possibility of ascertainment bias in the early diagnosis in those with familial disorders should be noted, as this could give rise to a longer perceived course of disease.

Another finding in the present work was the lower prevalence of tremor in the patients with α -synPD compared with the patients with sPD. During the course of the disease, the number of patients with tremor in both groups did not change significantly (table 3). Certainly in a group of patients with a very low prevalence of tremor and with a more akinetic-rigid presentation a less benign course of the disease would be expected. However, in the present study the overall clinical severity of the disease and the complications associated with treatment (dyskinesias and on-off fluctuations) did not differ significantly between patients with α -synPD and MsPD group (table 4). Absence of tremor

during the course of the disease was emphasised in the initial report presenting the Contursi family.¹³ However, when data (many historical) were more rigorously examined in 31 of the 60 affected members in the Contursi family, tremor was found in 58.1% of the patients.¹² Of the 16 affected members in the Greek-American family,⁶ tremor at onset was found in two of the four patients who were clinically examined, whereas tremor during the course of the disease was reported in 68.8% of all patients in this family. In the current study, the very low incidence of tremor at disease onset, and thereafter during the course of the disease when compared with previously reported patients with α -synPD living in the United States or Italy is difficult to explain. However, it could be speculated that the difference could be attributed to the influence of other environmental or genetic factors. The low incidence of tremor at disease onset in our patients with α -synPD is unlikely to be attributable to study design as the incidence of tremor, on clinical examination during the course of the disease, was found to be almost unchanged.

The sex ratio in our patients with α -synPD and those with sPD is similar to the sex ratio reported for idiopathic PD (3:2),¹⁴ the Contursi family (3.7:2),¹³ and the Greek-American kindred (2.7:2).⁷ Apart from tremor, the other clinical symptoms and signs, including intellectual impairment and depression, did not differ between the α -synPD and MsPD groups. Dementia and depression were also reported in other patients with PD with the α -synuclein mutation^{6, 12} but this did not seem to characterise the phenotype of the disease. All patients in the α -synPD and sPD groups in the present study were levodopa responders. Response to levodopa in patients with α -synPD has also been reported in two other families.^{6, 12}

Mutations in the α -synuclein protein are a rare cause of PD, as shown in studies of several hundred cases of familial PD in the United States,¹⁵⁻¹⁹ in Europe²⁰⁻²⁸ and elsewhere.²⁹ The mutation of G209A in the α -synuclein gene, which was not found in our patients with sPD, is also generally absent in patients with sporadic Parkinson's disease.^{30, 31}

The younger age of onset of the illness, the lower prevalence of tremor, and the longer duration of the disease characterise the clinical phenotype in this sample of patients with α -synPD. The other symptoms of the illness did not seem to differentiate the patients with α -synPD from those with sPD. A detailed study

is currently underway to compare the 15 patients with α -synPD with a large group of Greek patients with familial Parkinson's disease without the α -synuclein gene mutation.

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