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Self-reported urinary impairment identifies 'fast progressors' in terms of neuronal loss in multiple system atrophy

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ABSTRACT

Introduction: MSA is an adult-onset, sporadic, progressive parkinsonian syndrome characterised by the presence of akinesia, cerebellar dysfunction, autonomic failure and pyramidal signs. Annualized-whole-brain atrophy rate (a-WBAR) is an informative way to quantify disease progression. In this longitudinal work we investigate the correlations of a-WBAR with clinical scales for motor impairment, autonomic disability and cognitive decline in MSA and explore how atrophy progresses within the brain.

Method: Fourty-one MSA patients were studied using Structural Imaging Evaluation with Normalization of Atrophy (SIENA). SIENA is an MRI-based algorithm that quantifies brain tissue volume. Clinical parameters were explored using the 18-item Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, the Hoehn and Yahr Scale, the Frontal Assessment Battery and the Natural History and Neuroprotection in Parkinson Plus Syndromes scale (sub-items for orthostatic and urinary functions).

Results: The mean (± SD) age was 60.4 years ± 7.7 and a-WBAR was 1.65% ± 0.9. Demographics and clinical ratings at the time of the first scan were non-significantly associated with a-WBAR. The only exception was the baseline urinary score with a weak but significant association ($R2 = 0.15$, $p = 0.04$). Progression of grey matter atrophy was detected in the left superior temporal gyrus, right middle frontal gyrus, right frontopolar region and midbrain.

Conclusion: Urinary impairment at baseline may help to identify 'fast progressors' in terms of neuronal loss, particularly in the frontal and temporal lobes. Thus, urinary impairment should be recognized as a key target for disease modifying therapeutic interventions in MSA.

1. Introduction

The overlapping manifestations of striatonigral degeneration, olivopontocerebellar atrophy and progressive autonomic failure (Shy-Drager syndrome) were unified in 1969 by Graham and Oppenheimer under the concept of Multiple System Atrophy (MSA) (Graham and Oppenheimer, 1969). As common pathological findings, they observed neuronal loss in the intermediolateral cell column, olivopontocerebellar pathway, putamen, substantia nigra and, to a lesser degree, in the anterior horns in the spinal cord. However, it was in 1989 that MSA was accepted as a clinical-pathological entity, with the demonstration of glial cytoplasmic inclusions (GCIs) in the white matter of these three phenotypes (Papp et al. 1989). MSA is an adult-onset, sporadic, progressive parkinsonian syndrome characterised by the presence of akinesia, cerebellar dysfunction, autonomic failure and pyramidal signs in different intensities and combinations. This disorder affects both sexes, but it is slightly more common in men (Wenning et al. 1997). It begins in middle age (~54 years (range 33–78) (Wenning et al. 1997)). The age-adjusted prevalence (over 50 years) is about 4 per 100,000 (Schrag et al. 1999). The average annual incidence (for ages 50 to 90) has been estimated as 3.0 per 100,000. It is a rapidly progressive disease, with a mean survival time of 7 years (Bower et al. 1997). To date there have not been any disease modifying treatment for MSA and clinical trials are hampered by the absence of markers for *ante-mortem* diagnosis and the lack of surrogate endpoints (Politis 2014).

Autonomic insufficiency usually precedes the motor symptoms in MSA, with unexplained onset of urinary incontinence, frequency, urgency and incomplete bladder empting. As much as 18% of the MSA patients had urinary dysfunction as the sole initial clinical feature (Sakakibara et al. 2018). The mean interval from the onset of bladder dysfunction to the onset of motor symptoms has been reported 2.8 years (range 1–7) (Sakakibara et al. 2018). As a striking prognostic factor, the presence of autonomic dysfunction within the first 3 years from the disease onset is associated with a more rapid progression to death

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(Watanabe et al. 2002). Japanese authors have described cases with autonomic dysfunction predominating over cerebellar and parkinsonian features, suggesting a MSA-A (autonomic type) (Horimoto et al. 2002).

Whole-brain atrophy rates from magnetic resonance imaging (MRI) data is an informative way to quantify neuronal loss. In the present study, we used structural image evaluation, using normalization, of atrophy (SIENA) (Smith et al. 2004) to explore annualized whole-brain atrophy rates (a-WBAR) in MSA. This avenue has been extensively explored in Alzheimer disease (Fox and Freeborough, 1997; Schott et al. 2005) and also in other degenerative dementias such as frontotemporal dementia (Gordon et al. 2010) and Huntington disease (Hobbs et al. 2010). For normal aging, the a-WBAR has been estimated to be below 0.5% (Sluimer et al. 2008). For MSA a-WBAR has been estimated to be above 1% (Paviour et al. 2007). The clinical and pathological aggressiveness of MSA are likely to be due to the degeneration of specific brain pathways and/or grey matter structures. In this regard, SIENA may give insight in how atrophy progresses within the brain, by providing a voxelwise output for specific white matter tracts and grey matter nuclei and gyri.

In this work we investigate the correlations of a-WBAR with clinical scales for motor impairment, autonomic disability and cognitive decline and perform a longitudinal voxelwise testing of atrophy in MSA. We aimed to assess prognostic factors of rapid whole brain atrophy and therefore of rapid disease progression in MSA.

2. Materials and methods

2.1. Subjects and clinical assessment

Fourty-one MSA patients were recruited from the Movement Disorders Clinic at the Hospital San Juan de Dios, Santiago, Chile. Internationally established operational criteria were used to assess the diagnoses of MSA (Gilman et al. 2008). Thirty-five probable MSA patients were categorized as MSA-P (predominant Parkinsonian features) and six as MSA-C (predominant cerebellar features). All participants were assessed on their usual dopaminergic medication. The patients' demographics and clinical variables are presented in Table 1.

Clinical parameters were explored using the 18-item Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor symptoms (UPDRS III) (Goetz et al. 2007), the Hoehn and Yahr Scale (H&Y) (Hoehn and Yahr, 2001), executive function was assessed using the Frontal Assessment Battery (FAB) (Dubois et al. 2000) and the Natural History and Neuroprotection in Parkinson Plus Syndromes scale (NNIPPS scale) (Payan et al. 2011) sub-items for self-reported orthostatic and urinary functions (Table 2). At baseline, the mean supine blood pressures were 127/85 mm Hg, falling to 109/80 mm Hg at 2 min of quiet standing. Corresponding mean pulse rates were 72 bpm supine and 70 bpm after standing. Supine and standing systolic blood pressures were different ($p < 0.01$).

Table 1
Baseline demographics, clinical features and a-WBAR.

	Baseline (Mean ± SD plus range)	Annualized change (Mean ± SD plus range)
Age (years) Mean ± SD	60.4 ± 7.7	
Gender (M:F)	32:9	
Disease duration (years) Mean ± SD	4.3 ± 2.3	
a-WBAR[a] (Mean ± SD plus 95% confident interval)		1.65% ± 0.9 (1.3–1.9)
UPDRS III[b]	36.1 ± 18 (10–67)	6.1 ± 6.9* (3.9- 8.6)
H &Y[c]	3.0 ± 0.9 (1.0–5.0)	0.4 ± 0.4* (0.28–0.6)
FAB[d]	14.0 ± 3.3 (4–18)	−0.6 ± 2.08* (−1 to 0.17)
Orthostatic score	2.63 ± 4.1	0.67 ± 1.5
Urinary score	0.7 ± 4.4	0.2 ± 0.9
Urinary score	3.47 ± 2.1	0.21 ± 0.72

[a] a-WBAR: annual whole-brain atrophy rate.
[b] UPDRS III: Unified Parkinson's Disease Rating Scale Part III.
[c] H&Y: Hoehn &Yahr Scale.
[d] FAB: Frontal Assessment Battery.
* Difference between baseline and repeat score with a p value < 0.05 (Wilcoxon's signed rank test).

2.2. MRI acquisition

Between 2012 and 2016, patients underwent an MRI brain scan. MRI images were acquired on a 3.0 T Philips Medical System. Axial T1-weighted images of the whole brain were obtained using a 3D inversion recovery prepared spoiled gradient echo (IR- SPGR) sequence. The following parameters were used: repetition time of 8.1 ms; echo time of 3.7 ms; inversion time of 450 ms; voxel size of 0.699 × 0.699 × 1 mm; excitation flip angle of 8°; matrix size of 248 × 226; field of view of 24 cm; and 198 axial slice of 1 mm. An experienced neuroradiologist assessed the MRI scans of every patient to rule out gross anatomical abnormalities. Patients underwent a second MRI brain scan at the time of the last study visit (12 months after the baseline scan). Subjects were included in the study if they had two MRI scans of adequate quality and the brain extraction step in SIENA functioned correctly. None of the MRI images included in this study showed any structural abnormalities other than atrophy- related changes. These inclusion criteria were assessed by a visual inspection of the raw and processed data for each patient scan. For both the baseline and follow-up assessments, the clinical data and MRI scans were acquired within 1 week of each other. The mean scan interval was 1.04 ± 0.07 years.

2.3. Data analysis

All of the images were converted in NIFTI format using MRIcron software (http://people.cas.sc.edu/rorden/mricron/dcm2nii.html) in preparation for processing using SIENA. SIENA has been shown to have 0.5% brain volume accuracy in longitudinal studies (Smith et al. 2001). Before further processing, all of the data were anonymized by removing any reference to the patients' names from the image headers and ensuring that the file names were based on a unique ID rather than any of the patients' personal details, including their clinical group. The SIENA processing algorithm has been validated and described in detail elsewhere (Smith et al. 2001). Briefly, the processing stages are as follows: (1) Brain extraction (BET): segmentation of the brain from non-brain tissue for each scan, followed by skull extraction. (2) Registration: the segmented brain from the second (follow-up) scan is registered to that of the first (baseline) using a linear transformation. The two skull images are used as normalizing factors to constrain the scale and skew. (3) Tissue type segmentation: white matter and grey matter tissues are treated as one tissue and the cerebrospinal fluid (CSF) as another. (4) Change analysis: detection of the brain edges on both registered brain images and then estimation of the motion of the brain surface edges. The direction of movement from the first image to second image indicates whether atrophy or growth has occurred. Finally, the percentage of global brain volume change is obtained for each subject from the mean of all of the edge point motions.

Prior to voxelwise statistical analysis, mean displacement images were produced for each participant, dilated, and then registered to a normalised space (Bartsch et al. 2007). To make interpretation easier, Tailarach coordinates for each cluster were derived from the Montreal Neurological Institute (MNI) space coordinates (Chau and McIntosh, 2005) and these were used when describing cluster locations. A one-sample t-test was performed to test the areas where significant displacement of brain tissue occurred. Those areas with a significant

Table 2
NNIPPS scores for orthostatic and urinary symptoms.

Orthostatic symptoms	Urinary symptoms
1. In the past 12 months: History of faintness or dizziness soon after standing-up from a sitting or lying position 0 No 1 Yes IF YES COMPLETE THE FOLLOWING	**1. In the past 12 months did the patient ever leak urine or lose control of bladder function?** 0 None or few drops less than once daily. 1 A few drops staining clothes daily. 2 Large amounts, but only when asleep, no pad required during day. 3 Occasional large amounts in daytime: pad required. 4 Consistent, requiring diaper or catheter awake and asleep.
1. How frequent did the patient get these symptoms? 1 Rarely, once a week or less. 2 Occasionally, several times a week. 3 Frequently, at least once a day. 4 Almost always, several times a day	**2. In the past 12 months did the patient experience difficulties passing urine?** 0 Never. 1 Occasionally. 2 Frequently. 3 Constantly or catheter in site.
2. How does the patient rate the severity of these symptoms? 1 Mild. 2 Moderate. 3 Severe.	**3. In the past 12 months did the patient ever experience trouble completely emptying bladder?** 0 Never. 1 Occasionally. 2 Frequently. 3 Constantly or catheter in site.
3. For how long did the patient experience these symptoms? 1 < 3 months. 2 From 3 to 6 months. 3 From 7 to 12 months. 4 From 13 months to 5 years. 5 > 5 years. 6 As long as patient can remember.	
4. In the past 12 months, how often did the patient end-up fainting soon after standing-up 0 Never. 1 Once. 2 Twice. 3 Three times. 4 Four times.	

uncorrected *p*-value containing > 30 voxels per cluster were considered as a reliable measurement of atrophy and are reported.

2.4. Statistical analyses

Statistical analyses of the clinical data and clinical-imaging correlations were performed using the Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA, version 22). The results are presented as the mean ± SD. In all cases, a two-sided $p < 0.05$ was considered significant. Visual inspection of the data using histograms and QQ-plots was performed to test for violations of the assumption of a normal distribution. Levene's test of equal variances was used to verify the assumption of the homogeneity of variances. Because of these verifications, parametric and non-parametric statistical tests were used. The a-WBAR was calculated by dividing the WBAR values by the interscan interval in years. Clinical scores were also annualized by dividing the unit change between the assessments by years. Difference between baseline and repeat score were assessed using the Wilcoxon's signed rank test. The associations between annualized whole-brain atrophy rates and annualized changes in clinical scores were assessed using bivariate correlations. Linear regression analysis was used to assess the effect of baseline clinical scores on the MRI-derived measure.

2.5. Standard protocol approval, registrations and patient consent

Prior to inclusion, patients gave their informed written consent to participate in the study. The study was conducted according to International Standards of Good Clinical Practice (ICH guidelines and the Declaration of Helsinki). The project was approved by the local Research Ethics Committees of San Juan de Dios Hospital, Santiago.

3. Results

3.1. Demographics, clinical variables, and a-WBAR (Table 1)

The mean age was 60.4 years ± 7.7, disease duration 4.3 years ± 2.3 and a-WBAR 1.65% ± 0.9. The patients showed significant deterioration over the follow-up period on a range of clinical measures, but not on the orthostatic and urinary functions.

Demographics and clinical ratings at the time of the first scan were non-significantly associated with a-WBAR. The only exception was the baseline urinary score with a weak but significant association ($R2 = 0.15$, $p = 0.04$). No significant correlations were found between a-WBAR and annualized clinical assessments.

Progression of grey matter atrophy was detected in the left superior temporal gyrus (0.20 mm), right middle frontal gyrus (0.13 mm), and right frontopolar region (0.21 mm). White matter atrophy progression was seen in the midbrain (0.18 mm) (Table 3, Fig. 1).

3.2. Discussion

There is a need to characterise disease progression in MSA in order to fully understand their pathogenesis and to test the effectiveness of disease-modifying interventions. In this disorder, the *tempo* and magnitude (throughout the entire brain and the rest of nervous system) of neuronal death is unclear and the factors that influence disease progression are poorly understood. In this work, only baseline urinary score was associated with a-WBAR in MSA. The relationship between autonomic failure and shorter survival in MSA may depend upon different causes. Dysautonomic features frequently become a major clinical issue in the progression of the disease, triggering multiple medical complications and potentially life-threatening conditions. For example, urinary retention with large post-voiding residual volumes, typically increasing the risk of urinary tract infections and eventually of

Table 3
Progression of brain atrophy in MSA.

Tailarach coordinates			Anatomical area	Edge movement (mm)	Cluster level analysis	
x	*y*	*z*	Grey matter		Voxels (*n*)	*p* values
−69	−23	7	Superior temporal gyrus (BA 42)	0.20	50	0.021
38	55	16	Superior frontal gyrus (BA 10)	0.13	30	0.064
57	12	36	Middle frontal gyrus (BA 9)	0.21	84	0.004

Tailarach coordinates			Anatomical area	Edge movement (mm)	Cluster level analysis	
x	*y*	*z*	White matter		Voxels (*n*)	*p* values
2	−14	−9	Midbrain	0.18	40	0.036

uroseptic complications (Sakakibara et al. 2018). Early development of autonomic failure may reflect a more aggressive underlying CGI pathology and neuronal loss. In MSA-P neuronal loss is more severe within the striatonigral pathways (Wenning et al. 1997) with the putamen and substantia nigra being the most affected structures, whereas in MSA-C the middle cerebellar peduncles and pons are the most affected. However, clinical and pathological aggressiveness of MSA may be due to degeneration of the autonomic nervous system in the pons including the dorsal nucleus of the vagus and nucleus ambiguus (Benarroch et al. 2006), medullary serotonergic neurons(Benarroch et al. 2004), the locus ceruleus (Wenning et al. 1997), periaqueductal grey matter (Benarroch et al. 2010). Further involved areas are the Edinger-Westphal nucleus and posterior hypothalamus (Nakamura et al. 1996). At lower levels of the autonomic system lesions have been observed in sympathetic neurons in the intermediolateral column of thoracolumbar spinal cord (Wenning et al. 1997). In the sacral spinal cord, degeneration of the Onuf's nucleus may be particularly influential in the early disease process and drive early voiding dysfunction (Coon et al. 2018; Sakakibara et al. 2018).

It is plausible that a main contribution for whole brain atrophy occurs in lobar and subcortical structures in MSA with an important involvement of the autonomic nervous system. In the present report, progression of atrophy in the prefrontal cortex and superior temporal gyrus may reflect that these areas are involved in the control of the urinary bladder. Such a neuronal loss is not considered to be typical in MSA. However, Papp and Lantos described high densities of glial cytoplasmic inclusions in the supplementary and primary motor cortical areas and subjacent white matter and moderate densities of glial cytoplasmic inclusions in the premotor area, cingulate motor area, and corpus callosum in MSA (Papp et al. 1989). In a review of 203 proven

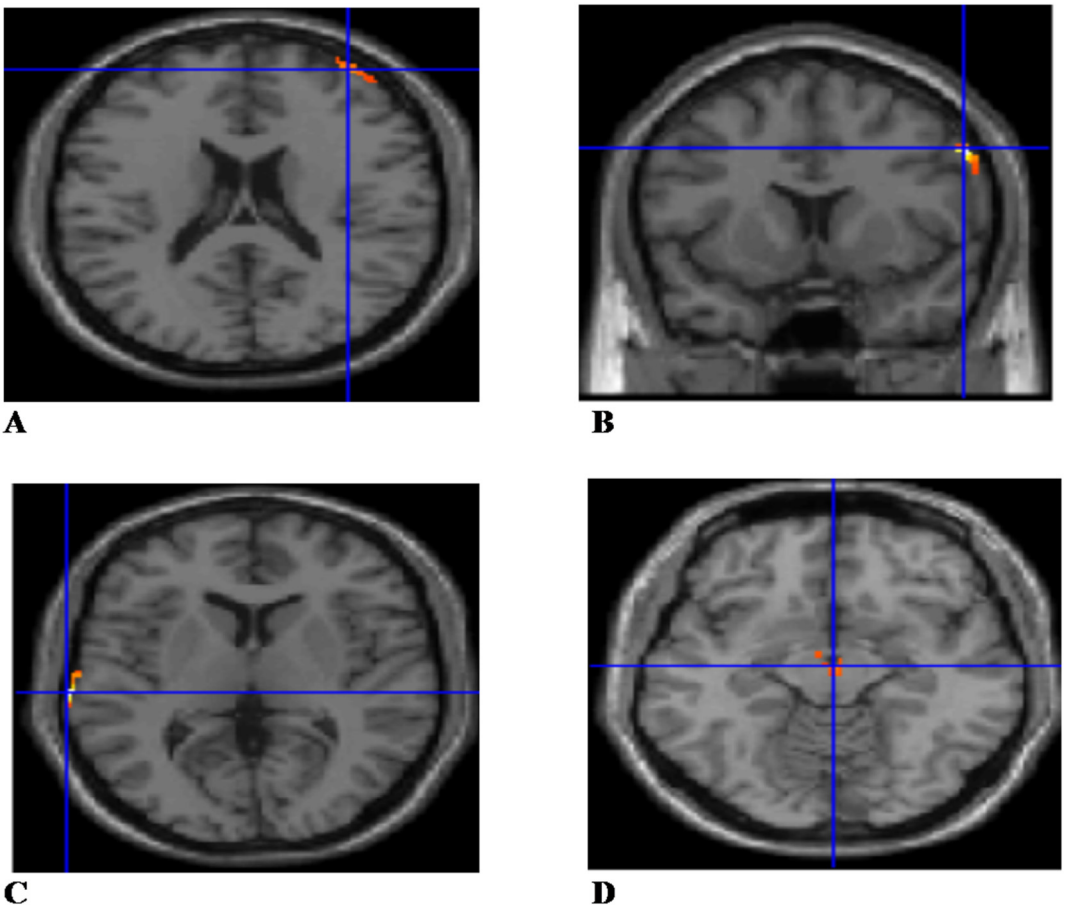

Fig. 1. Areas of progression of brain atrophy in MSA. A. Right frontopolar area. B. Right middle frontal gyrus. C. Left superior temporal gyrus. D. Right midbrain.

MSA cases, some degree of cortical atrophy was observed in 21% of cases (Wenning et al. 1997), and *post mortem* examinations showed severe frontal atrophy (Inoue et al. 1997; Wakabayashi et al. 1998). *In vivo* data in MSA showed hypometabolism in motor, premotor, and prefrontal cortices and parietal lobes (Kawai et al. 2008). A proton magnetic resonance spectroscopy study showed a significant reduction of *N*-acetylaspartate/creatine in the frontal cortex (Abe et al. 2000). Voxel-based morphometry studies have suggested that atrophy in the motor and prefrontal cortices is a common finding in MSA (Brenneis et al. 2003).

The effects of neurological lesions of the frontal lobe on detrusor function is known; patients with lesion of the anteroinferior portion of prefrontal area exhibit an unsuppressible detrusor reflex contraction on bladder filling, known as detrusor hiperreflexia (Bates et al. 1979). In line with our results, functional magnetic resonance imaging has identified clusters of brain activity in the parahippocampal gyrus, anterior cingulate gyrus, inferior temporal gyrus and inferior frontal gyrus during micturition (Krhut et al. 2012; Nardos et al. 2014; Nishijima et al. 2012).

We report the absence of significant correlations between atrophy rates and changes in clinical scales, including the orthostatic and urinary scores. To date, clinical scales assessing a range of symptoms and signs have largely been used to measure disease progression in therapeutic trials. However, a number of inherent limitations make them insufficient for tracking disease progression (Wild and Fox, 2009). Although reliability is adequate for many uses, they are not always ideal for clinical trials and routine use. They may show non-linearity, floor and ceiling effects, inability to differentiate symptomatic from disease modification changes, along with the influences of other co-occurring illness, behavioural fluctuations and the effect of medication.

Furthermore, the scales we report here do not fully assess the wide range of autonomic failures in MSA. A limitation of this study is the lack of quantitative evaluation of the autonomic failure. We only used NNIPPS items for assessing orthostatic hypotension and urinary functions. These items may be among the simplest ways for assessing autonomic function of both sexes in the routine clinical practice. However, quantitative laboratory approaches tend to reduce operator dependence and offer more objectivity when using numerical terms to reflect pathological processes, beyond the inherent limitations of clinical scales. In the future, it would therefore be beneficial to use residual urine volume estimation for performing correlations with MRI-derived data. Thus, cistometry may highlight stronger associations between brain atrophy rates with autonomic dysfunction of the urinary bladder.

According to the diagnostic criteria for probable and possible MSA used in this work, the diagnosis of orthostatic hypotension is made with different ranges of symptomatic falls in the systolic and diastolic blood pressures. Because of the varying criteria for the diagnosis of orthostatic hypotension, we did not perform correlations with blood pressure values. However, more specific assessments such as continuous non-invasive of blood pressure and heart rate during tilt table testing may provide more objective data for diagnostic and research purposes.

3.3. Conclusion

For disease-modifying trial, one challenge is to find biomarkers that accurately identify aggressive MSA early in the disease course. Urinary impairment at baseline as an expression of autonomic dysfunction may help to select ‘fast progressors’ in terms of neuronal loss. This subset of patients may be considered as one of poor outcome and ideally tailored disease modifying agents should be tested on them and urinary impairment should be recognized as a key target for therapeutic intervention in MSA.

Disclosures

Carlos Guevara reports no disclosures.

José de Grazia reports no disclosures.

Pablo Baabor reports no disclosures.

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