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Cervical cord area is associated with infratentorial grey and white matter volume predominantly in relapsing-remitting multiple sclerosis: A study using semi-automated cord volumetry and voxel-based morphometry

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Abstract

Background and purpose: Atrophy of the brain and the upper cervical cord, which both have major impact on the severity of clinical symptoms in multiple sclerosis (MS), may be interrelated by neuraxonal degeneration. Aiming to identify possible spatially remote effects of neuraxonal brain damage on spinal cord atrophy, we studied regional and global brain volumes and the upper cervical cord area (UCCA) in a large group of MS patients and a healthy control group.

Methods: In a group of 132 MS patients (71 relapsing-remitting MS; 61 secondary progressive MS; median [range] of EDSS: 5 [0-7], respectively 6 [2-8.5] and mean ± standard deviation of age/disease duration: 37 ± 11 years/6.7 ± 6.3 years; respectively: 49 ± 8 years/14.5 ± 8.0 years) and 45 healthy subjects UCCA, regional and global brain volumes, and brain lesion load were assessed. Associations between MRI results and clinical parameters in the entire cohort and differentiated according to MS-subtype were investigated using *t*-tests, partial correlation analyses, voxel-based morphometry and statistical parametric mapping.

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; EDDS, expanded disability status scale; UCCA, upper cervical cord area; GM, brain grey matter; WM, brain white matter; TBV, total brain volume; VBM, voxel based morphometry; SPM, statistical parametric mapping; 3D-T1w, three dimensional T1 weighted; FLAIR, fluid attenuated inversion recovery sequence; FWE, family wise error

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Results: Exclusively in RRMS, a significant positive correlation of UCCA with cerebellar cortical grey matter (GM) in the vermis and with regional white matter volume in the entire brainstem, corresponding to the corticospinal tracts, was detected. Although SPMS patients were considerably more affected by disability and decrease of UCCA (RRMS:75.2±10.4 mm^2; SPMS: 66.0±11.8 mm^2, controls: 84.5±8.7 mm^2), brain grey matter (RRMS:585.8±53.6 ml; SPMS: 528.2±61.5 ml, controls: 608.7±48.1 ml) and total brain volume (RRMS:1162.9±41.8 ml; SPMS: 1117.9±51.2 ml, controls: 1194.1±19.5 ml) than RRMS patients, significant positive associations in this group were found only between UCCA and a cluster of white matter in the medulla, but not in grey matter.
Conclusion: Cervical cord and brain atrophy were present in both, RRMS and even more severe in SPMS. Still, spatial associations between cervical cord area and remote cerebellar and brainstem volume, possibly driven by neuraxonal degeneration, were detected mostly in RRMS patients with predominantly short disease durations. Future longitudinal studies may elucidate the interplay between affection of spinal cord and infratentorial structures in MS, and contribute to the understanding of the conversion processes from relapsing-remitting to secondary progressive MS.

1. Introduction

Neuraxonal damage is an important pathologic feature of Multiple sclerosis (MS) occurring not only in the brain but also in the spinal cord. As shown by several magnetic resonance imaging (MRI) studies, both, brain and upper cervical cord atrophy, have impact on the severity of clinical symptoms in MS and are predictive for proceeding clinical disability (Kearney et al., 2014; Lukas et al., 2013; Bakshi et al., 2005; Liu et al., 1999; Rashid et al., 2006). Atrophy of the cerebellum on the other hand, driven by volume loss of the cerebellar cortex, has been shown to be a landmark for conversion to the secondary progressive disease state (Calabrese et al., 2013). The clinical relevance of cervical cord atrophy is related to its high anatomical-functional vulnerability, which has been emphasized in several recent studies (Bonati et al., 2011; Kearney et al., 2014; Lukas et al., 2015; Oh et al., 2013; Schlaeger et al., 2014; Valsasina et al., 2013).

Although until now the pathological substrate of spinal cord atrophy has not been fully elucidated, it is most probable that axonal loss is the dominant factor (Edwards et al., 1999; Evangelou et al., 2005). Whether cord atrophy is independent from brain atrophy, or is driven by remote effects, is still under debate (Cohen et al., 2012; Daams et al., 2014; Oh et al., 2013). However, there is evidence that it can, at least in part, occur secondary to tissue damage upstream in the brain, possibly due to anterograde degeneration (Bruck, 2005; Rocca et al., 2011; Vaithianathar et al., 2002). Furthermore, spinal cord atrophy seems to be only slightly influenced by local cord lesions, as shown by histological and imaging studies, also indicating, that spinal cord atrophy is partly determined by remote regional degenerative processes (Bergers et al., 2002; Biberacher et al., 2014; Evangelou et al., 2005; Nijeholt et al., 2001).

The current study aimed on the assessment of atrophy of the cervical cord and brain GM and WM, globally and in a voxelwise manner, to examine possible remote effects of neuraxonal brain damage on cervical cord area.

2. Materials and methods

2.1. Patients and healthy control group

In total, 132 patients with clinically definite MS were retrospectively included in this study: 71 with relapsing-remitting (RRMS, age: 37±11 years, male/female: 22/49) and 61 patients with a secondary-progressive (SPMS, age: 49±8 years, male/female: 29/32) disease course. Inclusion criteria were: clinical definite MS based on McDonald diagnostic criteria, and the availability of volumetric T1-weighted MRI images, being acquired according to a continuous standardized MRI protocol (Polman et al., 2005, 2011). Clinical disability according to the expanded disability status scale (EDSS), disease duration, and MS subtype at the date of MR imaging, were extracted from the patients charts (Kurtzke, 1983). A control group consisted of 45 age matched healthy subjects without a history of neurological disease or drug abuse. The study was approved by the local ethics committee.

2.2. Neuroimaging

We acquired all MRI data covering the head and the upper cervical cord at a single 1.5 T scanner using sagittal 3D-T1 weighted and axial FLAIR weighted sequences. Details of the MRI are given in the Supplementary material.

2.3. Quantitative image analysis and voxel based morphometry

2.3.1. Brain and cervical cord volumetry and FLAIR lesion quantification

Volumes of brain grey matter (GM), white matter (WM) as well as the total brain volume (TBV) were analyzed using the VBM8 pre-processing and segmentation tools with default parameters (VBM8 based on SPM8 and MATLAB 8.0) (FIL Methods, 2013; Gaser, 2009). Intracranial cavity volumes