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The Spinal Cord Lateral Tract Sign as an rAMIRA-based MRI sign for Upper Motor Neuron Involvement in Amyotrophic Lateral Sclerosis in a Clinical Setting

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Background In Amyotrophic Lateral Sclerosis (ALS), deficits of upper motor neurons (UMN) can be elusive and difficult to identify (Swash, 2012), particularly early in the disease, but are important for timely diagnosis (Shefner et al., 2020). One of the core macro- pathological features of ALS - the sclerosis of the spinal cord (SC) lateral tracts (LT) - was described by Charcot and shaped the name of the disease (Charcot, 1869). Histopathologically, these areas are characterized by axonal and myelin loss, diffuse astrocytic gliosis and microglial activation (Saberi et al., 2015; Vaz et al., 2021).

Averaged Magnetization Inversion Recovery Acquisitions (rAMIRA) is a novel MRI approach (Weigel & Bieri, 2018; Weigel et al., 2020) that enables high resolution imaging with improved contrast of SC gray and white matter in clinically feasible acquisition times at 3 Tesla. Based on a case report demonstrating LT hyperintensities in an UMN predominant ALS patient on T2*-MRI at 7 Tesla (Callot et al., 2021) and our own observations on rAMIRA imaging, the aim of this study was to define and to validate the SCLT sign and to investigate its sensitivity and specificity in a cohort of patients with ALS, healthy controls (HC) and pathologic controls with other lower-motor neuron (LMN) diseases.

Methods 38 patients with ALS (Gold Coast criteria, Shefner et al., 2020), 60 HC, 25 patients with post-polio syndrome (PPS, March of Dimes criteria), and 10 patients with genetically confirmed 5q-spinal muscular atrophy (SMA) type II and III were investigated by axial 2D-radial rAMIRA imaging perpendicular to the SC at intervertebral disc levels C2/C3 - C5/C6 (3T-PRISMA, Siemens Healthineers) (in-plane resolution 0.5×0.5mm^2, slice thickness 8mm). Clinical and demographic data of all participants were obtained. The SCLT sign was defined and validated in a multi-step process by four independent raters (Figure 1) and its sensitivity and specificity in detecting ALS were calculated (Table 1). To test reproducibility, 10 patients with ALS, 10 HC, and 5 patients with SMA were additionally investigated with the same protocol and rated regarding the presence of the SCLT sign by 3 independent raters blinded to participant status.

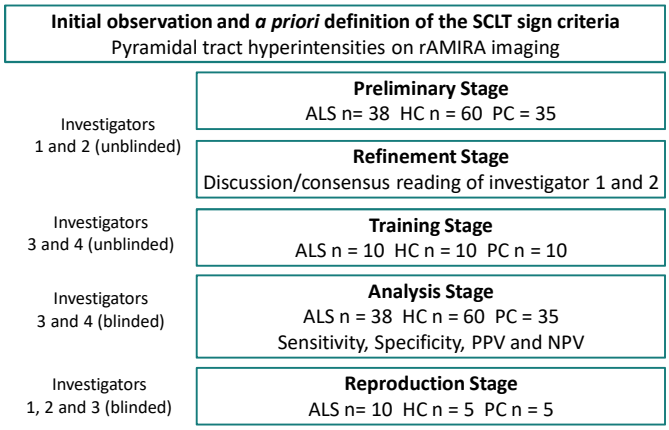

Figure 1: Multi-step definition and validation process of the spinal cord lateral tract sign. SCLT = spinal cord lateral tract; HC = healthy controls; PC = pathological controls; PPV = positive predictive value; NPV = negative predictive value

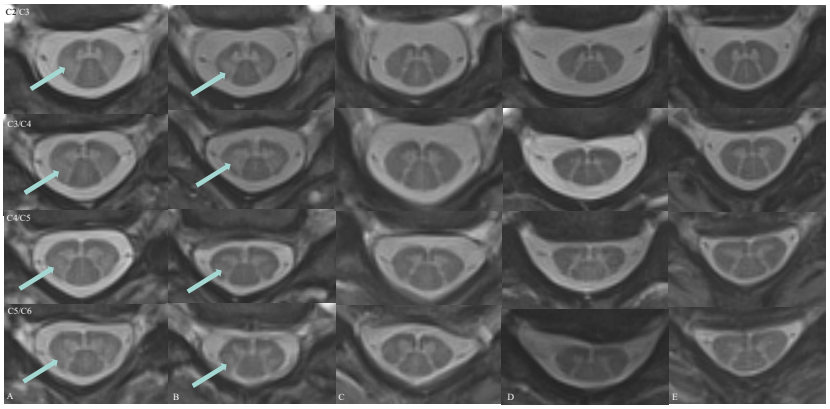

Image 1: The spinal cord lateral tract sign visible on axial 2D- rAMIRA imaging at intervertebral disc levels C2/C3, C3/C4, C4/C5 and C5/C6 (rows A-D) in two patients with ALS and upper motor neuron predominance (column A, f, 50 yrs, column B, w, 48 yrs), one patient with post-polio syndrome (column C, w, 63 yrs), one patient with spinal muscular atrophy (column D, m, 44 yrs), and one healthy control person (column E, w, 58 yrs). Note the marked presence of the spinal cord lateral tract sign at all levels in the two patients with ALS (column A and B, arrows) and its absence in the control subjects.

	C2/C3	C3/C4	C4/C5	C5/C6
Patients with ALS (n = 38) (%)	19/38 (50%)	18/37 (48.6%)	20/37 (54.1%)	15/32 (45.4%)
predominant UMN signs (n = 9)	8/9 (88.9%)	8/9 (88.9%)	8/9 (88.9%)	7/8 (87.5%)
Patients with PPS (n = 25)	1/25 (4%)	2/25 (8%)	1/24 (4.2%)	1/23 (4.3%)
Patients with SMA (n = 10)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)
Healthy controls (n = 60)	0/60 (0%)	0/60 (0%)	2/58 (3.3%)	0/57 (0%)

Table 1: Presence of the Corticospinal tract sign in patients with different clinical ALS subtypes, post-polio syndrome (PPS), spinal muscular atrophy (SMA), and healthy controls (HC). The second number gives the total n of analyzable/available images at the respective levels. UMN = upper motor neuron; LMN = lower motor neuron

Results The SCLT sign, defined as evenly spread, uni-or bilateral hyperintensities in the SC WM dorsolaterally to the anterior horns, was present in ALS patients in 50%, 49%, 54% and 46% at the respective levels C2/C3-C5/C6, and in up to 89% of ALS patients with UMN predominance. In the HC, PPS and SMA groups, the sign was present in 3%, 8%, and 0%, respectively, thus rendering a sensitivity of 58% and specificity of 98% at C3/C4 to identify ALS cases (Table 1). The sign was detectable irrespective of disease duration and persisted on consecutive imaging over two years. In a different, smaller dataset we were able to reproduce these results.

Discussion The SCLT sign shows a high specificity in distinguishing patients with ALS from HC and from patients with other LMN disorders. Further investigations of patients early in the disease course, particularly those without visible clinical signs of UMN dysfunction as well as asymptomatic mutation carriers and patients with other UMN disorders, are necessary next steps to estimate the potential of this novel and clinically feasible imaging method to improve the diagnostic process in ALS.

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