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Multiple System Atrophy: phenotypic spectrum approach coupled with brain 18-FDG PET

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Abstract:

Objective: The 2008 diagnostic criteria classify Multiple System Atrophy (MSA) patients in a predominantly parkinsonian (MSA-P) or cerebellar (MSA-C) type. Phenotypic descriptions have since highlighted a clinical heterogeneity among patients (e.g., mixed-type, cognitive impairment, atypical longer survival). This study attempts to identify different phenotypes of patients with MSA and to describe corresponding brain 18-FDG Positron Emission Tomography (PET) patterns.

Methods: Patients with a "probable" MSA diagnosis for whom a brain 18-FDG PET was performed were included. A retrospective analysis (from 2006 to 2017) was conducted using standardized data collection. We used Latent Class Analysis (LCA), an innovative statistical approach, to identify profiles of patients based on common clinical characteristics. Brain metabolism of different groups was studied at rest.

Results: Eighty-five patients were included. Three different profiles were revealed (entropy= 0.835): 1. extrapyramidal, axial, laryngeal-pharyngeal involvement (LPI) and cerebellar symptoms (n=46, 54.1%); 2. cerebellar and LPI symptoms (n=30, 35.3%); 3. cerebellar and cognitive symptoms (n=9, 10.6%). Brain metabolism analyses ($k>89$; $p<0.001$) showed hypometabolism of the basal ganglia, frontal/prefrontal, temporal cortices and left posterior cerebellum in profile 1. In profile 2 there was hypometabolism of the medulla, prefrontal, temporal, cingular cortices, putamen and bilateral cerebellar hemispheres. In

profile 3 there was hypometabolism of bilateral posterior cerebellar hemispheres and vermis.

Conclusion: Beyond the two most common phenotypes of MSA, a third and particularly atypical profile with cerebellar and cognitive symptoms but without LPI involvement is described. These profiles are supported by different brain metabolic abnormalities which could be useful for diagnostic purposes.

Introduction

The current diagnostic criteria for Multiple System Atrophy (MSA) classify patients into predominantly parkinsonian (MSA-P) or cerebellar (MSA-C) types [1]. Phenotypic descriptions over the last years have however uncovered patients with a mixed-type [2], with mild cognitive impairment in at least one third of cases [3,4], dementia [5], or with a more benign variant with long disease duration and late onset of autonomic failure [6]. Thus, there is a clinical heterogeneity within MSA patients and these atypical phenotypes are not captured by the currently used classification and diagnostic criteria. Using a non-a priori based classification method like the Latent Class Analysis (LCA) may help uncover these phenotypes.

As a diagnostic aid, brain magnetic resonance imaging (MRI) and brain 18-FDG Positron Emission Tomography (PET) provide information currently considered as additional features for the diagnosis of "classical" types of MSA [1]. In addition, 18-FDG PET provides information on the underlying pathophysiology by highlighting metabolic dysfunction of specific anatomical structures which can then be correlated with clinical symptoms [7]. Here also, the above-mentioned atypical phenotypes have so far not been characterized by specific cerebral metabolic patterns.

In the present work, we hypothesize that different phenotypes of MSA patients can be identified, using an innovative statistical approach: Latent Class Analysis (LCA). We further hypothesize that these clinical profiles involve specific brain networks as shown by brain 18-FDG PET patterns.

Materials and methods

1. Population studied

All patients with a "probable" MSA diagnosis [1] for whom a brain 18-FDG PET was performed between January 1, 2006 and July 31, 2017 were included. The minimum follow-up period was 2 years.

All patients had been examined by movement disorders experts in the Department of Neurology and Movement Disorders and had undergone a brain PET in the Department of Nuclear Medicine at the University Hospital of Marseille, France. The study was approved by our local ethics committee in accordance with the Declaration of Helsinki.

2. Data collection

A retrospective analysis was conducted using standardized data collection. We compiled clinical data documented during the first clinical evaluation that made it possible to make the diagnosis. The brain PET was performed over a 3-month period around clinical data collection. The clinical data were: Hoehn & Yahr, Schwab & England, UPDRS motor score, cerebellar signs (gait ataxia, limb ataxia, cerebellar nystagmus or oculomotor saccades), cephalic dyskinesia, axial involvement with antecolis, camptocormia, pisa syndrome, freezing of gait, early falls (within three first years), stridor or swallowing difficulties (laryngeal-

pharyngeal involvement; LPI) determined by a ENT specialist with expertise in parkinsonian syndromes, pyramidal syndrome, myoclonus, REM sleep behaviour disorders, usage of selective serotonin reuptake inhibitor (SSRI), cognitive assessment (Mattis Dementia Rating Scale [8], Frontal Assessment Battery (FAB) [9] and the motor and ideomotor apraxia scale [10]). Please note that concerning the FAB and motor and ideomotor apraxia data, we collected qualitative data from patients' charts by considering as "present" a dysexecutive syndrome or apraxia when the score was lower than the thresholds used in the literature and as "absent" when it was higher than the thresholds (Table 1) [9,10]. We did not analyze dysautonomia symptoms because they were a necessary criterion for the "probable" type and we could not quantify their severity (as the symptoms were treated). MRI data from all patients were collected as part of the standard care. The images were acquired, on different machines and were not the subject of a standardised protocol. Although this is not the objective of our study, MRI features are added In Table 2 for illustrative purposes.
Evolutional data was also collected retrospectively until the last patient visit: use of technical assistance, aspiration pneumonia, gastrostomy, occurrence and cause of death.

3. Statistical analysis

a. Latent class analysis (LCA) basis

LCA is an innovative statistical approach which has already been validated in observational public health studies to identify subgroups of patients ("classes" or "profiles") based on common clinical, behavioral or psychosocial characteristics, using an individual-centered approach [11,12]. Each patient is classified according to the probability of belonging to a particular class [11]. One of the advantages of the LCA is the possibility of simultaneously examining multiple clinical characteristics that define an individual's phenotype rather than analyzing them separately, the latter of which would increase the risk of type 1 or false positive error [12].

b. Preliminary stage before the LCA is implemented

We selected six clinical domains to define the phenotype of patients with MSA: 1. extrapyramidal, 2. axial, 3. cerebellar, 4. cognitive, 5. LPI, 6. Survival (Table 1). For each domain a score was established by adding points allocated to its constituent elements. If this score was higher than the median of the domain's total score, then it was retained as "present".
We decided to choose these 6 clinical domains because they reflect symptoms that are frequently found in patients with MSA. Indeed, they are part of the diagnosis (extrapyramidal or cerebellar) or part of the complication of the disease (axial, LPI symptoms) or are important atypical features (cognitive impairment, longer survival).

c. Statistical analysis of LCA

These analyses were performed with Mplus software version 7. From the 6 clinical domains, each with 2 possibilities (present or absent), there were 2^6 = 36 different theoretical profiles for each patient. The probability of belonging to a class and the quality of the classification of patients was assessed by the "entropy" index which varies from 0 to 1. Values close to 1 indicated good class separation [13]. After examining different classification models (two, three or four classes) a three-class model was selected and studied.

d. Other statistical analyses

Categorical variables are presented as numbers and percentages, and the quantitative results as a median with interquartile range as an index of dispersion. Comparisons between groups were made with Chi2 or Fisher tests for qualitative data and T-test or Mann-Whitney for quantitative data, as appropriate. A Cox model was applied to look for factors influencing survival, variables showing $p<0.2$ in the univariate analysis were included in multivariate analysis. A two-sided p-value of less than .05 was considered to indicate statistical significance.

4. Acquisition and analysis of brain images in 18-FDG PET

18-FDG PET brain metabolism was studied at rest, in a standardized manner, in all patients (acquisition of images after intravenous injection of 18-

Fluorodesoxyglucose, 150 MBq, by a Discovery ST PET/scanner camera, GE Healthcare, Waukesha, WI with an axial resolution of 6.2 mm allowing 47 contiguous transverse sections of the brain of 3.27 mm thickness). Images were reconstructed using the ordered subsets expectation maximization algorithm with 5 iterations and 32 subsets and corrected for attenuation using a CT transmission scan. Whole-brain statistical analysis was performed at voxel-level using SPM8 software (Wellcome Department of Cognitive Neurology, University College, London, UK). The PET images were spatially normalized onto the Montreal Neurological Institute (MNI) atlas. The dimensions of the resulting voxels were 2x2x2 mm. The images were then smoothed with a Gaussian filter (8 mm full-width at half-maximum) to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio.

This data set data was compared to that of healthy subjects. The healthy subjects database was previously acquired under the same technical conditions and is part of a local database of normal 18-FDG PET constituting a control population (Clinical Trials Ref: NCT00484523). The control group was comparable in age and sex to our sample of patients with MSA ($p > 0.05$, median age 66 years, 60.5 - 71.5 years).

Comparative SPM maps (T) were obtained for a significance threshold $p<0.001$ uncorrected, with a k size threshold >89 determined after Monte-Carlo simulations. This choice has been made to limit type-II error, as recommended [14]. Age, gender and duration of disease progression during PET were considered as nuisance covariates. Please note that similar findings were obtained for corrected threshold using FWE method when comparing patients to

healthy subjects. No significant voxel was however found between patients' groups at this threshold. The Proportional scaling was applied, giving the same global value to each PET examination, to correct for individual variations in global brain metabolism. The anatomical localization of the most significant voxels was then identified using Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html). The mean values of brain glucose metabolism were extracted at the individual level for each significant cluster.

Results

1. General patients' characteristics

Eighty-five "probable" MSA patients were included (Table 2 and Table 3). Only 6 patients were lost during follow-up (7%). Median follow-up duration was 6 years (5 – 9). Forty-six patients had died at the end of the study (59%) including 14 in the first 5 years of the disease (30.4%). Causes of death were as follows: 29 (63%) respiratory disorder including 23 (50%) severe aspiration pneumonia, 5 (10.9%) respiratory arrest due to stridor and 1 (2.2%) due to pulmonary embolism; 5 (10.9%) cardiac rhythm or conduction disorder; 1 (2.2%) severe sepsis with a urinary starting point; 1 (2.2%) metastatic breast cancer; 10 (21.7%) undetermined cause. Clinical elements associated with shorter survival are late-onset age ($p = 0.013$) and early stridor ($p = 0.038$).

2. Clinical profiles (Figure 1)

Out of the 85 patients, 60 were diagnosed with MSA-P (70.6%) and 25 with MSA-C (29.4%) based on the diagnostic criteria [1].

With the LCA analysis, the two-class model revealed a profile associating extrapyramidal, cerebellar, LPI and axial symptoms (profile A: 44 patients, 51.8%) and a profile associating cerebellar and LPI symptoms (profile B: 41 patients, 48.2%).

The three-class model revealed a profile with extrapyramidal, axial, LPI and cerebellar symptoms (profile 1: 46 patients, 54.1%), a profile with cerebellar and LPI symptoms (profile 2: 30 patients, 35.3%) and a profile with cerebellar and cognitive symptoms (profile 3: 9 patients, 10.6%).

The four-class model was non-convergent and therefore not useable.

The three-class model with the higher statistical reliability (3-classes entropy = 0.835 versus 2-classes entropy = 0.663) was selected and studied.

3. Brain metabolism abnormalities in 18-FDG PET

Hypometabolism of the putamen, frontal/prefontal/temporal cortices, medulla and cerebellum was found in MSA patients compared to healthy subjects ($k>89$; $p<0.001$). Using the current classification, The MSA-P type was characterized by more pronounced hypometabolism in the putamen and lenticular nuclei and the MSA-C type was characterized by more pronounced hypometabolism in the

brainstem and cerebellum. Below are the results for each profile obtained thanks to the LCA.

a. Comparison to healthy subjects ($k>89$; $p<0.001$) (Figure 2-A and Table 4).

Concerning profile 1, we found hypometabolism of the putamen and lenticular nuclei, frontal/prefrontal (Brodmann Area 6) and temporal (Brodmann Area 39) cortices. There was also hypometabolism restricted to the posterior left lobe of the cerebellum, more precisely the VIIb lobe and the tuber of the vermis.
In profile 2, there was hypometabolism of the medulla, prefrontal (supplementary motor area, subcallosal gyrus, olfactory), temporal (Brodmann's Area 39), cingular (Brodmann's Area 31) cortices, putamen and the cerebellum (anterior with the culmen, lobules IV-V and posterior with lobules VI-VII-VIII).
In profile 3, we found hypometabolism limited to bilateral cerebellar hemispheres (posterior lobes: lobes VIIa (Crus 1) and VIIb (Crus 2) and vermis (tuber and uvula)).

b. Comparison of each patients' profiles to each other ($k>89$; $p<0.001$) (Figure 2-B).

Hypometabolism in profile 1 was most pronounced in the left lenticular and putaminal nuclei (in comparison to profile 2) and the superior (Brodmann's Areas 8-9) and middle left frontal gyri (in comparison to profile 3).
In profile 2, hypometabolism was most pronounced in the anterior cerebellar region (right lobules IV / V; in comparison to profile 1), the superior (Brodmann's Areas 8-9), and middle (in comparison to profile 3) left frontal gyri.
In profile 3, hypometabolism was most pronounced in the right posterior cerebellar region (lobule VIIb - crus 2) (in comparison to profile 1; no difference found in comparison to profile 2).
It should be noted that we did not find any statistically significant difference between the three groups for MRI data.

Discussion

Our objective was to identify clinical profiles of patients with MSA, reflecting the heterogeneity of patients with this disease. Three distinct profiles have been revealed by the LCA method and are supported by different brain metabolic abnormalities.

1. Clinical profiles and brain PET metabolism

The two-class LCA analysis revealed two profiles: a first extrapyramidal, cerebellar, LPI and axial profile (profile A), and a second cerebellar and LPI profile (profile B). Although homogeneous in number, there was a clear split

between cerebellar patients (profile B) and patients with both parkinsonism (predominant symptom) and cerebellar symptoms (profile A). This division into two classes obtained statistically was quite similar to the historical classification of patients performed by an expert physician. However, the low entropy of this model suggested that this differentiation was not satisfactory and did not account enough for the different clinical features of the patients.

In contrast, the three-class LCA analysis revealed three relevant clinical profiles. Profile 1, with the largest number of subjects, was characterized by a high probability of having extrapyramidal phenotype, which was not surprising since there is a clear predominance of the Parkinsonian type in Europe [15]. It also combined axial, LPI and cerebellar symptoms. Metabolic abnormalities included basal ganglia, frontal/prefrontal, temporal cortices and cerebellar where compared to other profiles there was hypometabolism in left lenticular and putaminal nuclei and left superior and middle frontal gyri. This is consistent with the literature where hypometabolism of the putamen, pons and cerebellum was reported: the MSA-P type was characterized by more pronounced hypometabolism in the striatum and the MSA-C type was characterized by more pronounced hypometabolism in the pons and the cerebellum [7].

One third (35.3%) of patients had a profile characterized by the probability of having cerebellar and LPI symptoms (profile 2). PET analyses found a hypometabolism of the cerebellum (anterior and posterior), brain stem, putamen, prefrontal and cingulate cortices. In comparison to other profiles, the right anterior cerebellar region (IV / V lobules) and the left superior and middle frontal gyri were

more pronounced. This anterior cerebellar region is more involved in motor tasks than in cognitive tasks [16].

It is interesting to notice that we found, in both profile 1 and 2, a hypometabolism of basal ganglia even though the probability of having parkinsonian symptoms in profile 2 patients was almost inexistent. As it is known that almost all MSA patients would develop parkinsonian signs during progression regardless of the initial presenting symptoms [17], we hypothesize that striatal hypometabolism might precede the development of parkinsonian signs by several years, as it has been shown in pre-symptomatic Huntington disease patients [18].

LPI involvement is common in MSA and was indeed found in profiles 1 and 2 but not in profile 3. PET pattern of patients with LPI showed pronounced hypometabolism of the left superior (Brodmann Areas 8-9) and middle frontal gyri. The involvement of subcortical, motor and pre-motor cortical regions in swallowing has already been described [19], including the supplementary motor area and anterior cingulum [20]. These brain regions overlap with those found in our analyses, highlighting their active participation in swallowing. One could have expected to find brainstem hypometabolism associated with LPI since it is known that swallowing movements are controlled by structures in this area [21]. However, we only found a hypometabolism of the brainstem in profile 2 and not in profile 1 patients.

Concerning the last profile, 10.6% of patients were characterized by a high probability of having cerebellar involvement with cognitive symptoms and a probability near zero of having extra-pyramidal, axial or LPI symptoms (profile 3).

Thus, only a small number of patients had a cognitive decline and it was mild in most cases. Although not classically in favor of MSA [1], it is now well demonstrated that cognitive impairment is not uncommon. The proportion of patients with cognitive decline in our study is comparable to what has been reported in the literature. For example, Brown and al. [4] found that 42.3% of the MSA group scored below 15 on the FAB scale. Also, dementia was described in about 11% of the cases [5]. Up to this day, there is no evidence that one type of the disease is more frequently associated with cognitive impairment than another [3,4]. Nevertheless, Barcelos et al. [22] found that MSA-C patients exhibited worse performance in attentional function evaluated by the Mattis Dementia Rating Scale compared to MSA-P patients. In our cohort, cognitive impairment was more frequently associated with cerebellar symptoms and we found hypometabolism of the posterior cerebellum and the vermis with a more pronounced hypometabolism of the right posterior cerebellar region (lobule VIIb - crus 2). There was no cortical involvement, particularly of the frontal/prefrontal regions, but the major role of the cerebellum in cognition has been largely detailed in the literature [23]. Indeed, the lobule VIIb - crus 2 has been described as being involved in executive functions. It sends and receives projections with the prefrontal cortex (Brodmann's area 46) forming a closed loop distinct from the network involved in motor function [16,23]. Interestingly, the cognitive functions underlying this region correspond to those we evaluated (especially with the rapid frontal assessment battery). In a further analysis, we searched Brodmann's area 46 for hypometabolism, but no anomalies were found. This was likely related to a lack of power due to an insufficient number of patients in this group

(n = 9). It is conceivable that less pronounced hypometabolism in other cortical regions may be found in a larger patient cohort, especially since correlations between brain metabolism and cognitive impairment have previously been observed in orbital-frontal, mediofrontal regions, dorsal part of the pons, inferior parietal regions in MSA-C [24] and prefrontal; and in frontal, temporal and parietal cortices in MSA-P [25].

2. Prognostic factors and survival analysis

Of the entire sample, 14 deaths out of 46 (30.4%) occurred in the first 5 years of the disease; a high proportion of early deaths that has already been reported [26]. Late-onset age and stridor are found to be associated with shorter survival consistently in the literature [26].

Qualitatively, we were unable to identify a group with a better prognosis. Profile 1 patients were more likely to use technical assistance and gastrostomy in their progression. The need for assistance may be explained by the probability of having a higher extrapyramidal and axial impairment, causing a greater disability (Hoehn & Yahr and Schwab & England more severe). Amongst the morbidities for patients in this group are swallowing disorders which are associated with an over risk of undergoing gastrostomy.

It had historically been suggested that men were more affected than women, which was subsequently refuted [15]. Our study joins these last results since it seems that profiles 2 and 3 were mainly composed of men whereas profile 1

seemed to be more equal. Moreover, there have never been any reports of gender dominance for each type of MSA [15].

3. Limitations of the study

We conducted a retrospective analysis based on a standardized data collection. Only 6 patients were lost during follow-up (7%). We obtained the missing data by telephone contact with the patients, their families or the general practitioner. Thus, we were able to analyze a large amount of data acquired over a significant number of years.

The lack of anatomopathological confirmation was one of the weaknesses of the study. This was mitigated by the fact that we chose to include only patients who met the "probable" diagnostic criteria for whom the positive predictive value was 100% at initial clinical evaluation [27]. Major differential diagnoses of MSA were also eliminated before the patients were included in the study (toxic, metabolic, inflammatory and genetic causes including Friedreich's ataxia, fragile X tremor ataxia syndrome). In addition, the diagnosis never changed during the follow-up of these patients (at least 2 years, median of 6 years). Finally, in our analyses, brain 18-FDG PET results provided information in accordance with previously described features for the diagnosis of "classical" types of MSA [1].

Some clinical data was not used because it was not possible to integrate it into the different clinical domains or to group it into a new domain (early falls, myoclonus, REM sleep behaviour disorders and pyramidal syndrome). For LCA analysis, one symptom could not belong to several clinical domains. It was

impossible to determine *a priori* whether early falls, for example, were more likely part of the extrapyramidal domain, rather than the cerebellar or axial domains since their origin is most probably multifactorial. However, a complementary analysis including early falls in the "axial" domain or as a domain in its own right did not yield results different from those presented here. Furthermore, we did not analyze dysautonomia symptoms because they were a necessary criterion for the "probable" type and we could not quantify their severity (as the symptoms were treated). In any LCA model, one must be vigilant of the temptation to conclude that the set of latent classes identified in an analysis represent the actual types of individuals in the population. Instead, the LCA provides a useful heuristic for representing heterogeneity across the dimensions included in the model [12] at some point in the course of the disease.

We are aware that the cognitive work-up is limited. This is inherent to the retrospective nature of this study and also the fact that it was not designed to look for cognitive disorders in detail but rather extract different clinical phenotypes. Further studies with a more thorough cognitive and behavioral work-up are warranted to fully address this issue.

Obtaining unbalanced groups in terms of numbers makes the statistical power of comparative analyses between groups weaker, especially since we are interested in analyses of brain metabolism. However, these differences in numbers reflect the preponderance or rarity of the various clinical phenotypes encountered in real life. These analyses should be performed on a larger number of patients to limit this bias.

Conclusion

Three clinical profiles could be differentiated using a latent class analysis approach in our sample of MSA patients. This is an emerging statistical method that reveals latent profiles based on the clinical characteristics implemented in the model. We revealed two majority profiles recalling the two types of the disease proposed by the consensus classification: a profile with extrapyramidal, axial, LPI and cerebellar symptoms, a profile with cerebellar and LPI symptoms, and we also revealed a particularly atypical profile with cerebellar and cognitive symptoms but without LPI involvement. These profiles reflect the phenotypic diversity of the patients. One of the strengths of this study is that these profiles are supported by different brain metabolic abnormalities which could be useful for the diagnosis of this disease and highlights a potential area for further investigation in the future. Further studies on larger cohorts, implemented with more clinical and pathological data, are warranted.

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Figure caption:

Figure 1: Clinical profiles of AMS patients

LPI: laryngeal-pharyngeal involvement

a. Two-class model: entropy = 0.663
b. Three class model: entropy = 0.835

The axis of values (from 0 to1) refers to the probability of exceeding the median of the total score of a clinical domain (cf. Table 1).

Figure 2:

A - Anatomical localization of areas of decreased metabolism in patients with profiles 1, 2 and 3 in comparison to control subjects ($p < .001$, uncorrected, $k > 89$) projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template.

See Table 4 a, and c for corresponding values

B- Anatomical localization of areas of decreased metabolism by comparison of each patients' profiles to each other ($p < .001$, uncorrected, $k > 89$) projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template.

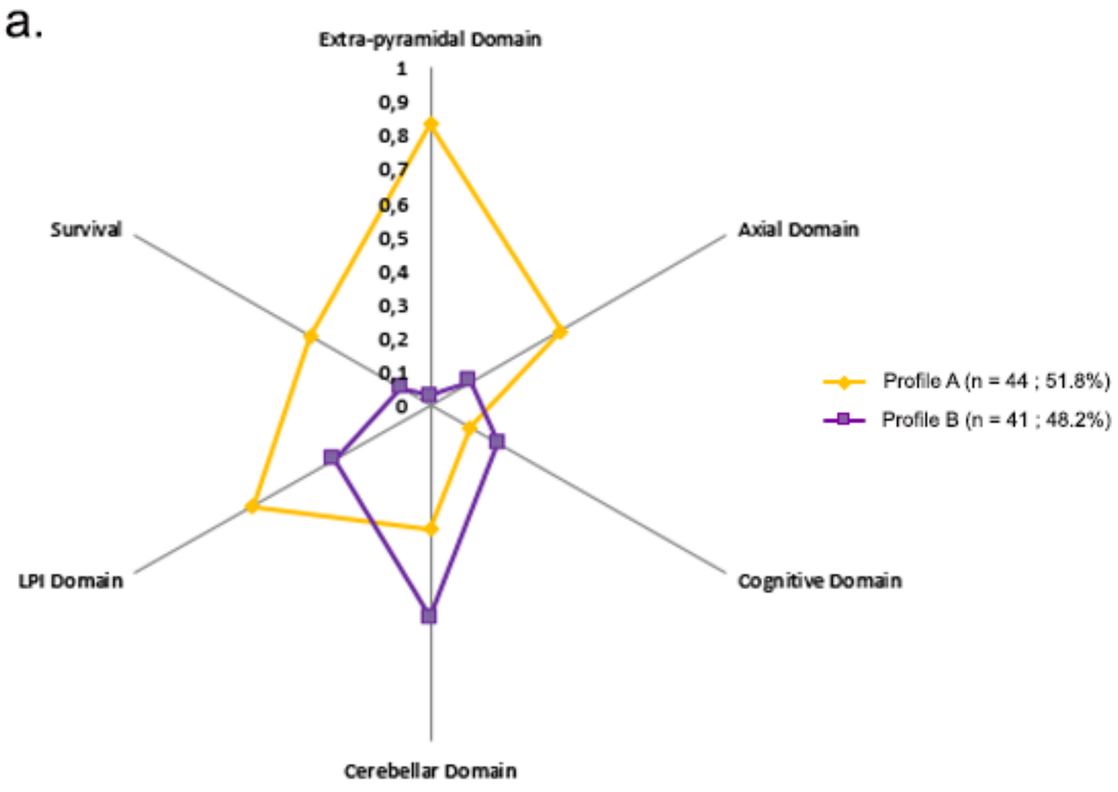
a. Left lenticular and putaminal nucleus (cluster dimensions: 282, x = -22 y = 2, z =4, Z-score peak = 4.27)

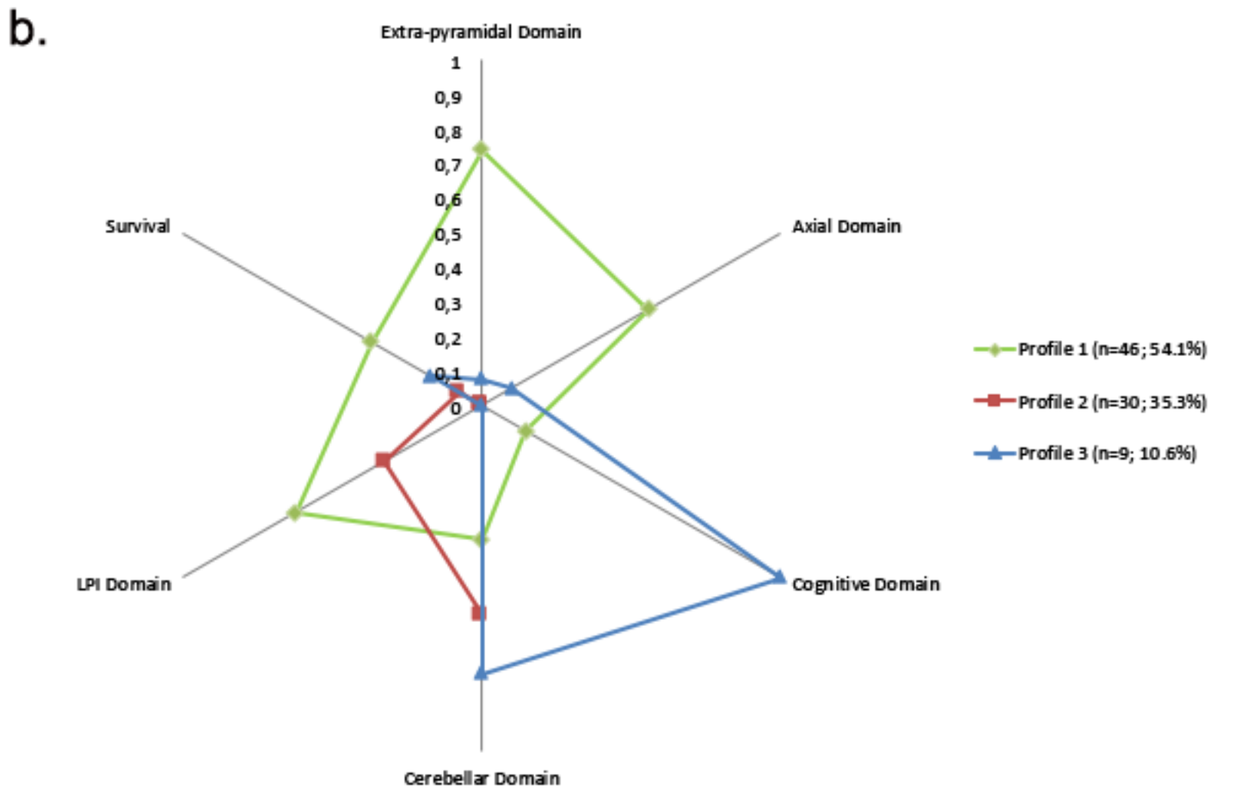
b. Superior (Brodmann areas 8-9) and middle left frontal gyri (cluster dimensions: 117, x = -28, y= 46, z = 42, Z-score peak = 4.73)

c. Anterior cerebellar region: right lobules IV / V (cluster dimensions: 128, x = 38, y= -46, z= -32, peak Z-score = 3.45).

d. Superior (Brodmann areas 8-9) and middle left frontal gyri (cluster dimensions: 127, x = -28, y= 46, z = 44, Z-score peak = 4.84).

e. Right posterior cerebellar region: lobule VIIb (crus 2) (cluster dimensions: 188, x = 20, y= -86, z = -34, peak Z-score = 3.87)


a.
Extra-pyramidal Domain
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Survival
Axial Domain
LPI Domain
Cognitive Domain
Cerebellar Domain
Profile A (n = 44 ; 51.8%)
Profile B (n = 41 ; 48.2%)

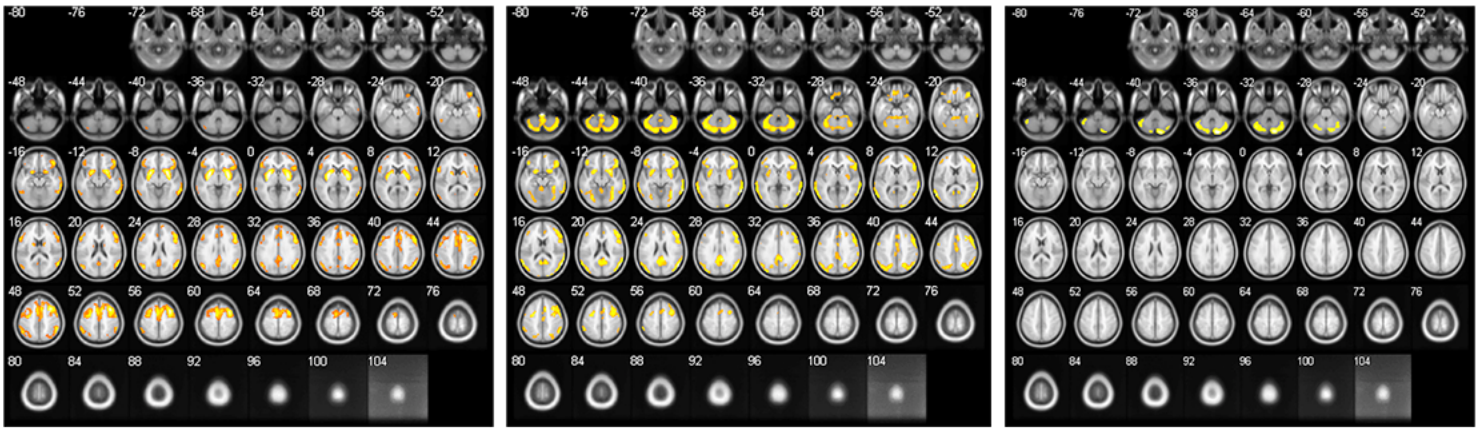

b.
Extra-pyramidal Domain
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Survival
Axial Domain
LPI Domain
Cognitive Domain
Cerebellar Domain
Profile 1 (n=46; 54.1%)
Profile 2 (n=30; 35.3%)
Profile 3 (n=9; 10.6%)

A - Comparison to control subjects

a. Profile 1

b. Profile 2

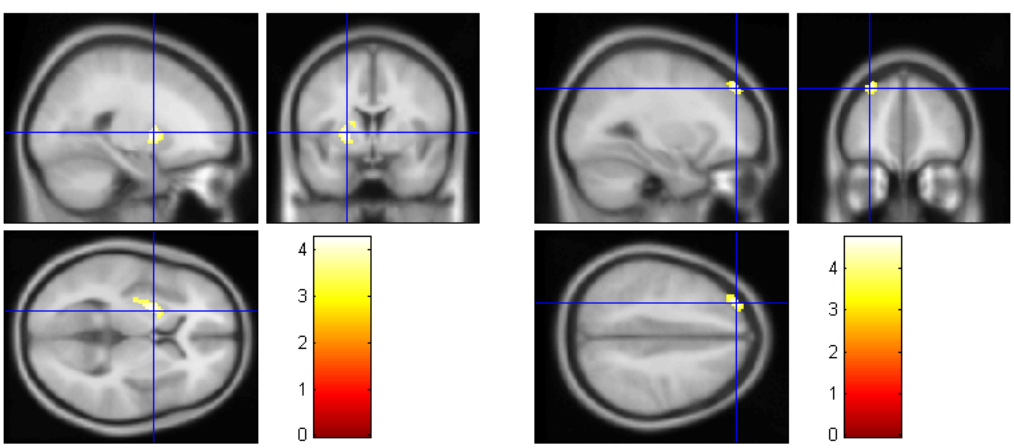
c. Profile 3



B - Comparison of each patients' profiles to each other

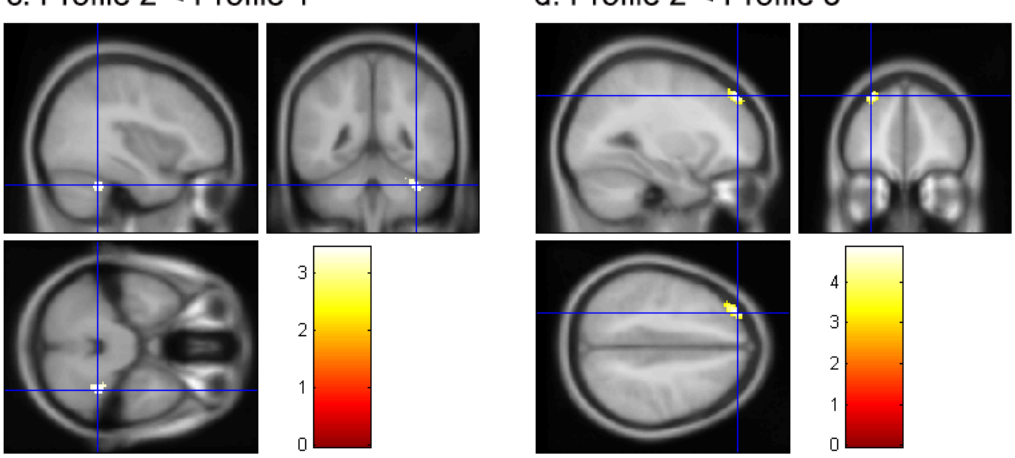
a. Profile 1 < Profile 2

b. Profile 1 < Profile 3



c. Profile 2 < Profile 1

d. Profile 2 < Profile 3



e. Profile 3 < Profile 1

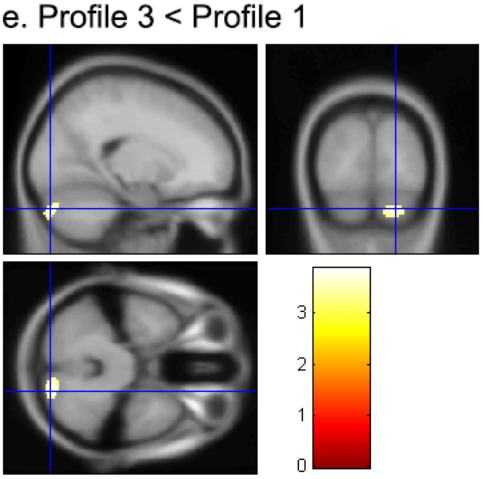


Table 1: Clinical domains and characteristics used for the Latent Class Analysis (LCA)

Clinical Domains	Clinical Characteristics	Points
Extrapyramidal domain	• "mild" extrapyramidal syndrome: UPDRS ≤ 32 [28]	1
	• "severe" extrapyramidal syndrome: UPDRS ≥ 33 [28]	2
	• cephalic or facial dystonia/dyskinesia	1
Axial domain	• freezing of gait	1
	• antecolis or camptocormia or Pisa syndrome	1
Cerebellar domain	• cerebellar syndrome	1
	• nystagmus or altered oculomotor saccades	1
Cognitive domain	• Mattis ≤ 137 [29,30]	1
	• dysexecutive syndrome with rapid frontal assessment battery (score ≤ 15) [9]	1
	• motor and ideomotor apraxia: score ≤ 18 if age ≤ 64 years and score ≤ 17 if age ≥ 65 years [10]	1
LPI domain	• stridor	1
	• swallowing symptoms	1
Survival	• longer survival than the median survival of the sample	1

LPI : laryngeal-pharyngeal involvement

Table 2: Profile distribution of the patients' characteristics. Number of subjects (%).

a. Qualitative data

	Profile 1 (n=46)	Profile 2 (n=30)	Profile 3 (n=9)	Total (n=85)	p-value
Male	20 (43.5%)	21 (70.0%)	7 (77.8%)	48 (56.5%)	**p = 0.034**
Female	26(56.5%)	9 (30.0%)	2 (22.2%)	37 (43.5%)	
Orthostatic hypotension	37 (80.4%)	26 (86.7%)	8 (88.9%)	71 (83.5%)	p = 0.76
Urinary incontinence	40 (86.9%)	24 (80.0%)	8 (88.9%)	72 (84.7%)	p = 0.75
Falls within 3 years	34 (73.9%)	18 (60.0%)	7 (77.8%)	59 (69.4%)	p = 0.38
RBD	25 (54.3%)	18 (60.0%)	6 (66.7%)	49 (57.6%)	p = 0.66
Pyramidal syndrome	15 (32.6%)	6 (20.0%)	4 (44.4%)	25 (29.4%)	p = 0.22
Myoclonus	5 (10.9%)	2 (6.67%)	0 (0%)	7 (8.2%)	p = 0.85
(S)SRI Treatment	13 (28.3%)	7 (23.3%)	3 (33.3%)	23 (27.0%)	p = 0.77
FAB score ≤ 15	12 (26.1%)	6 (20.0%)	**6 (66.7%)**	24 (41.4%)	**1 vs 3 : p = 0.02** **2 vs 3 : p< 0.01**
Motor and ideomotor apraxia score ≤ 18 (≤ 64 years-old) or ≤ 17 (≥ 65 years-old)	4 (8.7%)	2 (6.7%)	2 (22.2%)	8 (9.4%)	p = 0.36
<u>MRI features</u>					
No abnormality	18 (39.1%)	11 (36.7%)	2 (22.2%)	31 (36.5%)	p = 0.76
Cerebellar atrophy	6 (13.0%)	9 (30%)	2 (22.2%)	17 (20%)	p = 0.20
Pons atrophy	13 (28.3%)	8 (26.7%)	3 (33.3%)	24 (28.2%)	p = 0.88
Hot cross bun sign	8 (17.4%)	4 (13.3%)	3 (33.3%)	15 (17.6%)	p = 0.42
Hyperintense putaminal rim	8 (17.4%)	5 (16.7%)	0 (0%)	13 (15.3%)	p = 0.51
<u>Evolution</u>					
Technical assistance	**33 (71.3%)**	15 (50.0%)	5 (55.5%)	53 (62.3%)	**p = 0.024**
Aspiration pneumonia	17 (36.9%)	7 (23.3%)	3 (33.3%)	27 (31.7%)	p = 0.59
Gastrostomy	**10 (21.7%)**	0 (0%)	0 (0%)	10 (11.8%)	**p = 0.009**

RBD: REM-Sleep Behavior Disorder

(S)SRI: (Selective) Serotonin Reuptake Inhibitor

b. Quantitative data

	Median of the sample (inter-quartile interval or CI)		Median by profile (interquartile interval or CI)	p-value
Age at onset of the disease (years)	63 (57 - 68)	Profile 1	63 (59 – 70)	p = 0.23
		Profile 2	60.5 (56 - 65)	
		Profile 3	63 (60 – 69)	
Age at data collection and PET (years)	66 (60 – 72)	Profile 1	67.5 (62 – 72)	p = 0.23
		Profile 2	62.5 (59 – 69)	
		Profile 3	65 (64 – 71)	
Duration of disease progression at PET (years)	3 (3 – 5)	Profile 1	4 (2 - 5)	p = 0.23
		Profile 2	3 (2 – 5)	
		Profile 3	3 (2- 4)	
Hoehn & Yahr	3 (3 - 4)	Profile 1	**4 (3 – 4)**	**1 vs 2 : p< 0.001** **1 vs 3 : p = 0.027**
		Profile 2	3 (2 – 3)	
		Profile 3	3 (3 – 3)	
Schwab & England	70 (40 - 70)	Profile 1	**40 (40 – 70)**	**1 vs 2 : p< 0.001** **1 vs 3 : p = 0.03**
		Profile 2	70 (70 – 80)	
		Profile 3	70 (70 – 70)	
Survival (years)	8.0 (IC 95% 6.64 – 9.36)	Profile 1	6.5 (IC 95% 6.22 – 8.09)	p = 0.47 (Chi-square = 1.49 ; df = 2)
		Profile 2	6 (IC 95% 5.08 - 6.78)	
		Profile 3	6 (IC 95% 3.93 - 8.07)	
Mattis Dementia Rating Scale (/144)	137 (133 - 140)	Profile 1	138 (135 – 140)	**1 vs 3 : p< 0.001** **2 vs 3 : p< 0.01**
		Profile 2	139 (134 – 142)	
		Profile 3	**129.5 (126.5 – 132)**	

CI : 95% confidence interval