Journal of the Neurological Sciences 390 (2018) 227–230

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Multimodal neuroimaging analysis in patients with *SYNE1* Ataxia

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ARTICLE INFO

Keywords:
SYNE1
Recessive ataxia
Neuroimaging
Gray matter
Cerebellum

ABSTRACT

Background: The gene *SYNE1* is highly expressed in the cerebellum and its dysfunction is related to an autosomal recessive ataxia (*SYNE1*-ataxia). The disease was firstly considered a pure cerebellar ataxia however, recent studies have described a broader clinical presentation, including motor neuron disease symptoms.
Objectives: To investigate cerebellar and potential extra-cerebellar changes in *SYNE1*-ataxia using multimodal neuroimaging analyses.
Methods: Six patients completed clinical and imaging exams, and were compared to age-gender-matched healthy controls. Gray matter was analyzed using FreeSurfer and CERES for brain and cerebellum, respectively. White matter was analyzed with DTI-TBSS while we used SpineSeg for spinal cord analysis.
Results: We found significantly reduced cortical thickness ($p < 0.05$, *FDR*-corrected) in primary and association cortices, and volume reduction in subcortical structures, brainstem and cerebellum. White matter was found disrupted in both brain and cerebellum ($p < 0.05$, *FWE*-corrected). These results are consistent with the expression of the *SYNE1* mRNA and its encoded protein in the brain. We failed to demonstrate spinal cord changes.
Conclusions: *SYNE1*-ataxia is, therefore, a relatively common cause of recessive ataxia characterized by complex multisystemic neurostructural changes consistent with the phenotypic heterogeneity and neuroimaging configures a potential marker of the disease.

1. Introduction

The autosomal recessive cerebellar ataxia caused by *SYNE1* mutations was firstly described in French-Canadian population as a late onset pure cerebellar syndrome with retained reflexes [1]. This gene encodes a protein expressed predominantly in neurons of the cerebellum and brainstem [1]. Recently, other studies have demonstrated that *SYNE1*-ataxia may present with a more complex phenotype, with variable degrees of extracerebellar symptoms [2–6], possibly underlying a multisystemic neurodegenerative disease [2,3].

Despite that, few neuroimaging studies have evaluated *SYNE1*-ataxia. Conventional magnetic resonance imaging (MRI) usually shows marked cerebellar atrophy [2,4], and brainstem atrophy was reported in at least one patient [6]. A PET-scan study performed in two patients demonstrated ^{18}F-fluorodeoxyglucose uptake reduction in both cerebral hemispheres and one of them had pontine brainstem affected [4]. Two Saudi brothers with *SYNE1* mutations were reported with classical multiple sclerosis-like images [5].

The aim of this study is to perform an exploratory multimodal neuroimaging evaluation of *SYNE1*-ataxia patients in order to characterize cerebellar, cerebral and spinal cord damage.

2. Methods

We evaluated six patients with genetically confirmed *SYNE1*-ataxia followed at the Federal University of São Paulo. We included clinical, demographic, neurophysiological and imaging details in Table 1. Ataxia severity was estimated using the Brazilian validated scale for the assessment and rating of ataxia (SARA). Mean age and disease duration were 43.3 ± 11 and 10.2 ± 2.6 years, respectively.

The first clinical manifestation in five of the six patients was unsteady gait, while the other patient first presented with writer's cramp. All patients developed dysarthria, two of the six patients developed nystagmus and one had ophthalmoparesis. One patient had normal reflexes, while four had brisk reflexes. One had signs of upper and lower motor neuron dysfunction and cognitive decline.

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https://doi.org/10.1016/j.jns.2018.05.003
Received 15 January 2018; Received in revised form 17 April 2018; Accepted 3 May 2018
Available online 04 May 2018
0022-510X/

Table 1
Clinical and genetic evaluation of the patients with SYNE1 ataxia (n = 6).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	F	M	M	M	F	F
Age (years)	26	51	28	53	45	51
Age at onset (years)	16	36	23	24	37	42
Pattern of ataxia	AA, AP	AA > AP	AA, AP	AA > AP	AA > AP	AA
DTR	4+/4+	2+/4+	2+/4+	3+/4+	3+/4+	3+/4+
Pyramidal signs	Present	Absent	Absent	Present	Absent	Absent
Spasticity	Present	Absent	Absent	Absent	Absent	Absent
Speech disturbance	Dysarthria	Dysarthria	Dysarthria	Dysarthria	Dysarthria	Dysarthria
Oculomotor abnormalities	Slow saccade	Absent	Nystagmus	Nystagmus	Absent	Absent
Other symptoms	Absent	Absent	Absent	Absent	Dystonia	Dystonia
SARA	34	5	8	12,5	10	8
ICARS	64.5	18	23.5	34	28	17
Consanguinity	Absent	Absent	Absent	Absent	Absent	Absent
SYNE1 variant	c.21889A > T	c.12780G > A	c.16667G > A	c13021_13022delGT	c.12780G > A	c.12780G > A
Neuroimaging	CA	CA	CA	CA	CA	CA
EMG	Lower MND	Normal	Normal	Normal	Normal	Normal

AA: axial ataxia; AP: appendicular ataxia; DTR: deep tendon reflexes; CA: cerebellar atrophy; MND: lower motor neuron disease.

All patients provided written informed consent and local ethics committee approved this study.

2.1. Image acquisition

Six patients as well as six age-gender matched healthy controls underwent MRI on a 3T Phillips Achieva Scanner. Routine T2-weighted images were obtained and examined by an experienced neuroradiologist to exclude unrelated abnormalities. For FreeSurfer, CERES and SpineSeg analyses, we used high-resolution T1 volumetric images of the brain with sagittal orientation, voxel matrix 240 × 240 × 180, voxel size 1 × 1 × 1 mm^3, TR/TE 7/3.201 ms, and flip angle of 8°.

For TBSS analyses, we used a spin echo DTI sequence: 2 × 2 × 2 mm^3 acquiring voxel size, interpolated to 1 × 1 × 2 mm^3; reconstructed matrix 256 × 256; 70 slices; TE/TR 61/8500 ms; flip angle 90°; 32 gradient directions; no averages; max b-factor = 1000 s/mm^2; 6 min scan.

2.2. Image processing

2.2.1. Gray matter (GM)

Brain Gray Matter (GM) was evaluated using FreeSurfer v5.3, which estimates cortical thickness by surface-based analysis and performs volumetric segmentation in subcortical structures, both in native spaces [7]. The volume of subcortical structures was measured together with the estimated intracranial volume (eTIV).

Cerebellar GM was determined by CERES (CEREbellum Segmentation), an automated multiatlas segmentation tool that combines multiple reference atlas segmentations to create a new one that anatomically fits the target case [8]. The software provides volume and thickness of each cerebellar lobule in the subject's native space.

2.2.2. White matter (WM)

The WM of both supra and infratentorial structures was analyzed through tract-based spatial statistics (TBSS) which consists in a voxelwise analysis of diffusion tensor imaging (DTI) [9]. Fractional anisotropy (FA) of all white matter bundles is estimated for every patient and a group mean FA skeleton is built. Thereafter, the FA image of each patient is perpendicularly projected, voxel-to-voxel, onto the FA skeleton to find the maximum FA value. Other diffusion parameters as mean diffusivity (MD), radial diffusivity (RD) and axonal diffusivity (AD) are also estimated upon the FA skeleton. Finally, voxelwise statistics for each parameter on the skeleton space are carried out across all patients.

2.2.3. Spinal cord

Measures of spinal cord area and eccentricity (ECC) were obtained with SpineSeg, a semi-automatic segmentation and measurement tool [10]. We determined three consecutive slices at the mid-section of the intervertebral disc between C2 and C3 to insert seeds. For each of these levels an ellipse was fitted at the border points of the segmented spinal cord, so the mean area and ECC were obtained for each subject [11].

2.2.4. Statistical analysis

Statistical analyses were performed using Partek® Genomics Suite® software v6.6 [12]. Patients were compared with healthy controls using Mann-Whitney U test. All analyses took age and gender as covariates, whereas volumetric analyses were also adjusted for eTIV. False discovery rate (FDR) was used to correct for multiple comparisons.

In TBSS, a voxelwise analysis of the diffusion parameters is automatically done as a part of the algorithm. Threshold-Free Cluster Enhancement (TFCE) and family-wise error correction were employed for multiple comparisons correction.

We employed the Spearman's test to assess correlations between cerebellar morphometry and ataxia severity (SARA score).

For all analyses, the level of significance was set as alpha = 0.05.

3. Results

FreeSurfer demonstrated significant reduction of cortical thickness in primary and association cortices as well as symmetric volumetric reduction in diencephalon, basal ganglia and brainstem (Fig. 1). Cerebellar GM showed widespread atrophy affecting all the lobules bilaterally.

Regarding WM, there was FA reduction extending predominantly from the right precentral cortex to the internal capsule, mesencephalon and the cerebellum bilaterally. Mean diffusivity (MD) was increased in patients in a similar pattern. Axial diffusivity (AD) and radial diffusivity (RD) were also higher in patients, but while the first was altered solely in the cerebellum, the second was diffusely augmented predominantly at right hemisphere (Fig. 2).

SpineSeg demonstrated group differences in spinal cord area (mean area: patients = 59.1, controls = 65.8), however it did not reach statistical significance. We also failed to identify correlations between cerebellar volumetry and ataxia severity.

4. Discussion

SYNE1-ataxia has been recently associated with a broad range of clinical features, although cerebellar symptomatology still remains the major component of the disease. FANTOM5 and GTEx datasets have