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OPEN

PROGRESSIVE HEMIPARESIS (MILLS SYNDROME) WITH APHASIA IN AMYOTROPHIC LATERAL SCLEROSIS

The onset of motor symptoms in amyotrophic lateral sclerosis (ALS) is strikingly focal. In three-quarters of cases, weakness emerges unilaterally in one limb, typically spreading contiguously over months to become bilateral.[1] An extremely rare clinical syndrome of upper motor neuron–predominant, progressive hemiparesis was first described by American neurologist Charles Karsner Mills (1845–1930).[2] More typical ALS shares a common histopathologic signature with frontotemporal dementia (FTD), consisting of ubiquitinated neuronal and glial inclusions containing the DNA and RNA binding protein TDP-43. Cognitive impairment may be detected in at least one-third of ALS cases and involves mainly deficits in language, executive function, and fluency, with variable levels of behavioral impairments that all have overlap with the purer FTD syndromes. Frank FTD is seen in up to 15% of patients with ALS, in whom it typically occurs before or soon after the development of motor symptoms and is associated with a more rapid disease progression.[3]

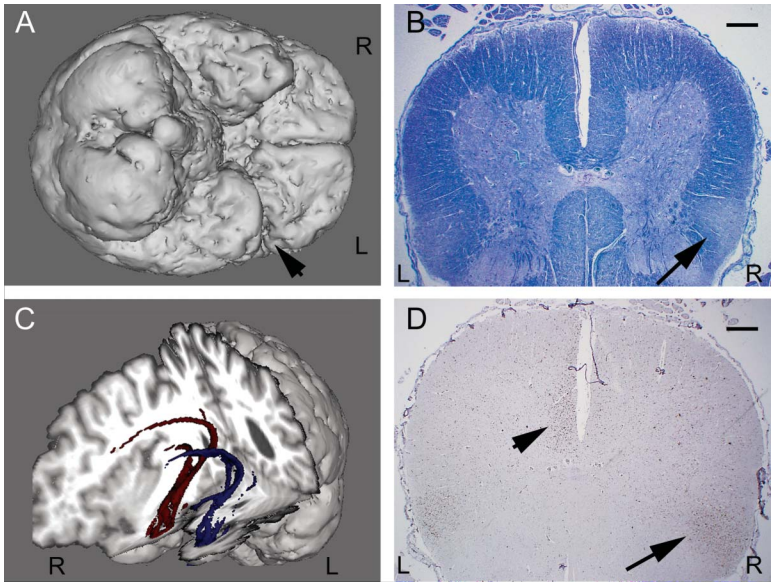
Case report. A 72-year-old right-handed man reported a 1-year history of progressively worsening speech difficulties and right-sided limb weakness. Bedside examination revealed adequate comprehension but a profound inability to generate speech (in the absence of obvious corticobulbar signs or apraxia), accompanied by a spastic right-sided hemiparesis affecting leg, arm, and face. MRI revealed marked atrophy of the left temporal lobe (figure, A). Over the subsequent months, he developed additional severe bulbar dysfunction with visible tongue wasting, and he died within 1 year of respiratory failure. Postmortem examination (tissue donated to the Thomas Willis Oxford Brain Collection) revealed striking left hemisphere atrophy involving the primary motor cortex and the frontal and particularly the left temporal lobe, accompanied by neuronal loss, gliosis, and TDP-43-positive neuronal and glial cytoplasmic inclusions. Bunina bodies, eosinophilic neuronal inclusions pathognomonic for ALS, were present in the medulla. The predominant right-sided hemiparesis was mirrored at the level of the spinal cord by asymmetric pallor of the corresponding crossed lateral corticospinal tract (figure, B), with marked microglial activation in both the crossed left hemisphere lateral corticospinal tract and the uncrossed anterior corticospinal tract (figure, D).

Discussion. The Mills phenotype is extremely uncommon and typically more slowly progressive than this case,[4] which was more in keeping with aggressive forms of classical, generalized ALS. Slow progression and aphasia, isolated for several years before the onset of more generalized frontotemporal dementia, has been long recognized.[5] Progressive hemiparesis has also been noted in the setting of frontal lobe degeneration.[6] Cases of ALS with progressive aphasia[7] and semantic dementia[8] have been reported, but are exceptional. The effortful speech pattern of our patient was in keeping with nonfluent progressive aphasia, while the pattern of temporal lobe atrophy is usually associated with the fluent, semantic variant. While semantic deficits may well have been present in our patient, the profound temporal atrophy might reflect more complex and widespread disruption of left hemisphere perisylvian networks manifest in the striking asymmetry of the corticospinal tract degeneration observed. Reconstruction of the temporal lobe white matter tract projections using diffusion tensor tractography confirmed reduced connectivity on the left (figure, C; imaging carried out with informed consent as part of The Oxford Study for Biomarkers in MND, approved by the South Central Oxford Research Ethics Committee—08/H0605/85).

A PET study in 2 patients with lateralized motor cortical degeneration syndromes (1 with Mills syndrome) demonstrated strikingly lateralized microglial activation in the hemisphere contralateral to the weakness.[9] In our case, CD68 staining for microglia was the most sensitive marker of axonal loss in the main crossed lateral corticospinal tract but also the anterior corticospinal tract carrying uncrossed descending fibers from the cortex to the cervical and thoracic spinal cord. The involvement of the anterior corticospinal tract in ALS has not been systematically studied or specifically highlighted before, and this clear demonstration of its pathologic involvement appears to support the wider concept of cortical dying-forward in contrast to the dogma of solely peripheral neuromuscular dying-back neurodegeneration.

The co-occurrence of aphasia and progressive right hemiparesis in ALS is exceedingly rare. This case

Figure MRI and histologic correlates of a case of amyotrophic lateral sclerosis with progressive aphasia and right hemiparesis



(A) A 3D-rendered volumetric T1-weighted MRI of the brain (underside shown) demonstrates marked left temporal lobe (arrowhead) atrophy. (B) Luxol fast blue/Cresyl violet staining of the spinal cord section demonstrates greater pallor in the right (crossed) lateral corticospinal tract (arrow). (C) Reconstruction, using diffusion tensor tractography, of the temporal lobe white matter projection tracts, using each hippocampus as the seed-base. This demonstrates reduced left-sided (blue) compared to right-sided (red) connectivity (tracts shown within superior oblique cut-out brain section viewed from left). (D) CD68 immunohistochemistry of the spinal cord section shows intense microglial activation of the right (crossed) corticospinal tract (full arrow) but also the uncrossed anterior corticospinal tract (arrowhead only). Scale bars = 700 μm.

further underscores the need to understand the fundamental basis for the marked clinical heterogeneity of ALS. There was no obvious abnormality of the corpus callosum in our case to explain the striking hemisphere bias to the phenotype. Nonetheless, we speculate that there are specific architectural properties of the interconnected motor and frontotemporal cerebral networks, and possibly their glial milieu, which influence both variable phenotype and speed of progression in ALS.

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