Familial Progressive Supranuclear Palsy: A Literature Review

Shinsuke Fujioka^a Jay A. Van Gerpen^a Ryan J. Uitti^a Dennis W. Dickson^b
Zbigniew K. Wszolek^a

Departments of ^aNeurology and ^bNeuropathology, Mayo Clinic, Jacksonville, Fla., USA

Key Words

Familial progressive supranuclear palsy · *MAPT*

Abstract

Background: Many genes/loci associated with Parkinsonian disorders have been identified. However, the genetic causes for a number of familial forms of Parkinsonian disorders remain to be elucidated. **Objective:** It was the aim of this paper to review the familial progressive supranuclear palsy (PSP) cases without any known gene mutations published in the English literature. **Methods:** We searched the PubMed database for reports of familial PSP cases without known mutations. **Results:** We found 19 PSP families. The mean age at onset was approximately 60 years, and the mean disease duration was about 8 years. Parkinsonism and ophthalmoplegia were most frequently reported, and a vast majority of patients manifested with these two symptoms. Other symptoms such as falls, postural instability and pyramidal signs were also common. A small subset of patients transiently responded to L-dopa therapy. **Conclusion:** There is an increasing number of reported familial PSP. A recently performed genome-wide association study indicated genetic factors for this condition. Furthermore, clinical, pathological and genetic investigations will open new avenues to the discovery of causative genes and new therapeutics for PSP.

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Introduction

Genetic research has revolutionized the understanding of the underlying mechanisms behind Parkinson disease and Parkinsonism. To date, a number of genes for Parkinsonian disorders have been identified [1]. Progressive supranuclear palsy (PSP) is a relatively common neurodegenerative disorder and is clinically characterized by Parkinsonism (mainly bradykinesia and rigidity) and the presence of additional features such as ophthalmoplegia, pyramidal signs, postural instability, falls, and frontal disturbances [2]. Familial forms of PSP, classically thought to be a sporadic condition, have been increasingly recognized, and several families have been reported to carry *MAPT* mutations [3]. However, a major genetic cause has never been identified for most familial PSP cases. In this paper, we review previously described familial PSP cases.

This study is based on the invited lecture provided by Z.K. Wszolek during the 11th International Conference on Alzheimer's and Parkinson's Disease in Florence, Italy, on March 7th, 2013.

Table 1. Summary of clinical features (yes/no/NA) of previously reported familial PSP cases

Family No.	MAO, years	MDD, years	Subjects	Falls	Bradykinesia and/or rigidity	Postural instability	Ophthalmoplegia	Pyramidal signs	Cognitive impairment	Dystonia	L-Dopa responsiveness	Ref.
1	58	6	6	5/0/1	6/0/0	2/0/4	6/0/0	6/0/0	2/0/4	2/0/4 ¹	0/3/3	5
2	24	NA	3	0/0/3	3/0/0	0/0/3	2/1/0	1/2/0	2/1/0	0/0/3	0/2/1	6 ³
3	59	1	2	0/0/2	2/0/0	0/0/2	2/0/0	2/0/0	2/0/0	0/0/2	2/0/0	7 ³
4	64	7	3	1/0/2	1/1/1	0/0/3	1/0/2	1/0/2	3/0/0	0/0/3	0/1/2	8
5	72	9	2	1/0/1	2/0/0	2/0/0	2/0/0	0/0/2	1/1/0	1/0/1 ¹	0/2/0	9
6	69	8	2	1/0/1	2/0/0	1/0/1	2/0/0	0/0/2	1/1/0	0/0/2	1/1/0	10
7	63	10	2	1/0/1	2/0/0	1/1/0	2/0/0	1/1/0	1/1/0	1/1/0 ¹	2/0/0	11
8	61	12	9	0/0/9	8/1/0	8/1/0	8/1/0	0/0/9	3/6/0	2/7/0	2/0/7	11, 12
9	67	11	3	2/0/1	2/0/1	0/0/3	1/1/1	0/0/3	2/0/1	1/1/1 ¹	1/0/2	11
10	68	7	3	1/0/2	2/0/1	1/0/2	1/1/1	0/0/3	0/0/3	0/2/1	0/1/2	11
11	75	11	3	1/0/2	3/0/0	0/0/3	2/1/0	0/0/3	2/1/0	2/1/0 ²	0/1/2	11
12	38	4	3	3/0/0	3/0/0	0/0/3	3/0/0	0/0/3	1/2/0	1/2/0 ¹	0/2/1	11
13	63	13	2	1/0/1	2/0/0	0/0/2	2/0/0	0/0/2	2/0/0	2/0/0 ¹	0/1/1	11
14	49	NA	2	2/0/0	2/0/0	0/0/2	1/1/0	0/0/2	2/0/0	1/1/0	1/0/1	11
15	71	8	2	1/0/1	2/0/0	2/0/0	1/1/0	0/0/2	1/1/0	1/1/0 ²	1/1/0	11
16	65	NA	3	2/0/1	2/0/1	0/0/3	2/0/1	0/0/3	0/2/1	1/1/1	0/2/1	11
17	44	6	3	2/0/1	3/0/0	2/0/1	3/0/0	0/0/3	0/0/3	0/0/3	0/0/3	11
18	67	NA	3	2/0/1	2/0/1	0/0/3	2/0/1	0/0/3	1/1/1	1/1/1 ²	0/2/1	11
19	61	NA	3	0/0/3	3/0/0	3/0/0	2/1/0	0/0/3	3/0/0	0/0/3	0/3/0	13
All	60	8	59	26/0/33	52/1/5	22/2/35	45/8/6	11/3/45	29/17/13	16/18/25	10/22/27	

NA = Not available; MAO = mean age at onset; MDD = mean disease duration; Ref. = reference.

¹ Dystonia affected both the axial part of the body and the limbs. ² Dystonia prominently affected the axial part of the body. ³ The authors of these papers were not able to rule out the possible diagnosis of other neurodegenerative disorders. ⁴ Cases where clinical details were unavailable were excluded.

Methods

We searched the PubMed database from 1968 to April 2013 for all papers published in English that contained the keywords ‘familial’ and ‘PSP’ in the title or the abstract. We included cases in which at least one family member had PSP and in which clinical details were available, and we excluded cases where known gene mutations were identified.

Results and Discussion

Fifty-nine affected patients from 19 published PSP families were identified for this study (table 1). We excluded cases without detailed descriptions of clinical symptoms. The mean age at onset was approximately 60 years, and the mean disease duration was about 8 years. Parkinsonism and ophthalmoplegia were most frequently reported, and a vast majority of patients manifested with the symptoms. Falls, postural instability, pyramidal signs, cognitive impairment, and dystonia were common symptoms as well; however, information was missing in

the majority of patients. A small subset of patients transiently responded to L-dopa therapy. Known gene mutations including *MAPT* mutations have not been identified or reported in these cases [2]. Therefore, it is possible that some of the patients could harbor *MAPT* mutations.

A genome-wide association study on autopsy-proven PSP identified several genetic variants, such as *MAPT*, *STX6* and *EIF2AK3* [4]. Undoubtedly, more genetic factors, including monogenic, polygenic and risk variants, as well as genetic-environmental interaction, will be discovered for this condition.

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