Amyotrophic lateral sclerosis (ALS): Everything you always wanted to know about ALS (but were afraid to ask)

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Learning objectives

- To familiarise the non-expert radiologist with ALS.
- To highlight imaging findings according to modality, especially in everyday practice.
- To accentuate the role of imaging in ALS.
Background

Amyotrophic lateral sclerosis (ALS; also known as motor neuron disease or Lou Gehrig's disease) is a widely heterogeneous multisystem neurodegenerative syndrome, which affects both the upper and lower motor neurons with a welter of pathophysiological mechanisms and multiple clinical phenotypes.

To add to the complexity of the entity, an overlap between ALS and frontotemporal dementia has been suggested, attributed to a common genetic cause (hexanucleotide repeat expansions in C9orf72), forming a probable continuum of a single multispectral disease. Special attention should be given to ALS mimickers such as primary lateral sclerosis (PLS), which targets exclusively the upper motor neuron and has a better prognosis than ALS. However, differentiating it from an initially upper motor neuron-predominant ALS can be challenging. Progressive spinal muscular atrophy (PSMA), characterised by lower motor neuron degeneration, has been debatably grouped under the umbrella of ALS variants, since autopsies have constated corticospinal tract (CST) involvement.

The vast majority of ALS cases are sporadic (around 90%), the rest being familial, mostly inherited as dominant traits. In terms of epidemiology, an estimation of 2.6-3.0 cases of ALS per 100,000 people of European ancestry has been described, with a mean age of onset being 65 years. Survival is variant, not exceeding though 3-4 years after initial presentation, mostly due to respiratory failure.

As for the clinical presentation, it is highly versatile and insidious, ranging from dysarthria to a foot drop, which may develop within weeks or even months. No treatment offers a substantial clinical benefit for patients with ALS up to date. Therapy is supportive and includes mainly riluzole which provides a limited improvement in survival.

Although conventional MRI is widely used in everyday practice, its use is restricted in excluding mimickers of ALS and in individual cases for disease monitoring.

Advanced neuroimaging techniques have been a game changer in the study of ALS (Diffusion tensor MRI-DTI in the study of the CST, Voxel-based morphometry-VBM in the study of Gray Matter, Spectroscopy etc).

DTI generates quantitative data about water diffusion in three-dimensional space. It should be noted that diffusivity is higher along fiber tracts compared to directions perpendicular to them. Diffusion is quantified using mean diffusivity (MD) and fractional anisotropy (FA). MD is a measure of the directionally averaged magnitude of diffusion and is related to the integrity of the local brain tissue. FA represents the degree of diffusion anisotropy and reflects the degree of alignment of cellular structures.
Findings and procedure details

Six (6) patients with progressive motor deficits presented to our Institution's Imaging Department with a working diagnosis of ALS, according to the revisited criteria El Escorial and Awaji. All patients underwent conventional MRI (3 Tesla) of the brain and cervical spine and, according to findings, further DTI tractography was performed.

The first ever abnormality described in imaging was high signal intensity along the CST from the centrum semiovale to the brain stem, on T2-weighted images (T2W), including fluid attenuated inversion recovery (FLAIR) images, PD-weighted images (Fig. 2, 4, 5), best documented in coronal planes (Fig. 3), which was indeed documented in all six of our patients. FLAIR images are more sensitive in the detection of brain changes in ALS patients. Nevertheless, it should be taken into consideration that increased signal along the CST has been noted in healthy subjects, more so in 3Tesla MRI as well as in patients with other conditions. The aforementioned finding is non pathognomonic and lacks significant sensitivity and specificity for a conclusive diagnosis of ALS. A quantitative analysis of signal intensity in FLAIR sequences has been recently proposed in order to boost its significance as a plausible diagnostic or stratification biomarker.

A thin line of cortical low signal intensity ("motor dark line" or "hypointense rim") of the - relatively atrophic (Fig. 7) - precentral gyrus on T2W/ FLAIR constitutes another finding in conventional MRI, indicative of advanced disease (Fig. 1).

As for the cervical spine, a degree of atrophy was observed in the majority of patients, as well as hyperintensity on T1 weighted images in the anterolateral column of the cord (Fig. 6).

As far as non conventional imaging is concerned, DTI is by far the dominant technique applied and researched at the moment. Studies have demonstrated that in ALS patients there is a decrease in FA and an increase in MD, best illustrated in the posterior limb of internal capsule. In addition, DTI technique allows fiber tracking - tractography - which in the case of ALS provides insights into changes in tissue structures and specifically degeneration of the CST (Fig. 8, 9, 10, 11). DTI has 65% diagnostic sensitivity and 67% diagnostic specificity for ALS.
Fig. 1: T2 FLAIR axial - low signal intensity ("motor dark line" or "hypointense rim") of the precentral gyrus.

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**Fig. 2:** T2 FLAIR sagittal - high signal intensity along the CST.

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Fig. 3: T2 FLAIR coronal - high signal intensity along the CST bilaterally more prominent on the left.

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Fig. 4: T2 FLAIR axial - high signal intensity along the CST.

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Fig. 5: T2 FLAIR sagittal - high signal intensity along the CST (same patient as Fig. 4).

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**Fig. 6:** T1W axial - hyperintensity in the anterolateral column of the cord.

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**Fig. 7:** T1W - Initial scan (left) and follow-up scan 7 years later (right) in a patient with ALS demonstrating atrophy of the motor cortex and the corpus callosum.

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Fig. 8: DTI reconstruction of corpus callosum in a healthy subject.

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**Fig. 9:** DTI reconstruction of corpus callosum in a patient with ALS.

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**Fig. 10:** DTI reconstruction in a patient with ALS.

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**Fig. 11:** DTI reconstruction demonstrating CST degeneration.

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Conclusion

ALS is a paralytic disorder characterised by degeneration of motor neurons in the brain and spinal cord with extreme phenotypic heterogeneity. Imaging findings have been indicative but not conclusive of ALS and clinical correlations have been limited until recent years. Even though they are not pathognomonic, familiarity of the radiologist with findings in conventional MRI along with more state-of-the-art methods is mandatory. The emergence of advanced neuroimaging techniques (DTI, VBM, high field MRI, functional MRI, PET/MRI, Proton magnetic resonance spectroscopy etc.) has shed new light on ALS along with thorough ground breaking research. In this context, the role of imaging is expanding not confined to being only a paraclinical tool but also an important biomarker for the diagnosis, monitoring and prognosis of ALS.
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