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Atypical hereditary spastic paraplegia mimicking multiple sclerosis associated with a novel SPG11 mutation

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Multiple sclerosis (MS) is an autoimmune neurological disease characterized by high clinical heterogeneity [1], sometimes presenting with insidious onset and progressive course.

Besides medical history, clinical evaluation and laboratory analysis, magnetic resonance imaging (MRI) represents an incomparable tool for a complete MS diagnostic work-up [2]; neuroimaging MS criteria have recently been improved to allow earlier diagnosis [3]. However, extensive use of MRI increases the likelihood of detecting incidental white matter (WM) abnormalities, requiring comprehensive investigations for correct diagnosis.

A 22-year-old female was referred to our MS Center because of subacute onset of gait disturbance and large periventricular WM abnormalities detected on brain imaging (Fig. 1).

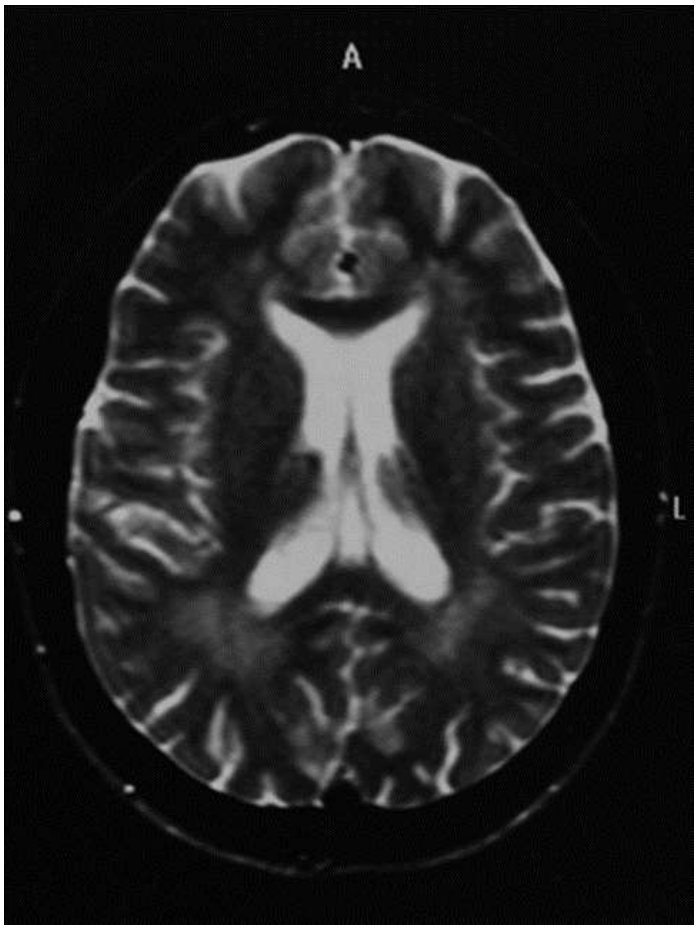

Figure 1. White matter abnormalities on the patient's axial MRI image.

In the following few months she manifested several falls, ‘cramps’, urge incontinence and slight memory disturbances. Her early psychomotor development had been normal with unremarkable family and personal past medical histories.

Neurological examination revealed asymmetrical pyramidal signs (mild spasticity, weakness and brisk reflexes in right leg, with extensor plantar reflex), mild right paresis during gait, mild dysarthria and right facial weakness, and diminished vibration sense at right ankle. Mini Mental State Evaluation (MMSE) was normal.

A second MRI confirmed WM T2/FLAIR hyperintense confluent lesions, without gadolinium enhancement, in the frontal, parietal and peritrigonal regions bilaterally, with a tendency to confluence. Furthermore, we noticed a previously undiagnosed atrophy and thinning of the corpus callosum (TCC) (Fig. 2). Spinal MRI was normal.

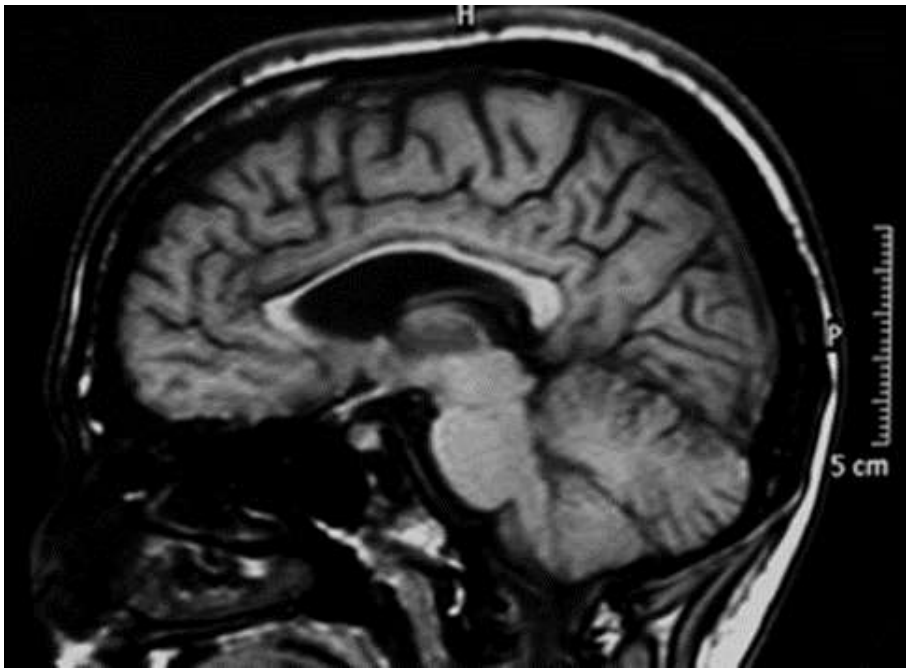

Figure 2. Thinning of corpus callosum on the patient's sagittal MRI image.

Considering that the medical history, clinical evaluation and MRI findings were not typical for MS, a leucoencephalopathy was suspected.

Complete immune-rheumatological and metabolic work-up in blood and cerebrospinal fluid was normal; neurophysiological tests did not reveal any signs of peripheral neuropathy, whereas motor and somatosensory evoked potentials showed mild bilateral central conduction delay.

Neuropsychological evaluation revealed mild memory impairment, deficit in selective and focused attention and reduced verbal fluency. Despite the absence of paraplegia and neuropathy, the combination of severe TCC, mild spastic hemiparesis and mental impairment raised the suspicion of a hereditary disorder and suggested testing for alterations in *SPG11*, a common cause of hereditary spastic paraplegia with TCC (ARHSP-TCC) [4]. In blood DNA from the proposita we found a novel c.4604_4605insC on the paternal allele in compound heterozygosity with a reported c.5989_5992delCTGT variant on the maternal allele, supporting the clinical diagnosis of ARHSP-TCC.

During a 2-year follow-up there was a slow disease progression with impairment also on the left leg and worsening of learning skills and verbal fluency. Brain MRI remained unchanged.

Mutations in *SPG11*, encoding spatacsin, a ubiquitously expressed protein believed to be involved in axonal transport [5], are the major cause of ARHSP-TCC, with over 100 mutations being reported and a worldwide prevalence of roughly 1:100 000 [4-6]. Onset is usually before the age of 25 with progressive spastic paraparesis, mental retardation/cognitive decline, dysarthria, bladder dysfunction and lower motor neuron degeneration [5]. On the basis of a few case reports, the possibility that atypical presentations could be related to specific *SPG11* mutations has been suggested [7-9]. MRI

typically shows TCC and periventricular WM abnormalities, sometimes resembling MS-like lesions. Importantly, a TCC may often go underdiagnosed in a routine MRI report, as in the present case.

Therefore we suggest considering ARHSP-TCC in the differential diagnosis of MS when extensive MRI abnormalities accompany an early onset, followed by progressive worsening of pyramidal signs and neuropsychological impairment. Moreover, although this is a single case report, a possible correlation between the novel c.4604_4605insC mutation and an atypical onset, with asymmetrical pyramidal involvement and a slight cognitive impairment, cannot be excluded.

In our case, only the detection of a striking TCC allowed us to put in a right diagnostic frame these relatively unspecific signs and to prompt the right genetic analyses to disclose a specific form of hereditary spastic paraplegia.

This case report demonstrates that the increasing finding of incidental WM abnormalities, with consequent request for neurological consultation in MS centers, needs a careful multidisciplinary approach [10]: a proper MS/leucoencephalopathies diagnosis requires not only a thorough study of patient medical history and neurological examination, but also cognitive, psychological and sometimes genetic evaluations, combined with accurate neuroradiological assessment.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Ethical standard

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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