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Comparison of clinical characteristics between familial and non-familial early onset Alzheimer's disease

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Abstract

Although familial Alzheimer's disease (FAD) is an early onset AD (EAD), most patients with EAD do not have a familial disorder. Recent guidelines recommend testing for genes causing FAD only in those EAD patients with two first-degree relatives. However, some patients with FAD may lack a known family history or other indications for suspecting FAD but might nonetheless be

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carriers of FAD mutations. The study was aimed to identify clinical features that distinguish FAD from non-familial EAD (NF-EAD). A retrospective review of a university-based cohort of 32 FAD patients with PSEN1-related AD and 81 with NF-EAD was conducted. The PSEN1 patients, compared to the NF-EAD patients, had an earlier age of disease onset (41.8 ± 5.2 vs. 55.9 ± 4.8 years) and, at initial assessment, a longer disease duration (5.1 ± 3.4 vs. 3.3 ± 2.6 years) and lower MMSE scores (10.74 ± 8.0 vs. 20.95 ± 5.8). Patients with NF-EAD were more likely to present with non-memory deficits, particularly visuospatial symptoms, than were FAD patients. When age, disease duration, and MMSE scores were controlled in a logistical regression model, FAD patients were more likely to have significant headaches, myoclonus, gait abnormality, and pseudobulbar affect than those with NF-EAD. In addition to a much younger age of onset, FAD patients with PSEN1 mutations differed from those with NF-EAD by a history of headaches and pseudobulbar affect, as well as myoclonus and gait abnormality on examination. These may represent differences in pathophysiology between FAD and NF-EAD and in some contexts such findings should lead to genetic counseling and appropriate recommendations for genetic testing for FAD.

Keywords

Dementia; Early onset Alzheimer's disease; Familial Alzheimer's disease; *PSEN1* gene

Introduction

Alzheimer's disease (AD) is the most prevalent degenerative dementia in the United States affecting an estimated 5.4 million Americans [1]. Of those Americans with AD, ~4–5 % develop early onset AD (EAD) with onset before 65 years of age [2]. Perhaps as many as 20 % of these patients with EAD have familial AD (FAD) due to autosomal dominant inheritance of fully penetrant mutations in the presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) genes [2, 3–5]. Mutations in the *PSEN1* gene are the most common cause of FAD [6].

Most patients with EAD do not have a clearly familial disorder [7]. Yet, due to its aggressive nature and autosomal dominant inheritance, it is important to identify those with FAD early on. Recent guidelines recommend offering genetic testing only to those EAD patients with two first-degree relatives [7]. However, some patients with FAD may lack a known family history or other reasons for suspecting FAD. It would be valuable for clinicians to have additional guidelines, in addition to a positive family history, for distinguishing FAD from non-familial EAD (NF-EAD) and for deciding when to pursue genetic testing.

Both FAD and NF-EAD have increased brain deposition of β-amyloid (Aβ), but they may differ in how Aβ deposition occurs. There is convergent evidence that *PSEN1, PSEN2*, and *APP* mutations cause FAD by increasing the absolute or relative amount of Aβ42 derived from *APP* [8]. This over-production of Aβ has not been clearly demonstrated in NF-EAD, and the prevailing theory of the etiology of NF-EAD is that it results from decreased clearance of Aβ [9]. Furthermore, FAD can have unusual pathological changes not present in NF-EAD, including increased deposition of amyloid in cerebellum relative to NF-EAD [10] and "cotton-wool" plaque pathology [11]. Differences in clinical features, such as gait abnormalities [11], early seizures, and myoclonus in FAD [12], may provide additional insight into the pathological differences between FAD and NF-AD.

This study examines clinical differences between a cohort of persons with FAD due to *PSEN1* and those with NF-EAD. First, we examine the differences in the presenting

symptom between the two groups. Second, we compare neurological traits occurring during the course of the illnesses between the two groups. To the best of our knowledge, there has not been a clinical comparative study between *PSEN*-related FAD, the most common FAD, and NF-EAD; therefore, an aim of this study is to document neurological differences between these two conditions. Based on the reported occurrence and our own observations of neurological signs and symptoms in FAD [13–17], we examined the frequency of six neurological features: headaches, seizures, myoclonus, gait abnormalities, hyperreflexia, and pseudobulbar affect. We hypothesize that patients with *PSEN1*-related FAD exhibit a younger and more aggressive course with more neurological signs and symptoms in comparison to patients with NF-EAD.

Methods

Subjects

This was a retrospective cohort study of NF-EAD patients ($n = 81$) and *PSEN1*-related FAD patients ($n = 32$). The study was approved by the Institutional Review Board (IRB) at University of California at Los Angeles (UCLA).

The FAD patients presented to or were referred to author JMR in the Department of Neurology at UC Irvine and at the Easton Center for Alzheimer's disease Research at UCLA between August of 1999 and January of 2010. Thirty-four patients were identified who, after a diagnostic evaluation, met criteria for clinically probable AD and had a positive family history for an early onset dementia among at least two first-degree relatives. Genetic testing of these patients was obtained and reviewed. All had *PSEN1* mutations except for two with an APP mutation. The two patients with *APP* mutations were excluded. The remaining 32 FAD patients with *PSEN1* mutations were entered into the study. DNA analysis among these *PSEN1* patients revealed 22 with A431E substitutions [18], two with the G206A substitution [19], three with the L235V substitution [20], and one each with the M146L [21], S212Y [22], R269H [23], I238M [22], and T245P [24] substitutions.

The NF-EAD patients presented to author MFM in the UCLA Neurobehavior Clinic between August 2001 and March 2011 for evaluation of a cognitive disorder. This study identified 97 patients who, after a diagnostic evaluation, had an age of onset less than 65 years, met criteria for clinically probable AD according to the NINCDS-ADRDA, and lacked a family history for an early onset dementia among first-degree relatives. The family histories of these patients were further extensively reviewed. Sixteen patients were excluded because of an unknown family history or one that indicated a questionable possibility of FAD. The remaining 81 NF-EAD patients were entered in the study.

Six of the 32 subjects with FAD were seen on a single occasion, whereas the record review for the remainder covered a variable follow-up period that was as long as 11 years. Patients had been seen for a mean duration of 29 months with an average number of six visits total. For patients with NF-EAD, the follow-up duration varied between a single visit to 8 years. The NF-EAD patients were seen approximately every 6 months for an average follow-up of two visits/year for 26 months. Many of these patients were continuing to be followed in MFM and JMR's clinical programs.

Procedures

This investigation began with a review of all the initial clinic visits from the patients with FAD and NF-EAD. The review focused on the presenting symptoms, disease onset and course, and the initial screening with Mini-Mental State examination (MMSE) (Folstein et al. 1975). Demographic data (age of onset, age at initial visit, ethnicity, and education) noted at the initial visit, were reviewed and used for analyses. The histories were reviewed and the

patients' most salient symptoms at the time of presentation were classified as either being problems with memory, language, visuospatial function, or "other". Second, this study assessed the occurrence, at any time over the course subjects were followed, of the following neurological deficits: headaches, seizures, myoclonus, gait abnormalities, hyperreflexia, and pseudobulbar affect. The history of headaches and seizures was based on the recorded medical history. If it was not stated in the medical history or clinic notes, the patient was considered to have a negative history for these neurological traits. The presence or absence of myoclonus was determined both by history and through examination of the patient. The presence or absence of hyperreflexia, gait abnormalities, and pseudobulbar affect were based on the recorded neurological examinations. Hyperreflexia was determined as any increased deep tendon reflexes thought to be pathological by the examiner, gait abnormalities were defined as any abnormal gait considered to have a neurological cause, and pseudobulbar affect corresponded to the occurrence of pathological laughter or crying.

Statistical analysis

SPSS version 19v (SPSS, Chicago, IL, USA) was used. χ^2 analyses were performed on categorical data. Logistic regression analyses controlling for the differences in age of onset, disease severity upon presentation, MMSE, and education were further performed.

Results

Demographic features

The two groups differed in several respects. Among the *PSEN1* patients, most ($n = 25$) came from families of Mexican origin, compared to the NF-EAD group, which was nearly entirely Caucasian. The ethnic Mexican FAD patients also had a lower level of education than the NF-EAD group (see Table 1). Furthermore, the *PSEN1*-related FAD group had a younger age of onset, lower MMSE scores, and longer disease duration at the time of initial clinic evaluation (see Table 1). Overall, the NF-EAD patients, compared to the FAD patients, had less advanced disease on initial clinic visit.

Presenting symptoms at initial clinic visit

Most patients in both groups presented with memory impairment; however, the NF-EAD patients were more likely to present with a non-memory symptom, particularly visuospatial deficits (see Table 2) than were patients with FAD. The FAD patients, compared to the NF-EAD patients, were significantly more likely to present with memory deficits ($\chi^2 = 8.45$; $p < 0.01$). Although not statistically significant, the NF-EAD patients, compared to FAD patients, had more visuospatial deficits on initial clinic visit and were significantly more likely to have them over the course of follow-up (26. vs. 1, $\chi^2 = 10.20$; $p < 0.001$). There were no differences in the frequency of language deficits, either on presentation or over the course of follow-up (ten additional FAD patients developed language difficulty an average of 5.1 ± 3.3 years after onset). However, when combined, the NF-EAD patients, compared to the FAD patients, were significantly more likely to present with either visuospatial or language deficits ($\chi^2 = 6.10$; $p < 0.05$). In sum, the NF-EAD group had more diverse presenting symptoms as compared to *PSEN1*-related EAD group whereas *PSEN1*-related EAD group presented primarily with memory deficits.

Neurological signs and symptoms

The prevalence of all six neurological signs and symptoms differed between *PSEN1*-related FAD and NF-EAD (see Table 3). Due to the differences in age of onset between the two groups, disease severity (MMSE) and education, logistic regression analyses controlling for these factors were performed. After logistical regression, the FAD patients continued to

have significantly more headaches, myoclonus, gait abnormalities, and pseudobulbar affect. Among the FAD patients, 13 had a history of headaches on initial presentation and most reported migrainous features with their headaches. Among the FAD patients, nine had a history of myoclonus or myoclonus on examination at the time of initial presentation, and four others developed it 1–8 years, or an average 3.75 (3.1) years after the initial visit. Among the four who developed myoclonus, most did so within a few years; it is possible that the one patient who developed it 8 years after the initial visit had had it previously, but it was missed. The myoclonus was spontaneous and generalized in nature. Among the FAD patients, nine had a gait abnormality on initial presentation, and four others developed it 1–3 years, or an average of 2.25 (0.96) years, after the initial visit. Lastly, pseudobulbar affect was initially present in 11 FAD patients, and one other developed it 5 years after initial visit.

Several other observations are of note. There were no statistical differences in the presence of seizures despite the fact that four FAD patients had seizures compared to only one with NF-EAD. Hyperreflexia was more common among the FAD group but also present in those with NF-EAD. Another observation is the complete absence of pseudobulbar affect among the NF-EAD group.

Discussion

This study is one of the first to compare relatively large cohorts of patients with the clinical diagnoses of familial (*PSEN1* mutations) and early onset AD patients without a family history of the disorder. This study corroborates the finding that FAD occurs earlier, on average 14 years earlier, than the average age of onset among non-familial patients. There were several FAD patients, however, with onset in their 50s reflecting an overlap in the age-of-onset distribution (see Fig. 1). By the time of presentation, the FAD patients were more advanced with longer disease duration and lower MMSE scores [15, 25]. In addition, the two groups varied significantly in their presenting symptoms. *PSEN1*-related FAD patients, by and large, presented with memory deficits [26], whereas those with presumed sporadic EAD were more likely to present with visuospatial or language deficits [25].

When demographic variability (age of onset, education, and MMSE scores) were controlled in a logistical regression model, the *PSEN*-related FAD patients had significantly more headaches, myoclonus, gait abnormalities, and pseudobulbar affect than the NF-EAD patients. Previous reviews have found a correlation between age, disease severity, and seizures in AD patients [27, 28]. In this study, it is surprising that seizures did not distinguish between the familial and non-familial EAD patients. This clinical data seems to indicate that seizures occur somewhat later (5–12 years after onset) than other neurological traits in FAD, and may have required a longer period of follow-up in order to detect them.

Clinicians who evaluate and manage patients with early onset dementias benefit from information regarding when to pursue genetic testing for *PSEN1* and other mutations causing young-onset AD. The current guidelines and practice are to suspect an autosomal dominant mutation in those patients with EAD and at least two first-degree relatives [7]. These guidelines may be insufficient as there are patients who lack a known or reliable family history for early onset dementia. Certain symptoms such as headaches and other neurological abnormalities are frequently associated with FAD, especially those cases due to *PSEN1* mutations, and may reflect other neuropathology such as cerebrospinal fluid involvement [13, 14, 16, 17, 29, 30, 39]. Though it is possible that the apparent increased frequency of headaches in persons with FAD is due to differential medication use (e.g., acetylcholinesterase inhibitors), most persons with NF-EAD were also on such medications. Furthermore, in a previous report [16] we observed an increased frequency of headaches in FAD mutation carriers who were in the preclinical stage of the disease and therefore none of

them were on such medications. The current study corroborates the observation that FAD is of particularly young onset, often in the 40s, has an aggressive course, and is frequently associated with neurological abnormalities.

These clinical features can guide clinicians towards consideration of FAD, particularly in the presence of a progressive neurodegenerative disorder presenting in the early 50s or younger. The presentation is typically with memory impairment; presentations with other cognitive or behavioral deficits are more consistent with sporadic EAD, including early language impairment, visuospatial deficits, apraxia, and behavioral/executive dysfunction [3–6, 13, 31] [3, 4, 13, 25, 32]. Although visuospatial deficits suggest the non-familial form, it is noteworthy that one FAD patient in the current study with a relatively late age of onset (55 years; R269H mutation) presented with visuospatial difficulties, suggesting that such deficits may more related to a patient's age rather than to genetic etiology.

The current study expands on the literature regarding clinical characteristics of FAD and NF-EAD. Prior studies have examined biological and neuroimaging markers (MRI, PET scans) to diagnose EAD [33, 34]. Such studies have shown an association of temporo-parietal neocortical atrophy with EAD and hippocampal atrophy with late-onset AD [35], suggesting that neuroimaging can be helpful in distinguishing EAD from the typical late-onset AD [36]. Imaging with Pittsburgh Compound B has revealed an atypical pattern of amyloid distribution in *PSEN1*-related FAD, namely early and severe deposition in the striatum [37] and sometimes in the cerebellum [38], apparently reflecting a distinct pattern of the progression of amyloid pathology. Our group has identified a distinct pattern of Aβ peptides in the cerebrospinal fluid of carriers of the A431E *PSEN1* mutation compared to late-onset AD [39], again suggesting different pathogenetic mechanisms in the causes of FAD and NF-AD. Relating the clinical characteristics of FAD to pathological and biomarker changes can help us understand how the pathophysiological cascade of FAD is similar to or distinct from NF-AD and late-onset AD.

There are several limitations to this study. First of all, it is clinical and retrospective, based on recorded differences on clinical assessments and with variable follow-ups. Using such an approach, it is possible that the presence of certain symptoms may have been underestimated. However, there is no reason to suspect any systematic differences in ascertainment of symptoms or signs between the FAD and NF-EAD populations. The observed differences corroborate previous observations regarding differences between FAD and NF-EAD. Second, the two groups are significantly different in ethnic backgrounds, age of onset, and disease progression and severity. Although this study could not eliminate the effects of ethnicity on a genetic disease such as *PSEN1*-related FAD, the subsequent logistical regression helped control for the other factors. As the majority of subjects with FAD (22/32) in this cohort had the common A431E substitution representing a founder effect [18], the findings may not entirely generalize to persons with other *PSEN1* mutations or to persons with *APP* or *PSEN2* mutations. Finally, the use of MMSE scores for disease severity can be influenced by language abilities and lower education level among the FAD patients. However, the fact that subjects with FAD were seen later in the course of their symptoms than those with NF-EAD (mean of 5.1 vs. 3.3 years after symptom onset) provides support for FAD subjects being in a more severe stage of the disease. Taking age, MMSE score, and severity into account in logistic regression analyses helped reduce their influence on the occurrence of neurological abnormalities in that analysis.

In conclusion, in addition to a much younger age of onset, clinicians can recognize FAD patients with *PSEN1* by abnormalities on the neurological history and examination. In the absence of a reliable family history, an early and progressive age of onset with a history of headaches, myoclonus, gait abnormalities and pseudobulbar affect suggests that genetic

testing of EAD patients might be informative. These findings should lead to genetic counseling and related recommendations for these patients. Further studies with different populations and larger sample sizes could corroborate the current findings and, particularly when related to imaging, pathological, and biochemical differences, shed light on distinct or common mechanisms between FAD and NF-EAD.

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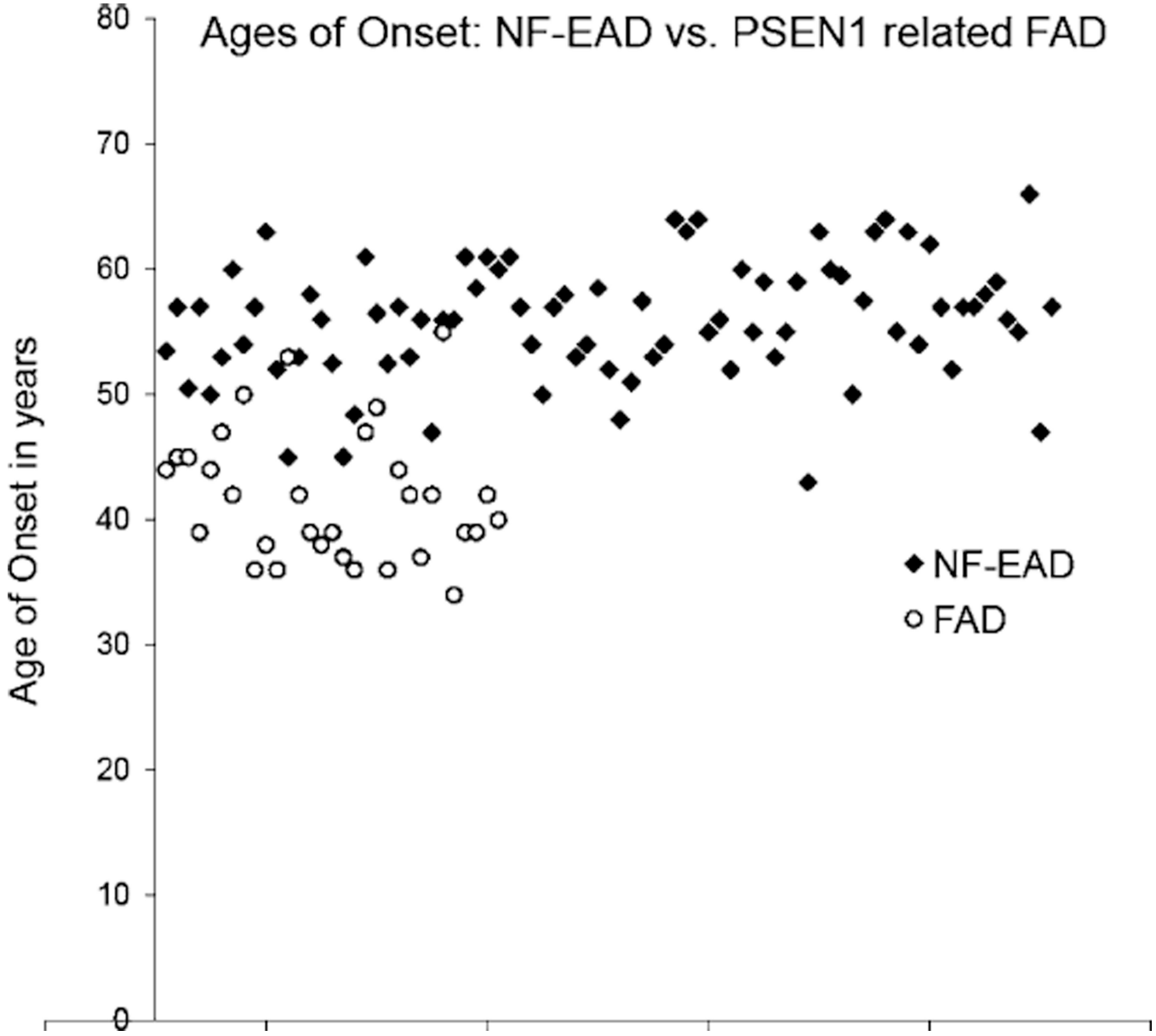

Fig. 1.
Scatter plot of ages of onset of the two patient groups

Table 1

Presenilin-1 (*PSEN1*) familial Alzheimer's disease (FAD) versus nonfamilial early onset Alzheimer's disease (NF-EAD): demographics and clinical characteristics

	***PSEN1*-related FAD (*n* = 32)**	**NF-EAD (*n* = 81)**	**Significance, *p* value**
Male/female	17/15, 53.1 % male	36/45, 44.4 % male	$\chi^2 = 0.39$; ns
Age at onset (years)[a]	41.8 (5.2)	55.9 (4.8)	$t = 13.74$; $p < 0.001$
Number with Mexican ethnicity	25, 78.13 %	0	$\chi^2 = 60.94$; $p < 0.05$
Education level (years)[a]	8.3 (4.8)	15 (2.6)	$t = 9.54$; $p < 0.001$
Age at initial clinic visit (years)[a]	46.9 (5.3)	59.2 (5.3)	$t = 11.12$; $p < 0.001$
Initial clinic MMSE[a]	10.74 (8.0)	20.95 (5.8)	$t = 7.54$; $p < 0.001$
Mean disease duration on initial clinic visit (years)[a]	5.1 (3.4)	3.3 (2.6)	$t = 3.03$; $p < 0.01$

MMSE Mini-Mental State Examination

[a]Mean and standard deviation in parentheses

Table 2

Presenilin-1 (*PSEN1*) familial Alzheimer's disease (FAD) versus nonfamilial early onset Alzheimer's disease (NF-EAD): presenting symptoms on initial clinic visit

Symptom	*PSEN1*-related FAD (n = 32)	NF-EAD (n = 81)	Significance, p value
Memory	27 (84.37 %)	47 (58.02 %)	$\chi^2 = 5.91$; $p < 0.05$
Visuospatial	1 (3.12 %)	14 (17.28 %)	$\chi^2 = 2.86$; ns
Language	3 (9.38 %)	14 (17.28 %)	$\chi^2 = 1.48$; ns
Other	1 (3.12 %)[a]	6 (7.4 %)[b]	$\chi^2 = 0.18$; ns

[a] Apathy for the *PSEN1* related FAD patient

[b] Personality changes $n = 3$; writing impairment $n = 2$; paranoid ideation $n = 1$

Table 3

Presenilin-1 (*PSEN1*) familial Alzheimer's disease (FAD) versus nonfamilial early onset Alzheimer's disease (NF-EAD): neurological traits

	***PSEN1*-related FAD, (*n* = 32)**	**NF-EAD (*n* = 81)**	**Significance and *p* value after**	
			χ^2	**Logistic regression**
History of headaches	13, 40.6 %	10, 12.3 %	9.8; $p < 0.01$	$p < 0.05$
History of seizure	4, 12.5 %	1, 1.2 %	7.1; $p < 0.01$	ns
History of myoclonus	13, 40.6 %	2, 2.5 %	30.1; $p < 0.001$	$p < 0.001$
Hyperreflexia	19, 62.5 %	9, 11.1 %	29.66; $p < 0.001$	ns
Gait abnormalities	13, 40.6 %	1, 1.2 %	33.5; $p < 0.001$	$p < 0.01$
Pseudobulbar affect	12, 37.5 %	0	36.2; $p < 0.001$	$p < 0.001$