



Primary Lateral Sclerosis (PLS) vs. Hereditary Spastic Paraparesis (HSP) in Presenilin-1 (PSEN1) Related Dominant Dementia

Ghazaleh A. Jazi PhD, Jonathan Cauchi MD, Ali Aamer Habib MD, Namita A. Goyal MD, Tahseen Mozaffar MD.

University of California, Irvine-MDA ALS and Neuromuscular Center, Orange, CA



Background

PLS and HSP are rare manifestations of pyramidal tract dysfunction. Whereas PLS is usually associated with pure upper motor neuron dysfunction, HSP may have other manifestations such as peripheral neuropathy. They are both characterized by a slowly progressive spastic paraparesis, with upper extremities and bulbar region traditionally spared in HSP. Moreover, PLS might be associated with cognitive decline and dementia, often frontotemporal dementia. Mutations in the Presenilin-1 gene (PSEN1) gene, a known cause of early Alzheimer's disease have been demonstrated to also lead to spasticity in the absence of any association in spastic paraparesis genes. Up to this point, this has been classified as dementia manifesting an HSP phenotype.

Design and Methods

Case series of 3 patients seen at the University of California Irvine ALS Center with PSEN1 mutations, dementia and primary lateral sclerosis.

Results

We report three male patients, aged 40-44 years, with previously described pathogenic mutations in the PSEN1 gene (A431E in patients 1 and 2 and L381V in patient 3). Patients 1 and 2 were Mexican-American brothers (from Michoacán, the state neighboring Jalisco in Mexico), while case 3 was a Vietnamese man. Patients 1 and 2 presented with frontotemporal dementia as an initial symptom but developed marked spastic quadriparesis (legs>arms). Both developed bulbar dysfunction and spastic anarthria. Patient 3 had a cognitive problem since childhood, then developed progressive spastic quadriparesis and bulbar dysfunction (dysphagia and spastic anarthria). Additional features were myoclonus in patient 1, sympathetic storming in patient 3, and pseudobulbar affect in Patient 1 and 2. MRI showed mild global cerebral atrophy in all 3 cases.

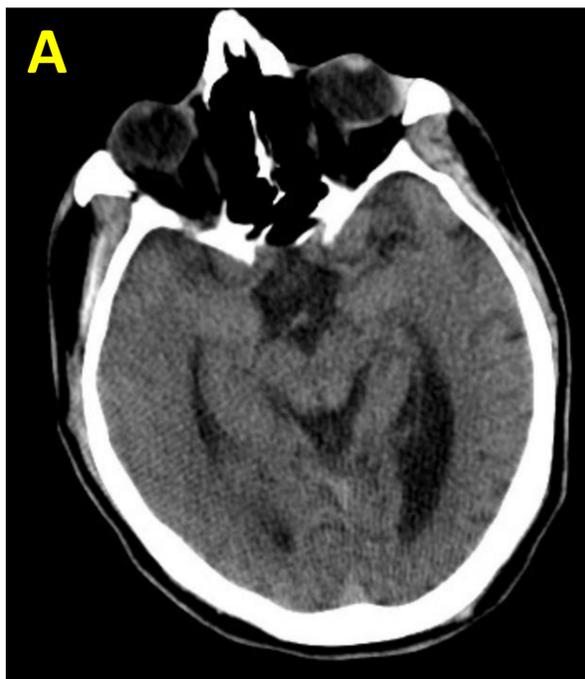
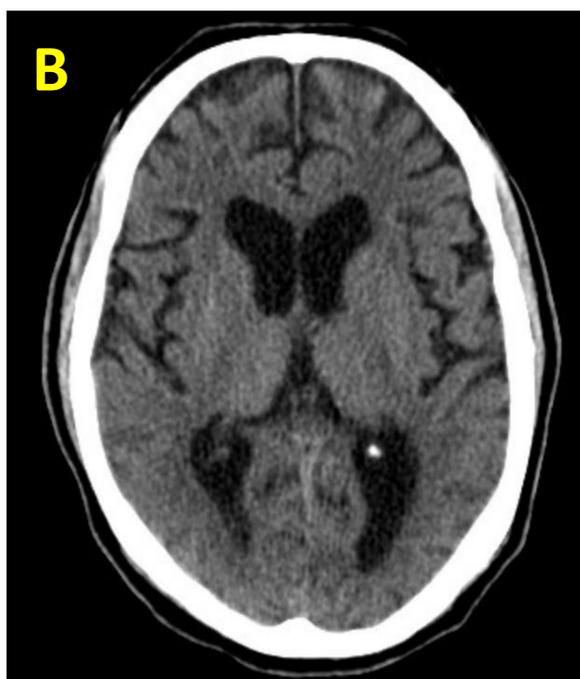


Figure A and B: CT head, axial cut at level of midbrain [A] and basal ganglia [B] demonstrating marked generalized cortical atrophy in a 39-year-old male with severe cognitive impairment. Further investigation revealed mutation in Presenilin-1 (PSEN1).



Conclusion

We report on three patients presenting with predominantly cognitive or pseudobulbar features with later onset of spasticity, first in the lower extremities. While the spasticity component in the legs is reminiscent of HSP, a preceding and progressive frontotemporal impairment or pseudobulbar affect are not typical presentations. There is reported dementia in certain rare subtypes of HSP though these tend to be autosomal recessive subtypes and it is not described as the presenting feature. All three of our patients were heterozygous for PSEN1 mutation, an autosomal dominant allele. In addition, a case report by *Parker et al.* described a homozygous patient with a mutation of A431E in PSEN1 that developed severe dementia beginning in his mid-thirties with subsequent and aggressive development of spastic quadriparesis. We do concede that there are no large-scale studies specifically looking at the preponderance of dementia in HSP though the absence of neuropathy, spasticity in the upper limbs and pseudobulbar features are not reported features typical for HSP. These features are commonly seen in PLS patients however, and each of our reported patients had UMN features for more than four years meeting the accepted Singer criteria. It is for these reasons that we conclude that the overall presentation seen in certain patients with PSEN1 mutations is more consistent with a PLS phenotype rather than HSP. We therefore feel that it is prudent to consider screening PLS patients or ALS/Dementia patients in ALS clinics for PSEN1 mutations, especially from at risk regions, such as Jalisco or Michoacán, Mexico.

References

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