contribution was the inclusion of FLAIR sequence to the RECIST criteria (RECIST-F).

Based on the recruitment of a large number of patients from the AVAglio trial and after failing to demonstrate the usefulness of antiangiogenic therapy as a first line treatment after surgery in patients with glioblastoma, other authors also establish criteria to assess the response to this therapy and for this to be done uniformly.[6]

Our understanding of neuroradiology is expanding in parallel to the different surgical treatments and chemotherapies for patients with brain tumours. Although our gold standard continues to be anatomical pathology complemented by genetic/molecular techniques, advanced magnetic resonance imaging makes categorisation of tumours quicker and more reliable, which provides clarity in decision-making regarding these patients.

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# Clinical and magnetic resonance imaging abnormalities of the tongue in patients with amyotrophic lateral sclerosis☆

## Anormalidades clínicas y por resonancia magnética en lengua de pacientes con esclerosis lateral amiotrófica

*Dear Editor:*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by rapid clinical deterioration. Survival times in patients with the condition range between 15.7 and 47 months from disease onset (mean, 29.1 months), depending on the series.[1,2] The clinical features of the disease are heterogeneous and have been attributed to the combination of neurological signs and symptoms of upper and lower motor neuron dysfunction and death.[3]

Dysarthria and tongue atrophy with fasciculations are salient clinical features of bulbar- and bulbospinal-onset ALS, and also appear at later stages of spinal-onset ALS. Abnormalities of the tongue are caused by damage to the hypoglossal nucleus, which leads to flaccid dysarthria, a typical feature of lower motor neuron dysfunction. Upper motor neuron death results in corticobulbar tract dysfunction, which causes spastic dysarthria. Nasal voice may be observed in some patients with ALS who have no structural alterations in the tongue.[4] Previous studies of patients with ALS report an incidental finding called the ''bright tongue sign'' in sagittal MR images of the brain. This sign has been associated with degeneration of the tongue and proposed as a useful radiological feature for diagnosing ALS.[5—8] However, the significance of this magnetic resonance imaging (MRI) finding is still unknown. All patients with ALS and tongue abnormalities undergo brain MRI scans. However, clinicians frequently pay little attention to these abnormalities if patients show clinical signs of tongue atrophy and fasciculations.

We present a series of patients with ALS and tongue abnormalities, displaying a correlation between clinical and radiological (MRI) findings (bivariate analyses, *t* test, chi-square test, Mann—Whitney *U* test). We analysed the following clinical data: phenotype at baseline, disease severity, and progression time at the time of the MRI scan. We evaluated 43 patients with ALS according to the revised El Escorial clinical and neurophysiological diagnostic criteria.[9] All patients completed the revised ALS Functional Rating

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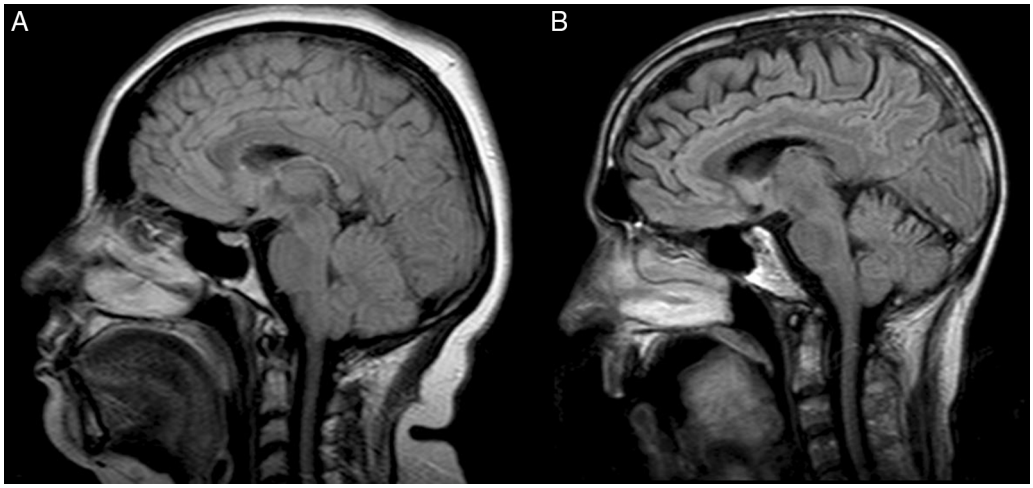


**Figure 1** MRI scan. Sagittal, T1-weighted FLAIR sequence. (A) A 41-year-old woman with bulbospinal-onset ALS manifesting 6 months previously. The shape, position, and signal intensity of her tongue were normal, including the internal structures. (B) A 49-year-old man with bulbospinal-onset ALS manifesting 23 months previously. Abnormalities can be observed in the shape, position, and signal intensity of the tongue; the internal structure is lost.

Scale (ALSFRS-R) at baseline. Tongue hyperintensity, as compared to surrounding soft tissue, on T1-weighted FLAIR sequences was considered abnormal. On MR images: (1) the tongue completely fills the oral cavity; (2) it has a round shape; (3) the dorsal surface of the tongue forms an arch which touches the hard and the soft palate; and (4) the apex touches the posterior surface of the incisor teeth. The absence of at least 2 of these criteria was interpreted as constituting a structural abnormality of the tongue. Furthermore, we compared these findings to those of sagittal T1-weighted MR images from 15 sex- and age-matched healthy individuals.

Tongue MRI results were normal in 19 patients (44%) and abnormal in 24 (54%) (Fig. 1). Mean disease progression time was 10 months in patients with normal MRI findings, and 18 months in patients with tongue abnormalities ($P = .0071$). No statistically significant association was found between disease severity and clinical phenotype. However, the patients with tongue abnormalities scored lower on the ALSFRS-R ($29 \pm 6.01$) than those with normal MRI findings ($32.47 \pm 9.14$).

In ALS, clinical alterations of the tongue are caused by the death of lower motor neurons of the hypoglossal nerve and upper motor neurons of the motor cortex, which results in corticobulbar tract dysfunction.[8] Over half of the patients in our series displayed clinical and radiological structural abnormalities of the tongue. We found an association between presence of MRI abnormalities and disease progression time. MRI hyperintensity is thought to be due to the replacement of tongue muscles, which atrophy due to chronic denervation, with fatty tissue.[5] We found no association between ALS phenotype (bulbar, bulbospinal, or spinal) and the presence of MRI abnormalities; however, patients who scored lower than 30 on the ALSFRS-R were found to be more likely to display tongue abnormalities.

Presence of structural MRI abnormalities in the tongue does not constitute a reliable diagnostic criterion for ALS, but rather a complementary diagnostic criterion for lower motor neuron involvement in patients with ALS. Early detection of these alterations may indicate greater disease severity.

## Author's contribution

All authors contributed to the manuscript and meet the ICMJE criteria for authorship.

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# Myelopathy secondary to copper deficiency: The great imitator☆

## Mielopatía por déficit de cobre: la gran simuladora

*Dear Editor:*

Longitudinally extensive transverse myelitis (LETM) consists of an inflammatory lesion affecting 3 or more consecutive spinal cord segments. Onset may be acute or subacute. Aetiology varies, and includes tumours; infections; inflammation; demyelination; dysimmune, vascular, or metabolic disorders; and nutritional deficiencies.[1,2] Despite its relatively low incidence (1—8 cases per million person-years), LETM is associated with considerable neurological morbidity. We present a case of LETM secondary to copper deficiency, which was initially thought to be due to concomitant vitamin $B_{12}$ deficiency. Copper deficiency is an infrequent aetiology; very few cases have been reported, mainly in patients undergoing gastrectomy.[3—5]

Our patient was an 86-year-old woman of medium-high socioeconomic level and no relevant medical history. She began to experience subacute symptoms of paraesthesia in the lower limbs, mild sensory gait ataxia, and alterations in vibration sense at C7-T1 and joint mobility in the left lower limb. A complete blood count and radiological study revealed vitamin $B_{12}$ deficiency. The patient was diagnosed with subacute combined spinal cord degeneration and started vitamin $B_{12}$ replacement therapy (intramuscular administration; one vial per day for one week, followed by one vial per week for 4 weeks, and finally one vial per month), which achieved significant clinical improvements.

Six months later (while vitamin $B_{12}$ replacement therapy was still being administered), symptoms worsened and the patient developed predominantly proximal right-sided brachial monoparesis accompanied by allodynia. The neurological examination revealed distal limb hypoalgesia, abolished arthrokinetic reflexes (except in the left arm), generalised hyporeflexia, and extensor plantar reflex in the right foot. The patient showed normal cognitive function. A complete blood count revealed normocytic normochromic anaemia (haemoglobin: 8.1 g/dL) and normal vitamin $B_{12}$ levels. A brain MRI scan (Fig. 1) showed multiple round lesions of varying size and morphology (some were ring-shaped with thick walls, others were ill-defined) in both cerebellar hemispheres and in the right bulbar region and middle cerebellar peduncle, with no diffusion restriction and some paramagnetic contrast uptake; no associated vasogenic oedema was observed. We also observed white matter involvement in the periauricular area and the globus pallidus bilaterally, with no contrast uptake. A full spine MRI scan revealed diffuse involvement of the posterior column, with patchy contrast uptake predominantly at C1-C5. A CT scan and a tumour marker test ruled out the presence of a tumour. Serological tests for HIV, syphilis, Lyme disease, and hepatitis C virus, and the autoimmunity study for thyroperoxidase (TPO) antibodies, complement, ANA, ENA, ANCA, and NMO-IgG yielded negative results (Table 1). A CSF analysis showed non-specific alterations, with moderate lymphocytosis and presence of oligoclonal bands. Regarding metabolic and nutritional parameters, plasma levels of vitamin $B_{12}$, folic acid, zinc, and vitamins A and E were within normal ranges. Homocysteine levels were slightly elevated (13.9 μmol/L). The latter finding was suggestive of vitamin $B_{12}$ deficiency, despite normal plasma vitamin $B_{12}$ levels. Total copper and serum ceruloplasmin levels were low (46.9 μg/dL and 15.10 mg/dL, respectively), with 24-h urine copper within the normal range. As the patient had not undergone gastrointestinal surgery, was not receiving iron supplementation, and had normal zinc levels, we performed a gastroscopy to determine whether malabsorption was responsible for the deficiency; we observed only mild, chronic antral gastritis. The patient was diagnosed with copper deficiency of unknown origin and started treatment with copper sulfate (2 mg/24 hours), oral and intramuscular vitamin B complex, and folic acid (5 mg/24 hours). The patient also received botulinum toxin injections in the right forearm, which improved spasticity and relieved pain.

Gait progressively improved in the months following onset of copper replacement (the patient needed a crutch to walk long distances); the mild paraesthesia and pain in the left arm persisted, with slight paresis in the right arm and difficulty performing manipulation tasks with the right hand. At a sensory level, arthrokinetic reflexes were

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