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The motor band sign in ALS: presentations and frequencies in a consecutive series of ALS patients

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ABSTRACT

The primary role of magnetic resonance imaging (MRI) in routine diagnostic work-up of motor neuron disease patients is currently still largely limited to exclusion of relevant non-degenerative pathologies. We here present an illustrative case of a 63-year-old woman with early stage Frontotemporal-Dementia-Amyotrophic-Lateral-Sclerosis (FTD-ALS) spectrum disorder showing a striking hypointense signal of the cortical band along the precentral gyrus, termed "motor band sign" (MBS). Based on this finding, we analysed the frequency of the MBS in clinical routine MRIs in a large consecutive series of ALS patients (MRIs available from 157 patients). MBS was present in 5% patients of the total series, but in 78% of patients where susceptibility-weighted images (SWI) were available. These findings suggest that the MBS is a recurrent finding in ALS, which can be identified even on clinical routine 3 T-MRI, and as part of more complex motor neuron syndromes, such as FTD-ALS. Moreover, they indicate that SWI sequences should be considered as part of the clinical routine MRI protocol in the diagnostic work-up of ALS patients.

1. Introduction

The diagnosis of motor neuron disease can be challenging, for example in early stages of disease or complex clinical manifestations. The primary role of magnetic resonance imaging (MRI) in the diagnostic work-up is currently still largely limited to *exclude* relevant non-degenerative pathologies. While more sophisticated MRI techniques and methods - including susceptibility-weighted sequences, multimodal imaging and high tesla field intensities - have allowed to unravel also positive findings indicative of motor neuron diseases like amyotrophic lateral sclerosis (ALS) (e. g. a T2 or FLAIR hyperintensity along the corticospinal tract [1]), their value has not yet been demonstrated in clinical routine MRI imaging. As one of the main intriguing MRI findings, the motor band sign (MBS) has been described in single ALS patients: a band-shaped T2- and/or SWI-hypointense signal change along the precentral gyrus of the primary motor cortex [2]. However, descriptions of the MBS have been largely limited to single cases, while more in-depth information on its presentations and frequencies on clinical routine MRI in larger series of ALS patients is missing.

Here we aimed to provide first data on the presentations and frequencies of the MBS in different MRI sequences from a larger, strictly consecutive series of ALS patients, introduced by an illustrative case vignette of the MBS in a patient with Frontotemporal-Dementia-Amyotrophic-Lateral-Sclerosis (FTD-ALS).

2. Methods

Based on the initial identification of a FTD-ALS index case showing a striking MBS (see case vignette in 3.1), we conducted a retrospective analysis to evaluate the presentations and frequency of the MBS in a consecutive series of ALS patients seen in the ALS clinic, Center for Neurology, University of Tübingen, between 2009 until July 2019. Only MR images available from clinical routine imaging (but not from specific research studies with complex imaging protocols and/or high tesla field intensities) were included, acquired both at external radiology departments and at our own radiology department. All MR images were reviewed by to independent assessors (B.R., B.B.).

MBS was defined as positive for each MRI sequence by the presence of a band-shaped hypointense signal along the primary motor cortex in (i) susceptibility-weighted images (SWI): (ii) T2; (iii) T2* (iv) fluid-

Abbreviations: ALS, Amyotrophic lateral sclerosis; MRI, Magnetic resonance imaging; SWI, Susceptibility weighted imaging

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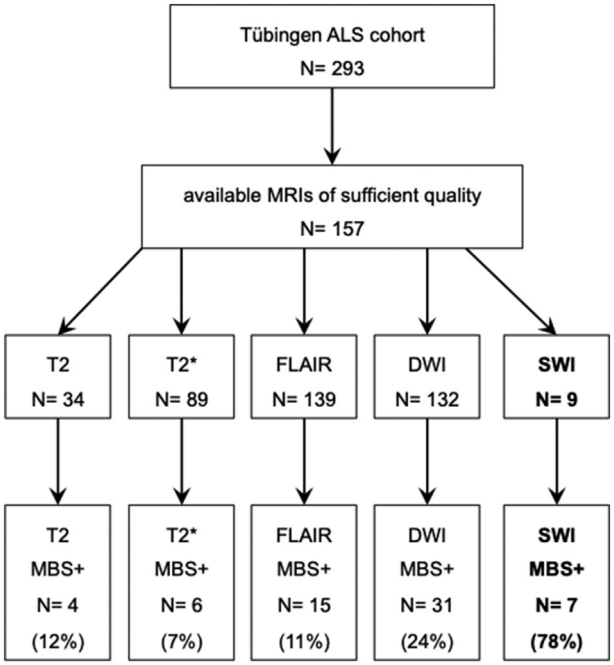

Fig. 1. Frequencies of the MBS in different MRI sequence modalities in a consecutive series of ALS patients. In our retrospective analysis, 157 out of 293 consecutive ALS patients had a MRI of sufficient quality, with different MRI sequence modalities available. The relative frequency of the MBS varied between the different MRI sequence modalities.

attenuated inversion recovery (FLAIR); and/or (v) diffusion-weighted images (DWI). Following a conservative approach, we only counted those patients as MBS positive (MBS+) in the overall analysis who also showed the MBS on SWI. Patients showing the MBS only on the other MRI modalities, but lacking a SWI validation, were counted as positive in the modality-specific sub-analysis, but not in the overall analysis (see flow chart diagram in Fig. 1). In addition to the MBS, we reviewed T2, T2*, FLAIR and DWI sequences also for presence of additional signal changes of the precentral gyrus, the pyramidal tract and the internal capsule.

3. Results

3.1. Case vignette of the ALS-FTD index case

A 63-year-old woman presented with right-sided weakness and impairment of fine motor skills since 4 years, and progressive spastic-paretic gait and frequent falls since 2 years. Dysarthria and dysphagia had developed in the last 6 months. On clinical examination there was slight spasticity on all extremities and generalized muscular atrophy, most pronounced in the shoulder girdle and small hand muscles. These motor neuron features were complicated by right-sided hypokinetic-rigid parkinsonism, cognitive decline with deterioration in the domains vocabulary and memory for names (scoring 23 of 30 points in the Montréal Cognitive Assessment [MoCA]), and ideomotoric limb apraxia. Electromyographic studies showed signs of acute denervation and fasciculations each in 2 of 4 regions (cervical and lumbosacral), transcranial magnetic stimulation revealed upper motor neuron dysfunction affecting both upper and lower extremities. A clinical diagnosis of ALS was made according to the revised El Escorial criteria [3], which was still early stage according to the King's College ALS staging [4], and – given the cognitive decline, apraxia and additional parkinsonism – was part of a broader Frontotemporal-Dementia-Amyotrophic-Lateral-Sclerosis spectrum disorder (FTD-ALS). 3 Tesla MRI (3 T-MRI) revealed a hypointense signal of the cortical band along the precentral gyrus on both T2- and susceptibility-weighted images (SWI) (Fig. 2A & B).

3.2. Presentations and frequencies of the motor band sign in a consecutive series of ALS patients

From a total of 293 ALS patients of our consecutive Tübingen cohort, 157 patients (including the index patient) had clinical routine MRI of sufficient image quality for evaluation. SWI sequences, available for 8 patients in addition to the index patient, demonstrated a positive MBS in 6 additional patients (total 7/9 = 78% of all patients with available SWI; 7/157 = 5% of the overall cohort with available MRI) (for illustrative SWI MBS images, see Fig. 2E–J). Patients SWI-positive for MBS included not only sporadic ALS patients, but also an ALS patient with a D90A SOD1 mutation (Table 1). Review of additional sequences – if available – yielded MBS+ in (i) 12% on T2-; (ii) 7% on T2*-; (iii) 11%

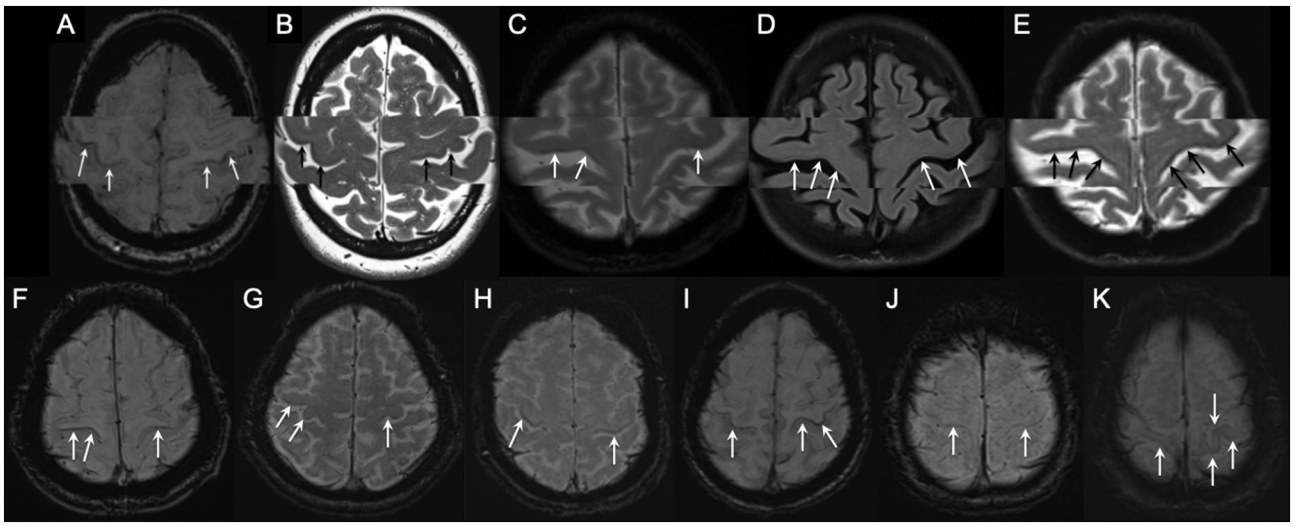

Fig. 2. Susceptibility weighted (SWI; A, arrows) and T2 turbo spin echo images (B, arrows) at 3-Tesla revealed hypointensity of the cortical band along the precentral gyrus in the index case (= case #1). Illustrative images of the Motor Band Sign (MBS) on different MRI sequence modalities are shown for T2 (B; case #1), T2* (C; case #2), FLAIR (C; case #2) and diffusion-weighted (D; case #2) images. Only patients with a MBS on SWI were taken as clear MBS+ subjects. SWI images of all these MBS+ patients, in addition to case #1 (A), are shown (F-K; in numerical order: case #2 - #7). Image sections demonstrating the specific pathological signal changes of the primary motor cortex are shown as zoomed-in overlays of the respective MRI sequence.

Table 1
Clinical, genetic and MRI characteristics of patients with positive Motor Band Sign on susceptibility-weighted images (SWI).

	Case #1 (=index case)	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7
Sex	f	m	m	f	f	m	m
Age at MRI, years	63	58	72	44	53	67	73
Age at onset, years	59	57	70	41	52	64	73
Disease duration at time of MRI, years	4	1	2	3	1	3	0
Clinical phenotype	FTD-ALS-Parkinsonism	sporadic ALS	sporadic ALS	sporadic ALS	sporadic ALS	sporadic ALS	genetic ALS
ALSFRS	38	31	28	NA	NA	NA	NA
Mutated gene	Negative for all known ALS genes	Negative for all known ALS genes	Negative for all known ALS genes	Negative for all known ALS genes	Negative for all known ALS genes	Negative for all known ALS genes	SOD1 D90A
Motor band sign							
SWI	+	+	+	+	+	+	+
T2	+	NA	NA	NA	NA	NA	NA
T2*	+	+	NA	NA	+	NA	NA
FLAIR	+	+	−	+	+	−	−
DWI	+	+	−	+	+	−	+
Hyperintensities on T2 or FLAIR images							
Of the precentral gyrus	+	−	−	−	−	−	−
Of the pyramidal tract	+	+	+	+	+	+	−
At the internal capsule	+	+	+	+	+	+	−

MRI = magnetic resonance imaging; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; SWI = Susceptibility-Weighted Imaging; FLAIR = Fluid Attenuated Inversion Recovery; DWI = Diffusion-Weighted Imaging; FTD = Frontotemporal Dementia; ALS = Amyotrophic lateral sclerosis; SOD1 = Superoxid Dismutase 1; f = female; m = male; + = signal alteration present; − = signal alteration absent; NA = not available.

on FLAIR-; and (iv) 24% on DWI images (for illustrative exemplary MRI images from each modality, see Fig. 2A–D; for an overview of relative frequencies, see Fig. 1). In 2 MBS+ patients, both SWI and T2* sequences were available for evaluation. Here the MBS appeared more vague on T2* than on SWI sequences, likely due to the lower sequence resolution of T2*. Clinical characteristics of MBS+ patients and frequency of signal changes of the precentral gyrus as well as the pyramidal tract and the internal capsule are presented in Table 1.

4. Discussion

4.1. MBS is a recurrent MRI sign in ALS

Providing the first data on the MBS from a larger, consecutive patient series, we here show that the MBS is a recurrent positive MRI finding in ALS – even in clinical routine MRI. A conservative estimate indicates that it can be observed at least in 5% of ALS patients, with frequencies rising up to 78% where SWI sequences are available. These estimates are still preliminary in nature, as they warrant (i) validation in prospective studies with more standardized, complete multimodal MRI datasets, (ii) inclusion of non-ALS neurodegenerative control groups (to determine the sensitivity and specificity of the MBS in ALS against the background of other neurodegenerative diseases), and (iii) inclusion of random non-neurodegenerative case-controls (to correct for a potential bias that the interpreting rater is “expecting” MBS in known ALS). Moreover, while MRIs in the current study have already been assessed by two independent assessors including one experienced senior neuroradiologist, future studies need to exploit a stringent rating approach by two independent neuroradiologists including data on inter-rater reliability.

Despite these limitations, our findings already provide preliminary hints that the MBS might possibly serve as a positive supportive MRI imaging sign in ALS, even in the routine clinical work-up without access to highly sophisticated MRI protocols and high tesla field intensities. As exemplarily indicated by the MBS+ patients reported here, the MBS can even be observed in relatively early stages of ALS (e. g. case #1 according to the King's College staging system), as part of more complex syndromes, such as FTD-ALS (case #1), and in genetic forms of ALS (case #7).

4.2. The MBS in different MRI sequence modalities

The high yield of MBS+ positive patients in our SWI subgroup indicates that in particular SWI sequences should be included in the diagnostic routine MRI work-up of ALS patients. SWI might be particularly helpful in identifying the MBS sign, as SWI sequences usually have higher resolution than T2*-weighted images and might be more sensitive to iron deposition due to neurodegeneration of neurons of the primary motor cortex (as indicated by our findings from two subjects where both SWI and T2* was available), while subtle hypointense signal alterations might not yet be visible on T2-, FLAIR or DWI sequences. However, these findings require confirmation in future studies with larger patient cohorts receiving the full set of these MRI modalities in parallel.

Our observations from clinical routine MRI complement recent observations from more sophisticated MRI techniques. A MRI study using T2* imaging and quantitative susceptibility mapping (QSM) found significant correlations of clinical scores of UMN impairment of the hands and lower limbs with magnetic susceptibility of the deep cortical layers of patients' corresponding M1 subregions potentially indicating UMN burden in these patients [5]. Similarly, a whole-brain QSM study demonstrated significantly higher susceptibility of the motor cortex and several basal ganglia subregions (i. e. substantia nigra, globus pallidus and red nucleus) in ALS patients compared to healthy controls, with QSM measures correlating with diffusion metrics of the corticospinal tract, thus indicating neurodegeneration of the UMN [6].

4.3. The pathophysiological basis of the MBS

While T2-hypointense cortical signals can also be found in other neurodegenerative diseases (e.g. Alzheimer's and Parkinson's disease [7]), the confinement of the signal change specifically to the *primary motor cortex* - as defining for the MBS and observed in ALS - indicates microstructural changes particularly in this most proximal part of the upper motor neuron. The MBS has also been reported, albeit rarely, in single instances of other neurodegenerative diseases such as Alzheimer's and Parkinson's disease [7], suggesting a *neurodegenerative* disease process underlying these microstructural changes. Correspondingly, a study correlating iron-sensitive SWI at 7 and 3 Tesla with brain post-mortem histopathology [8], indicated that the MBS might represent microglial iron accumulation due to phagocytosis of degenerating

neurons in the primary motor cortex. This notion is supported by several MRI studies focussing on iron accumulation in ALS, which demonstrated increased iron levels in the motor cortex of ALS patients using different iron-sensitive MRI sequences and MRI analysis methods [9,10]. One study combining SWI and post-mortem studies provided additional evidence for iron deposition in the motor cortex in ALS by demonstrating decreased signal intensity on SWI in association with intense antiferritin staining of macrophages and microglia in the precentral gyrus of ALS patients [10]. Future prospective studies combining comprehensive MRI protocols with neuropathology in ALS as well as other neurodegenerative diseases which affect the motor cortex will thus help to further elucidate our finding of the MBS as a recurrent finding in ALS.

Ethical standards

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Ethical approval was granted by the ethics committee of the medical faculty of the University Tübingen (ethical approval #054/2013B01). All individuals gave written informed consent prior to their inclusion in the present study.

Disclosures

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Author contributions

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

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Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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