Leukoencephalopathy with Neuroaxonal Spheroids Presenting as Frontotemporal Dementia

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Leukoencephalopathy with neuroaxonal spheroids is a rare form of presenile dementia, supported by magnetic resonance imaging findings of predominantly frontoparietal cerebral white matter involvement [1,2]. The age of onset and the course vary considerably but most patients present at the age of 30–50 years with behavioral and cognitive decline, unsteady gait, urinary incontinence, seizures and involuntary movements. Overt dementia, abulia, dysphagia and severe motor dysfunction with pyramidal signs or primitive reflexes usually develop later and eventually progress to death over a long period – up to 34 years. Although the disorder is considered in the differential diagnosis of frontotemporal dementia, reported details of cognitive evaluation are very limited [2].

The cause of LENAS is unknown. Autosomal dominant inheritance in some families suggests an underlying genetic defect [1-4]; isolated cases may be interpreted as resulting from *de novo* mutations [2]. Neuroaxonal spheroids represent the pathological hallmark of LENAS but occur also in a range of other disorders [2-4], most notably in polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy caused by mutations in DAP12 (TYROBP) and TREM2 [5]. Because both disorders also share some neurological and imaging features, we speculated that one of these genes might be responsible for LENAS presenting as isolated frontotemporal dementia in our patient.

LENAS = leukoencephalopathy with neuroaxonal spheroids

Patient Description

A 57 year old man of Ashkenazi Jewish origin presented with progressive behavioral changes of 18 months duration. He stopped working as a farmer and became socially withdrawn, disinterested, unmotivated, and inconsistent in performing regular daily activities. His family members characterized his mood as good but noted episodes of compulsive eating and obsessive activities. The family history was negative. Formal neurological examination showed only prominent bilateral frontal release signs. Neuropsychological testing demonstrated marked lack of spontaneity and initiative, prominent distractibility, reduced concentration span, sustained attention deficit, cognitive and motor perseverations, and impaired abstract thinking, set shifting and verbal fluency. Memory retrieval and learning were impaired. Language was moderately anomic, but comprehension, sentence repetition, reading and writing were normal. The Addenbrook Cognitive Test pattern was typical for frontal dysfunction

The results of routine laboratory tests, cerebrospinal fluid studies, and infection, endocrine and metabolic screen, including vitamin E, were normal. Electroencephalography showed slow activity over the frontal leads, and peripheral nerve conduction study was normal. Brain MRI showed marked frontal atrophy, ventriculomegaly, and prominent diffuse involvement of the frontal subcortical and periventricular white matter with loss of volume and with thinning of the corpus callosum [Figure A]. Isolated foci of signal intensity changes were also present in the parietal white matter, whereas the subcortical U-fibers were spared. FDG-PET (fluoro-2-deoxy-D-glucose and positron emission tomography) demonstrated reduced frontal and to a lesser degree parietal and temporal metabolism [Figure B].

Residua from an old sport-induced right ankle fracture were seen on X-ray without cystic bone changes, and no basal ganglia calcifications were present on brain computed tomography. Open frontal biopsy revealed leukoencephalopathy characterized by comparable loss of myelin and axons, and mild gliosis accompanied by numerous neuroaxonal spheroids immunoreactive with neurofilaments protein and ubiquitin consistent with the diagnosis of LENAS [1-4]. Overlying cortex was unremarkable and no cortical abnormalities were noted with immunostain for tau, ubiquitin, alpha-synuclein and beta-amyloid [Figure C].

Over the following 2 years, there was a progressive deterioration in the patient's cognitive and motor functions. He became emotionally labile, disinhibited, had a severely reduced verbal output, and later

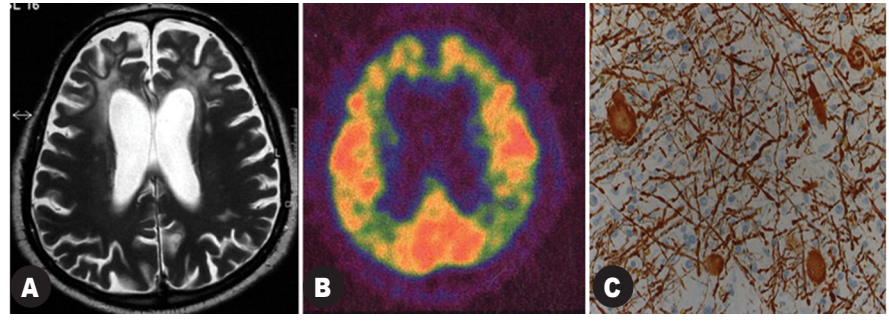
developed dysphagia, incontinence, seizures and bilateral pyramidal signs. Repeat formal neuropsychological examination became impossible.

Sequence analysis of DAP12 and TREM2 genes was performed as previously described [5] on DNA extracted from peripheral blood of the patient with informed consent of his legal guardian. Sequencing of the coding regions and all the exon-intron boundaries of both genes revealed no mutations.

Comment

This patient presented with isolated presenile cognitive decline associated with MRI findings of predominantly frontal atrophy, white matter involvement and callosal thinning. Additional symptoms developed later, after the pathological diagnosis. While a similar presentation occurs in LENAS [4], the initial course is usually dominated by seizures [2], unsteady gait [3], sphincter incontinence and motor symptoms [3]. His main early manifestations included executive dysfunction, impaired abstract thinking and set shifting, perseverations, and reduced attention and verbal fluency – a pattern typical of frontotemporal dementia. Although white matter changes may accompany disorders with frontal cortical degeneration [2], their extent and pattern favored alternative diagnosis in our patient.

Consistent with the clinical findings, FDG-PET in our patient showed reduced glucose metabolism in the frontal areas. However, no cortical neuronal alterations or loss was identified pathologically. A sample error is always a consideration in brain biopsy, but autopsy studies in LENAS report no cortical involvement [3,4] and single photon emission tomography demonstrates frontal hypoperfusion [1,4]. A possible explanation of these observations may be related to the effect of white matter damage on cortical function exerted preferentially in the frontal lobes.



Cerebral imaging in the patient. [A] Axial T2-weighted MRI showing frontal atrophy, ventriculomegaly and diffuse involvement of the frontal subcortical and periventricular white matter. **[B]** FDG-PET showing reduced frontal and to a lesser degree parietal metabolism. **[C]** Frontal biopsy showing a group of 5 neuroaxonal spheroids in the subcortical white matter (x 400, neurofilament protein immunostain).

Early frontal lobe syndrome also characterizes PLOSL, which shares with LENAS cerebral atrophy, leukoencephalopathy sparing the U-fibers and glucose hypometabolism of a similar distribution, as well as the main neuropathologic findings. However, unlike in our patient, PLOSL is an autosomal recessive disease typically associated with basal ganglia calcifications and often with cystic alterations in the distal bones of the extremities. Because some phenotypic variability and different mode of inheritance may result from different mutations in one gene, we sequenced DAP12 and TREM2 and found no alterations. These observations expand the range of early LENAS phenotype to include isolated presenile frontotemporal dementia and probably exclude DAP12 and TREM2 as candidate causative genes in sporadic cases.

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PLOSL = polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy

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