Atrophy of the Cervical Spinal Cord Gray Matter: a new surrogate marker in Amyotrophic Lateral Sclerosis

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Background There is an urgent need for valid and reliable imaging biomarkers to reduce the diagnostic delay, to monitor the disease course, and to evaluate drug efficacy in upcoming trials in amyotrophic lateral sclerosis (ALS). The novel AMIRA (Averaged Magnetization Inversion Recovery Acquisitions) method enables high resolution imaging with improved contrast of spinal cord (SC) gray matter (GM) and white matter in clinically feasible acquisition times at 3 Tesla (Weigel & Bieri, 2018; Weigel et al., 2020). The aims of this study were to compare cervical SC GM areas between patients with a diagnosis of ALS and healthy, age- and sex-matched control subjects (HC) and to assess the associations of cervical SC GM areas and established measures of clinical disability, the revised ALS functional rating scale (ALSFRS-R; Cedarbaum et al., 1999) and of respiratory impairment via the sniff nasal inspiratory pressure (SNIP; Capozzo et al., 2015) in ALS.

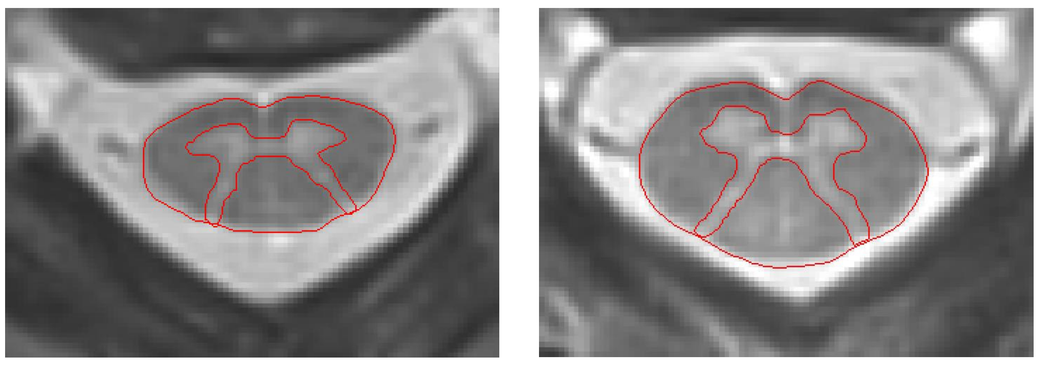

Image 1: axial 2D- rAMIRA imaging at disc level C3/C4 (in-plane resolution 0.5x0.5mm^2):
a) patient with ALS
b) age- and sex matched healthy control

	Patients with ALS	HC
Sex (male/female)	22/14	22/14
Mean age (SD) (years) Min - max	61.7 (12.6) 30.2 – 92.9	63.1 (12.1) 29.5 – 87.4
Mean disease duration (SD) (months) Min - max	32.87 (38.9) 6.0 – 223.2	NA
Disease onset type - bulbar - spinal	 6 (16.6%) 30 (83.3%)	NA
Mean ALSFRS-R (SD) Min - max	37.7 (7.3) 22 - 48	NA
SNIP (SD) (cmH_2O) Min -max	68.1 (30.5) 15-132	92.3 (26.6) 47-146

Table 1: Demographics of patients with ALS and healthy control subjects

Methods Using axial 2D radial (r)AMIRA imaging at the cervical intervertebral disc level C3/C4 acquired at a 3T PRISMA scanner (Siemens healthineers) and a semi-automated segmentation approach (JIM7, www.xinapse.com), we compared SC GM areas of 36 patients diagnosed with ALS according to the Gold Coast criteria (Shefner et al., 2020) (mean age 61.7yrs, 14 women, with bulbar and spinal onset, mean disease duration 32.9 months) and 36 age- and sex-matched HC. The associations between SC GM area and disability metrics (ALSFRS-R and SNIP) were assessed by multivariable regression analyses with adjustment for age and sex.

Results SC GM area at the level C3/C4 was significantly reduced in patients with ALS compared to HC (mean GM area in mm^2 (SD): ALS 16.6 (2.3); HC 19.65 (2.7); relative reduction 15.4%, p<0.0001).
In a subgroup analysis comparing different types of onset, we found significant GM area atrophy in patients with spinal onset, but not with bulbar onset compared to HC (see Table 3) with adjustment for age and sex.
In multivariable regression analyses adjusting for age and sex, GM area at C3/C4 explained 36.1% of ALSFRS-R variance (p=0.0001) and 32.2% of SNIP variance in patients with ALS, respectively.

Group	Mean GM area (mm^2)	SE	Difference	SE of the difference	p	95% CI	95% CI
ALS **HC**	16.61 19.65	0.40 0.46	-3.03	0.66	**<0.001**	-4.35	-1.72

Table 2: Spinal cord gray matter areas (in mm^2) at the intervertebral disc level C3/C4 of patients with ALS (n=36) and age- and sex matched healthy control (HC) subjects, paired t-tests

Group	Adjusted mean GM area (mm^2) / SE	Difference between means / SE	95% CI of the mean difference	95% CI of the mean difference	p
Bulbar onset	17.94 / 1.25	-1.75 / 1.32	-4.39	0.89	0.1908
Cervical onset	16.18 / 0.68	-3.51 / 0.81	-5.13	-1.90	**<0.0001**
Lumbar onset	16.57 / 0.66	-3.12 / 0.79	-4.70	-1.54	**0.0002**
HC	19.69 / 0.43				

Table 3: Spinal cord gray matter areas at the intervertebral disc level C3/C4 of patients with a bulbar, cervical or lumbar disease onset and healthy controls. Means are least square means with adjustment for age and sex. 95% CI= 95% confidence interval. Differences refer to HC, respectively.

Conclusions Cervical SC GM area in patients with ALS is significantly reduced compared to age- and sex matched HC and correlates with established measures of clinical disability and respiratory impairment, namely ALSFRS-R and SNIP. Further longitudinal investigations, particularly of patients early in the disease course, are necessary next steps to evaluate the potential of this novel and clinically feasible imaging marker for monitoring and predicting the disease course, and its potential as a surrogate in upcoming drug trials.

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