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Dissociation of grey and white matter reduction in spinocerebellar ataxia type 3 and 6: A voxel-based morphometry study

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Abstract

The aim of this study was to examine the different patterns of cerebellar and/or brainstem atrophy in spinocerebellar ataxia (SCA) type 3 and 6. Eighteen patients (SCA3 $n=9$, SCA6 $n=9$) and 15 healthy volunteers were studied. Voxel-based morphometry (VBM) was applied to segmented grey matter (GM) and white matter (WM) of high-resolution T1-weighted brain volumes of each group. We found reduction of grey matter in the pons as well as in the vermis in SCA3 as compared to control subjects. In SCA6 significant grey matter loss was found in hemispheric lobules bilaterally as well as in the vermis. White matter analysis revealed significant changes in SCA3, especially in the pons, in the white matter surrounding the dentate nucleus (DN) and in the cerebellar peduncles, whereas no significant white matter reduction was found in SCA6 patients. Our results demonstrate different patterns of grey and white matter affection detected by magnetic resonance imaging (MRI) in SCA3 and SCA6 patients, confirming the pathological concept of cortical cerebellar atrophy in SCA6. In contrast, SCA3 represents a form of ponto-cerebellar atrophy with predominant affection of pontine nuclei and fibre tracts.

Keywords: Spinocerebellar ataxia type 3 and type 6; Voxel-based morphometry; MRI; Atrophy; Cerebellum

Spinocerebellar ataxias (SCA) comprise a group of clinically and genetically heterogeneous autosomal dominantly inherited disorders characterized by progressive ataxia. The genetic subtypes SCA3 and SCA6 are defined by CAG repeat expansions in the responsible genes MJD1 and CACNA1A [9,13,23,32]. Recent data suggest that these mutations result in different patterns of neurodegeneration. SCA6 is regarded as a "pure" cerebellar atrophy although clinical, neuropsychological, electrophysiological and neurometabolic studies provide evidence for minor affection of additional systems causing peripheral neuropathy, spasticity and fronto-executive dysfunction in at least some SCA6 patients [4,6,11,24,26]. In SCA3, it is well established that the degenerative process involves wide parts of the brain including the cerebral cortex, basal ganglia, pontomedullary systems and peripheral nerves in addition to cerebellar structures [3,17,22,28,29].

Conventional magnetic resonance imaging (MRI) in particular has proven to be sensitive for detecting cerebellar atrophy in SCA. Different approaches aimed to assess cerebellar volume changes in SCA [10,14,15,19]. Semi- and fully-automated techniques have been proposed to quantify cerebellar structures including two-dimensional planimetric and three-dimensional volumetric techniques. Voxel-based morphometry (VBM) provides an automated unbiased analysis of structural MRI scans [1]. In SCA, VBM has been performed only in patients carrying the SCA2 mutation so far [2].

In the present study, we used VBM to characterize atrophy patterns in SCA3 and SCA6 in comparison with healthy controls and demonstrated characteristic differences in the genetically distinct SCA subtypes.

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Three groups consisting of 9 patients with genetic verified SCA3 (mean age 53 ± 9.8 years; 4 men, 5 women), 9 patients with genetic verified SCA6 (mean age 66 ± 5.1 years; 6 men, 4 women), and 15 healthy age-matched volunteers (mean age 60 ± 10 years; 9 men, 6 women) without neurological impairment were compared in this study. Mean age at disease onset in the SCA6 group was 47 years, in SCA6 60 years, respectively. Disability was assessed according to the International Cooperative Ataxia Rating Scale (ICARS) [30]. Mean ICARS in SCA3 was 30 ± 12.4, in SCA6 28.5 ± 9.8, respectively. In SCA3 the mean CAG repeat length was 64 (range 58–73). Mean CAG repeat length in SCA6 was 21.4 (range 21–22). The study protocol was approved by the local ethical committee (Ethical committee of the Ruhr-University of Bochum, Germany). All individuals gave their written informed consent to MRI examinations and the further use of anonymized data.

High-resolution T1-weighted 3D MRI data (MPRAGE) were acquired on a 1.5 T Magnetom Symphony^{TM} scanner (Siemens, Erlangen, Germany). The scans were Turbo FLASH 3D sequences with a TE of 3.93 ms and a TR of 1900 ms. One hundred and twenty-eight sagittal slices with a resolution of 1 mm × 1 mm × 1.5 mm were recorded. All analyses were performed on a PC using Matlab 6.5 (Mathworks Inc., Natick, MA, USA; http://www.mathworks.com/) and SPM2 software (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm).

Voxel-based morphometry was performed using the modified procedure of Good et al. [7] by creating customized templates and prior images of grey and white matter (WM) as well as cerebrospinal fluid (CSF) (http://dbm.neuro.uni-jena.de/vbm.html). Images of all subjects were normalized to the anatomical standard space defined by the Montreal Neurological Institute (MNI) brain provided with SPM2 using 12 parameter affine transformation. Normalized images were averaged and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). This new template was used to control for differences in scanning procedures and population specific effects in all further analyses. Afterwards individual images were analyzed using SPM2 by extracting grey matter (GM), white matter and cerebrospinal fluid from the normalized images by means of the formerly created template for warping and spatial normalisation. To remove non-brain voxels a series of morphological erosions and dilations was applied to the segmented images [7]. Resulting images were smoothed with a Gaussian kernel of 10 mm FWHM.

An ANCOVA with age and sex as covariate was applied with no global normalization and no grand mean scaling. To avoid edge effects on the border between grey and white matter, voxels with a grey or white matter volume of <0.2 (maximum 1) were excluded. All contrasts were thresholded to a $p < 0.001$ by applying a false discovery rate (FDR) approach to correct for multiple comparisons. Only clusters with a minimum of 10 voxels were included in the results. Anatomical labelling was performed as described by Suchan et al. [27]. Exact localisation of cerebellar regions were identified according to the human cerebellar atlas of Schmahmann et al. [20].

Postmortem cerebellar tissue of a male patient with clinically diagnosed and genetically confirmed SCA3 (age at disease onset: 30 years; age at death: 56 years; 74 CAG repeats in the mutated SCA3 allele) and a male patient with clinically diagnosed and genetically confirmed SCA6 (age at disease onset: 51 years; age at death: 76 years; 22 CAG repeats in the mutated SCA6 allele) were analyzed for cerebellar white matter changes. The examination of these brains was approved by the Ethical board of the Faculty of Medicine at the J. W. Goethe-University Frankfurt/Main. Subsequent to the fixation of the brains, the right cerebella of the SCA3 and SCA6 patients were embedded in polyethylene glycol (PEG 1000, Merck, Darmstadt, Germany) and cut into uninterrupted series of 100 μm thick sagittal sections [25]. In each instance a serial collection consisting of the 1st, 11th, 21st, etc. of these cerebellar sections was processed according to a modified Heidenhain procedure to assess the structural integrity and myelinization of the cerebellar white matter [8]. Upon routine neuropathological examination the SCA3 patient together with an atrophic cerebellum showed neuronal loss in the cerebellar dentate nucleus (DN), pallidum, substantia nigra, red and subthalamic nuclei, as well as in Clarke's column. The SCA6 patient under consideration along with an atrophy of the cerebellum, displayed demyelinization of the cerebellar white matter, loss of cerebellar Purkinje cells and neurodegeneration of the inferior olive.

Comparison between healthy controls and SCA3 patients yielded significant grey matter differences in vermis lobules I, II, IV, VII B and IX. Additionally, grey matter reduction was observed in the pons close to the midline (Table 1 and Fig. 1).

SCA6 patients showed significant clusters of reduced grey matter volume compared to controls bilaterally in the hemispheric lobules III, IV, V and VI. This reduction was most pronounced in the right hemispheric lobule VI and left lobule IV and also in the left vermal area of lobule V (Table 1). Additional reduction was found bilaterally in the cerebellar lobules Crus I and II. Fig. 1 illustrates areas of grey matter loss in SCA6. Inverse contrast for SCA3 and SCA6 to controls did not show any significant differences. SCA6 patients demonstrated pronounced grey matter reduction if compared to SCA3 bilateral in the cerebellar lobules IV and VI, as well as in the right hemispheric lobule VIII B and Crus I.

A large cluster of white matter reduction was observed in SCA3 patients in the pons as compared to controls, with the changes accentuated in the pontine tegmentum. Furthermore, this cluster comprised areas of white matter reduction corresponding to the white matter surrounding both dentate nuclei. Additional clusters of significantly reduced white matter were found in both cerebellar peduncles and left cerebellar lobule IX in SCA3 (Table 2 and Fig. 1).

No significant areas of white matter decrease were observed by comparing controls to SCA6 patients. The inverse contrasts for both groups showed no significant differences.

Comparison of SCA6 and SCA3 patients yielded white matter reduction mainly in the cerebellar peduncle in the SCA3 group (Table 2).

Comparison of slices through the cerebellum at the level of the dentate nucleus demonstrated pronounced reduction of cerebellar white matter in SCA3 in comparison to SCA6 (Fig. 2). In addition, the dentate nucleus was severely degenerated in SCA3.