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MRI characteristics of periaqueductal lesions in multiple sclerosis ☆

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Abstract
Background: In multiple sclerosis (MS), periaqueductal lesions (PAL) have been described histopathologically.
Objectives: We sought to investigate the frequency and characteristics of PAL on magnetic resonance images (MRIs) in patients with MS or clinically isolated syndrome (CIS).
Methods: We analyzed proton density (PD)-weighted MRIs of 247 MS and 10 CIS patients. PAL were identified based on their abnormal hyperintensity and lesion shape on at least two consecutive slices. Patients with and without PAL were compared for clinical characteristics in a propensity score weighted analysis.
Results: We identified PAL in 48/257 patients (18.7%), 34 of which had CIS or relapsing-remitting MS and 14 a progressive disease course. The shape of PAL was often circular (65%), or/and wedge-like (42%). Multi-planar image analysis in a subgroup of patients with double inversion recovery

Abbreviations: CIS, clinically isolated syndrome; DIR, double inversion recovery; EDSS, expanded disability status scale; FS, functional system; MRI, magnetic resonance image; MS, multiple sclerosis; NMO, neuromyelitis optica; NRS, numerical rating scale; PAG, periaqueductal gray matter; PAL, periaqueductal lesions; PD, proton density

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sequences revealed that 36% of PAL were periventricular lesions of the third ventricle extending towards the aqueduct. We found an association of PAL and brainstem functional system.
Conclusions: Although PAL may be underreported in MS, they are relatively frequent and found at all clinical stages and in CIS. They could be considered as a variant of periventricular lesions in the supratentorial midbrain and thus be useful in the diagnosis of MS.

1. Introduction

The aqueduct of Sylvius is a small channel that traverses the midbrain connecting the third with the fourth ventricle. It is surrounded by densely layered neurons, forming the periaqueductal gray matter (PAG). The exact functions of the PAG neurons are not fully understood, but experimental data suggest an important role in analgesia (Bartsch et al., 2004; Knight et al., 2002) and the PAG region is thought to be associated with migraine (Rocca et al., 2006; Welch et al., 2001). Furthermore PAG-neurons seem to be involved in the regulation of the micturition reflex in animals (Marson, 2004) and humans (Athwal et al., 2001; Benarroch, 2010; Fowler, 2008; Sakakibara et al., 1997). In multiple sclerosis (MS) patients, periaqueductal lesions (PAL) are a typical finding according to neuropathological data (Prineas and McDonald, 1997). However, PAL do not receive much attention in daily clinical practice. In the scientific literature PAL have been reported in MS patients only in association with headache, especially migraine (Gee et al., 2005; Fragoso and Brooks, 2007; Haas et al., 1993; Tortorella et al., 2006).

In this cross-sectional observational study, we aimed to determine the frequency of PAL and their magnetic resonance imaging (MRI) characteristics in a relatively large cohort of patients with MS and clinically isolated syndrome (CIS).

2. Material and methods

2.1. Patients

We analyzed the MR Images of all 257 patients (247 MS and 10 CIS patients) participating in an ongoing prospective observational study on the phenotypic–genotypic characterization of all clinical subtypes of MS, obtained at study baseline (2005). At the time of the MRI the patients were treated with best individually selected disease modifying treatments. All patients were clinically stable. Patients with an acute relapse were not examined and the MRI scan was postponed at least 30 days after the last dose of steroid treatment. In addition, 11 healthy control subjects (4 women and 7 men with a mean age 33.5 years) were also included, in order to study the normal MRI characteristics of the periaqueductal area. Informed consent was obtained in writing from all subjects, in accordance with the local ethics committee approval.

2.2. Analysis of the MR images

MRI was obtained with a 1.5 T system (Avanto, Siemens Medical systems, Erlangen, Germany). The brain MRI protocol consisted of axial, double-echo proton density (PD)/T2-weighted sequences (repetition time (TR): 3980 s, echo time (TE): TE1/TE2=14 ms/108 ms, inplane resolution of 0.98 × 0.98) as well as post contrast T1-weighted images (T1w spin-echo scan with TR: 550 ms, TE: 17 ms, inplane resolution of 0.98 mm × 0.98 mm and 3 mm slice thickness), positioned parallel to the inferior borders of the corpus callosum. The T2- and T1-hypointense lesions were marked on the axial PD-weighted (-w) and T1-w post contrast images respectively and then segmented by means of the commercially available semiautomatic thresholding contour software AMIRA 3.1.1 (Mercury Computer Systems Inc) to calculate their total volumes. The majority of patients was willing to also undergo spinal cord MR (n=201) and a biplanar review (sagittal and axial planes of PD-w and T2-w images) was performed to include the number of spinal cord lesions in the analysis.

The axial PD-w MR images of the 247 MS, 10 CIS patients and 11 healthy controls were analyzed using a structured reporting scheme. The brainstem/midbrain area was evaluated on 5 consecutive 3 mm slices. Two experienced readers (AP and AG), unaware of patient identity and clinical characteristics, evaluated the images by consensus. In order to avoid false positive results, we used the following conservative criteria for the detection of PAL: they had to be identified on a minimum of two consecutive slices, to be hyperintense, have an asymmetrical or wedge-like shape or/and clearly exceed the normal, circular PA gray matter (Fig. 1).

In 22 patients with PAL, a further 3-dimensional Double Inversion Recovery (3D DIR) sequence (repetition time (TR): 7.5 s, echo time (TE): 311 ms, inversion time (TI): 3 s, slice thickness: 1.5 mm and inplane spatial resolution 1.33 mm × 1.33 mm) was performed. PAL were then reviewed in particular for their topographical relationship to surrounding anatomical structures in a multiplanar reconstruction mode visualizing 3 anatomical planes simultaneously.

2.3. Acquisition of the patients' clinical and imaging-characteristics

The demographic and clinical characteristics of the patients (age, gender, disease duration, disease course, Expanded Disability Status Scale (EDSS) score and Functional System (FS) scores, presence of migraine, presence and severity of pain) were obtained at the time of the MRI (presented in Tables 1 and 2). On the day of the MRI all patients underwent a standardized neurological examination by certified physicians (http://www.neurostatus.net), including the assessment of the brainstem- and bowel/bladder FS scores. The brainstem FS score refers to the cranial nerve functions and varies from 0 (normal) to 5 (inability to swallow or speak). It includes the assessment of extraocular movements impairment and nystag

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