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Autosomal dominant cerebellar ataxias: Imaging biomarkers with high effect sizes

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ABSTRACT

Objective: As gene-based therapies may soon arise for patients with spinocerebellar ataxia (SCA), there is a critical need to identify biomarkers of disease progression with effect sizes greater than clinical scores, enabling trials with smaller sample sizes.

Methods: We enrolled a unique cohort of patients with SCA1 (n = 15), SCA2 (n = 12), SCA3 (n = 20) and SCA7 (n = 10) and 24 healthy controls of similar age, sex and body mass index. We collected longitudinal clinical and imaging data at baseline and follow-up (mean interval of 24 months). We performed both manual and automated volumetric analyses. Diffusion tensor imaging (DTI) and a novel tractography method, called fixel-based analysis (FBA), were assessed at follow-up. Effect sizes were calculated for clinical scores and imaging parameters.

Results: Clinical scores worsened as atrophy increased over time ($p < 0.05$). However, atrophy of cerebellum and pons showed very large effect sizes (> 1.2) compared to clinical scores (< 0.8). FBA, applied for the first time to SCA, was sensitive to microstructural cross-sectional differences that were not captured by conventional DTI metrics, especially in the less studied SCA7 group. FBA also showed larger effect sizes than DTI metrics.

Conclusion: This study showed that volumetry outperformed clinical scores to measure disease progression in SCA1, SCA2, SCA3 and SCA7. Therefore, we advocate the use of volumetric biomarkers in therapeutic trials of autosomal dominant ataxias. In addition, FBA showed larger effect size than DTI to detect cross-sectional microstructural alterations in patients relative to controls.

1. Introduction

Spinocerebellar ataxias types 1 (SCA1), 2 (SCA2), 3 (SCA3) and 7 (SCA7) are rare autosomal dominant ataxias caused by expanded CAG triplet repeats (Durr, 2010; Rüb et al., 2013). Among the dominantly inherited SCA, SCA7 presents additional non-neurological symptoms such as retinal degeneration and cardiomyopathy, commonly found in patients with mitochondrial dysfunction. Currently, the most common clinical scores for rating the disease severity are the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006) and the Composite Cerebellar Functional Severity Score (CCFS) (du Montcel et al., 2008). However, they cannot be used to evaluate pre-manifest individuals and their small effect size would require large numbers of patients in clinical trials, which is an issue due to the scarcity of SCA. As gene-based therapies are showing promise in preventing or reversing SCA pathophysiology (Keiser et al., 2015; 2016), there is a need for biomarkers with effect sizes greater than clinical scores, which can be used in trials on small sample sizes.

Abbreviations: CCFS, composite cerebellar functional severity score; CFE, connectivity-based fixel enhancement; CSD, constrained spherical deconvolution; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; FBA, fixel-based analysis; FC, fiber cross-section; FD, fiber density; FDC, fiber density and cross-section; FOD, fiber orientation distribution; FOV, Field of view; GRAPPA, generalized autocalibrating partial parallel acquisition; MPRAGE, magnetization-prepared rapid gradient-echo; MRI, magnetic resonance imaging; RD, radial diffusivity; SARA, scale for the assessment and rating of ataxia; SCA, spinocerebellar ataxias; SNR, signal-to-noise ratio; TBSS, tract-based spatial statistics; TE, echo time; TR, repetition time

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In Huntington disease, another trinucleotide repeat disorder, magnetic resonance imaging (MRI) techniques have been shown to be more sensitive than motor or cognitive tasks to track disease progression (Tabrizi et al., 2013). In SCA, longitudinal volumetric studies that measure the rate of atrophy and evaluate the effect size are not that numerous (Durr, 2010; Alcauter et al., 2011; D'Abreu et al., 2012; Jacobi et al., 2013; Reetz et al., 2013; Rüb et al., 2013; Mascalchi et al., 2014; Hara et al., 2016; Moriarty et al., 2016). One main study that sought to address this issue in a cohort of patients with SCA1, SCA3 and SCA6, reported on longitudinal volume loss using a 1.5 T MRI system, and the effect sizes of clinical and imaging parameters (Reetz et al., 2013). Here, we report on patients with SCA1 and SCA3, but using a 3 T MRI system, as well as in patients with SCA2 and SCA7. The primary aim of this study was to identify robust and reliable imaging biomarkers of disease progression with very large effective sizes (relative to baseline) that can be used in upcoming multicentric clinical trials in SCA. Furthermore, most studies on microstructural changes in SCA (Della Nave et al., 2004; Guerrini et al., 2004; Prakash et al., 2009; Alcauter et al., 2011; Guimarães et al., 2013; Kang et al., 2014; Hernandez-Castillo et al., 2015; Mascalchi et al., 2015; Rozenfeld et al., 2015; Yoo and Oh, 2017) reported only diffusion metrics such as fractional anisotropy (FA) that is unable to properly evaluate fiber density, particularly in brain areas with multiple fiber populations. Hence, our secondary objective was to evaluate the ability of a novel tractography technique to measure brain microstructural alterations in SCA (relative to controls) with a larger effect size than conventional methods.

2. Methods

The local ethics committee (AOM10094, CPP Ile de France VI, Ref: 105–10) approved the study. All participants were over 18 years and signed a written informed consent before they participated in the study.

2.1. Recruitment of participants

Participants were recruited as part of the BIOSCA study (NCT01470729) (Garali et al., 2017) and only those who could perform MRI and complete the follow-up imaging protocol are reported: 15 patients with SCA1, 12 patients with SCA2, 20 patients with SCA3 and 10 patients with SCA7. Twenty-four healthy individuals of similar general characteristics – median age, sex and BMI – were also enrolled (Table 1). The general characteristics of patients and controls were matched to reduce the problems of confounding factors. Subjects were excluded from the study if they were < 18 years, were unable to perform MRI, had history of significant head injury, could not complete the study protocol or unable to comprehend an informed explanation of the study protocol. Ataxia severity was evaluated with the SARA score, which ranges from 0 (no cerebellar symptoms) to 40 (most severe cerebellar symptoms) (Schmitz-Hübsch et al., 2006), and the CCFS, a composite score obtained from a nine-hole pegboard test and a click test (du Montcel et al., 2008).

2.2. Imaging protocol

MRI acquisitions were performed on a 3 T whole-body Siemens MAGNETOM Trio scanner (Siemens Medical Solutions, Erlangen, Germany) using a standard Siemens transmit body coil and 32-channel receive head coil array. The MRI system was upgraded during the study period and hence twelve datasets were acquired on a 3 T whole-body Siemens MAGNETOM Prisma scanner (Siemens Medical Solutions, Erlangen, Germany). Several phantom and volunteer scans were performed after the change to ensure that there was no difference in the data obtained on the new system. A 3D *T1*-weighted magnetization-prepared rapid gradient-echo (MPRAGE) volumetric image (T_R = 2530 ms, T_E = 3.65 ms, T_I = 900 ms, flip angle = 9°, voxel size = 1 mm isotropic, field of view (FOV) = 256 × 256 mm^2) was acquired at baseline and follow-up for volumetric analyses. Images were inspected immediately after acquisition and those with motion artifacts were reacquired immediately. Additionally, a *T2*-weighted sagittal image (T_R = 4200 ms, T_E = 80 ms, flip angle = 120°, voxel size = 0.6 × 0.5 × 5.0 mm, FOV = 240 × 240 mm^2) was acquired for each subject. The *T2*-weighted images were not included in volumetric analyses but were reviewed by a neurologist to rule out incidental brain abnormalities that could interfere with results.

Due to method development, diffusion imaging was only performed at follow-up. Diffusion data were acquired along 60 isotropic directions with echo-planar spin-echo sequence (T_R = 10,000 ms, T_E = 89 ms, voxel size = 2 mm isotropic, FOV = 220 × 220 mm^2, GRAPPA acceleration factor of 2, *b* value = 1500 s/mm^2). The directions were interleaved with five non-diffusion-weighted reference images (b0 images, *b* value = 0 s/mm^2) at every 12 directions. Another b0 image with opposite phase-encode blip was acquired. The data were corrected for motion, eddy current geometric distortions, and susceptibility-induced off-resonance field distortions.

Table 1
Demographic parameters of controls and patients with SCA.

Variable	Control	SCA1	SCA2	SCA3	SCA7
# Participants	24	15	12	20	10
Sex (M/F)	11/13	9/6	7/5	8/12	5/5
Age (yr)	50 ± 13 [26–67]	43 ± 15 [18–66]	45 ± 13 [24–59]	51 ± 12 [31–69]	48 ± 14 [23–76]
Follow-up (months)	24.3 ± 1.8 [23 − 30]	24.7 ± 2.3 [22–29]	23.6 ± 0.7 [23–25]	24.5 ± 2.1 [23–30]	23.7 ± 0.9 [23–26]
BMI (Kg/m^2)[a]	25.3 ± 3.9 [20.0–33.9]	23.6 ± 6.3 [18.2–42.8]	25.7 ± 4.6 [19.4–37.3]	23.7 ± 4.5 [15.4–38.7]	22.1 ± 1.8 [19.5–25.3]
BMI (Kg/m^2)[b]	25.3 ± 3.6 [19.7–33.6]	23.6 ± 6.7 [17.0–43.6]	26.6 ± 4.4 [21.7–38.2]	24.1 ± 4.8 [15.7–40.7]	22.7 ± 2.6 [17.7–26.1]
SARA score[a]	0.8 ± 0.8 [0.0–3.0]	10.7 ± 6.3† [0.5–23.5]	12.6 ± 6.0† [3.0–22.0]	13.0 ± 7.2† [0.0–24.5]	8.3 ± 7.4† [0.0–21.5]
SARA score[b]	0.7 ± 0.7 [0.0–2.0]	13.2 ± 7.0† [1.5–24.5]	14.4 ± 6.3† [5.0–29.0]	15.2 ± 7.5† [1.0–28.0]	9.5 ± 8.3† [0.0–23.0]
CCFS[a]	0.9 ± 0.1 [0.8–1.0]	1.0 ± 0.1† [0.9–1.3]	1.1 ± 0.1† [0.9–1.4]	1.0 ± 0.1† [0.9–1.2]	1.0 ± 0.2† [0.8–1.3]
CCFS[b]	0.8 ± 0.0 [0.8–0.9]	1.1 ± 0.2† [0.9–1.3]	1.1 ± 0.2† [0.9–1.5]	1.1 ± 0.1† [0.9–1.3]	1.0 ± 0.2† [0.8–1.5]
CAG length	–	47 ± 7 [40–62]	40 ± 3 [36–46]	69 ± 6 [50–75]	41 ± 3 [36–44]
Disease duration[a]	–	7 ± 6 [1 − 21]	10 ± 6 [2 − 20]	9 ± 5 [1–16]	9 ± 6 [2–18]
Disease duration[b]	–	9 ± 6 [3 − 23]	12 ± 6 [4–22]	11 ± 5 [3–18]	11 ± 5 [4–20]

Data are presented as mean ± standard deviation. $^{\dagger}p \leq 0.001$ and $^{\#}p \leq 0.01$ represent significant differences between SCA and controls obtained with the analysis of covariance, controlling for age, and with the step-down Bonferonni multiple correction. There was no difference in demographic parameters between the SCA.

[a] Parameters at baseline.

[b] parameters at follow-up.