NEUROANATOMICAL, CLINICAL, ELECTROPHYSIOLOGICAL, RADIOLOGICAL, AND FUNCTIONAL IMAGING FEATURES IN MOTOR NEURON DISEASES

Abstract
In this review, we will highlight the importance of integrating neuroanatomical, clinical, electrophysiological, radiological, and functional imaging features in motor neuron diseases. The major concepts will be discussed through a case of a 69-year-old woman with progressive gait difficulties. Step by step, divided by sections, the clinical reasoning is explained, together with questions for consideration.

Keywords
Amyotrophic lateral sclerosis • Primary lateral sclerosis • Pyramidal tract • Motor neuron disease • MRI • FDG-PET • EMG

Section 1:
A 69-year-old woman, without medical or family history, presented with progressive gait difficulties since 4 months. She noticed reduced muscle force in both lower limbs with a right-sided predominance, with especially a weak right foot dorsiflexion with slight foot drop causing near falls when she walked fast. There were no symptoms of dysphagia, sphincter dysfunction, or cognitive impairment.

Clinical examination confirmed right predominant lower limb weakness, with weakness most prominent in the right foot dorsiflexors (4+/5). Right predominant lower limb spasticity, and generalized hyperreflexia was seen, together with bilateral Babinski’s and Hoffman’s sign and exaggerated jaw jerk. There were no fasciculations and no muscle atrophy, and sensory testing was strictly normal.

Question for consideration:
1. How would you localize the lesion?

Section 2:
The presence of bilateral muscle weakness, spasticity, hyperreflexia, and Babinski sign localizes to both pyramidal tracts.

Questions for consideration:
1. How the presence of exaggerated jaw jerk could help in localizing the lesion?
2. What is the differential diagnosis of progressive upper motor neuron (UMN) dysfunction?
3. What tests should be performed?

Section 3:
The pyramidal tract is the long-fiber connection between the cerebral cortex and the spinal cord. Fibers from the motor, premotor, supplementary motor cortices, and portions of the parietal cortex converge in the corona radiata, descend through the posterior limb of the internal capsule, basis pedunculi, basis pontis, and medulla, decussate at the lower end of the medulla, and terminate mainly in relation to nerve cells in the intermediate zone of spinal gray matter (internuncial neurons) from which motor impulses are then transmitted to the anterior horn cells. As the corticospinal tracts descend in the brainstem, they send collaterals to motor nuclei of the cranial nerves. Exaggerated jaw jerk localizes the lesion at the lower brainstem or above.

Differential diagnosis of progressive involvement of the pyramidal tracts (especially when involving the lower limbs) includes spinal spondylosis, (primary or secondary) spinal neoplasm, Arnold Chiari malformation, spinal cord arteriovenous malformation, progressive multiple sclerosis, motor neuron disease, spinocerebellar ataxias, hereditary leukodystrophy (e.g. adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe leukodystrophy), subacute combined degeneration of the cord (due to vitamin B12 deficiency), abetalipoproteinemia, deficiency of vitamin E or copper, infection (e.g. HTLV-1, syphilis, HIV, Lathyrus sativus), and hereditary spastic paraparesis.
Spinal cord MRI, including T1-weighted gadolinium enhanced imaging, in our patient was strictly normal. Brain MRI showed moderate diffuse atrophy together with severe bilateral atrophy localized in the rolandic sulcus (Figure 1), in absence of signal changes. CSF analysis was normal, in absence of oligoclonal bands. Levels of vitamin B12/vitamin E/copper, thyroid function, serology for syphilis/HIV/HTLV-1, cholesterol levels, and enzymatic analyses in search for hereditary leukodystrophies were all normal.

Absence of brain and spinal cord lesions, and normal blood and CSF analysis make most of the cited disorders unlikely, except for hereditary spastic paraparesis and motor neuron diseases.

Since most patients with hereditary spastic paraparesis show symmetric clinical involvement, early symptom onset, and autosomal dominant heritance, the clearly asymmetrical muscle weakness, the relatively late onset of symptoms, and the absence of family history made hereditary spastic paraparesis unlikely in our patient. However, ruling out hereditary spastic paraparesis completely is not possible since several subtypes exist and sporadic cases are not rare.

Rolandic atrophy, together with increased MRI signal involving the pyramidal tracts on T2- and FLAIR-weighted imaging (absent in our patient), are often encountered in motor neuron disease. Since these radiological abnormalities are unconstant, the absence of these signs does not rule out motor neuron disease. The most common motor neuron disorder is amyotrophic lateral sclerosis, defined by progressive degeneration of both UMN and lower motor neuron (LMN).

An electromyography (EMG) in our patient, including extensive exploration of bulbar, cervical, thoracic, and lumbar muscles, in search for (asymptomatic) LMN dysfunction, was normal.

Primary lateral sclerosis (PLS) - characterized by the presence of isolated UMN signs, and progressive muscular atrophy - characterized by the presence of isolated LMN signs, are part of the group of motor neuron diseases.

We suspected a diagnosis of PLS in our patient.

Questions for consideration:

1. Can ALS be excluded because of the absence of LMN dysfunction on EMG?
2. What tests could be performed in order to find arguments in favour of motor neuron disease?

Section 4:

Since isolated UMN or LMN dysfunction may predominate at ALS symptom onset, evolution to ALS cannot be excluded in early stage disease. When patients with initial isolated UMN signs develop later LMN signs (and thus ALS), they do so mostly during the first years of the disease.

Criteria for clinically pure PLS include the presence of evident UMN, no focal muscle trophy or visible fasciculation, age at onset after 40, secondary and mimicking conditions excluded by laboratory and neuroimaging, and no denervation in EMG 4 years from symptom onset [1]. PLS is rare, perhaps accounting

Figure 1. Brain MRI showing severe bilateral atrophy localized in the rolandic sulcus on T1-weighted imaging (A, axial view; B, sagital view of the right paramedian brain; C, sagital view of the left paramedian brain). 3D FDG-PET reconstruction images of the brain showing hypometabolism in both perirolandic sulci (D, superior view; E, right internal view; F, left internal view).