Frontal Variant of Alzheimer's Disease: Clinico-CSF-Pathological Correlation

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A 56-year-old right handed sailor was admitted to our department for evaluation of cognitive impairment. His first complaints started four years before when he returned from the ship and his wife noticed increased apathy that spontaneously improved in several weeks. Two years before she noticed extreme change in his behavior, he became introverted, his spontaneous speech became very sparse, he was too sensitive to external stimuli and cried a lot, even to a meaningless joke. He was disoriented in time, and had problems with driving the car. Despite this, his memory was relatively spared. His coworkers also observed that he turned incapable of performing his duties anymore, mainly because of behavioral problems. In the next year, his condition progressed further, he became aggressive and irritable, his speech became very sparse and he spoke only a few words. He was admitted to local psychiatry department and treated for depression. Several months before admission to our department, he developed difficulties on walking and involuntary muscle twitching.

On admission, neurologic examination revealed a severely uncooperative, but alert patient. He was disoriented in time, place and towards others, his speech was characterized by perseveration of the words he would hear other patients say, but no contact could be obtained with him. He could not sit or stand on his own. He had vertical eye movement paralysis. Frontal release signs were present. He had rigor of all four extremities, more pronounced on the left, and positive Babinski sign on the left. When attempting to move, he had severe myoclonic jerks, most pronounced on his arms. He also suffered from urinary incontinence.

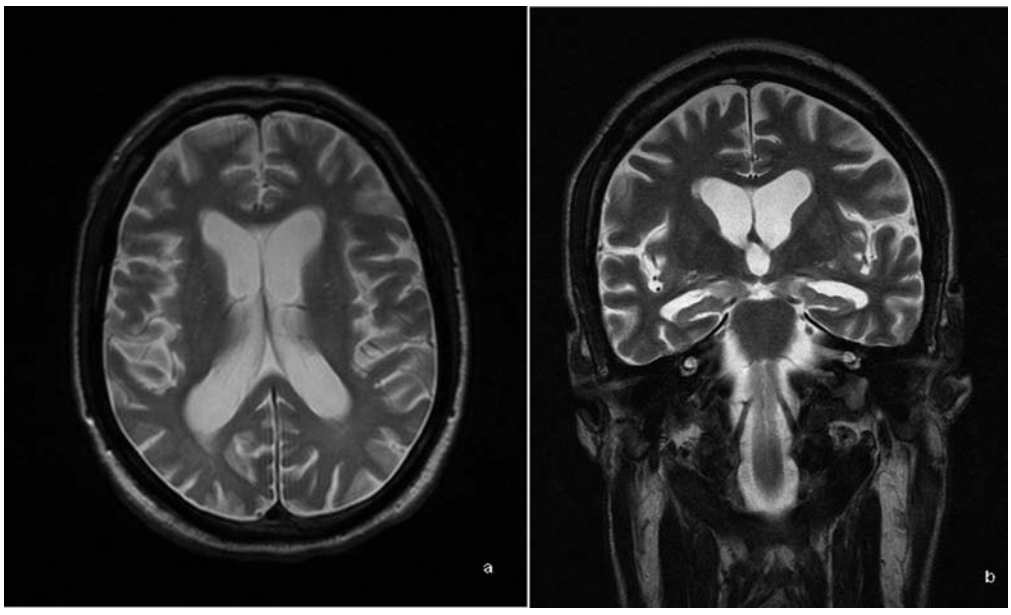

Figure 1: *Brain MRI, T2 sequences; a) coronal view showing bilateral hippocampal atrophy; b) transversal view showing moderate frontal lobe atrophy.*

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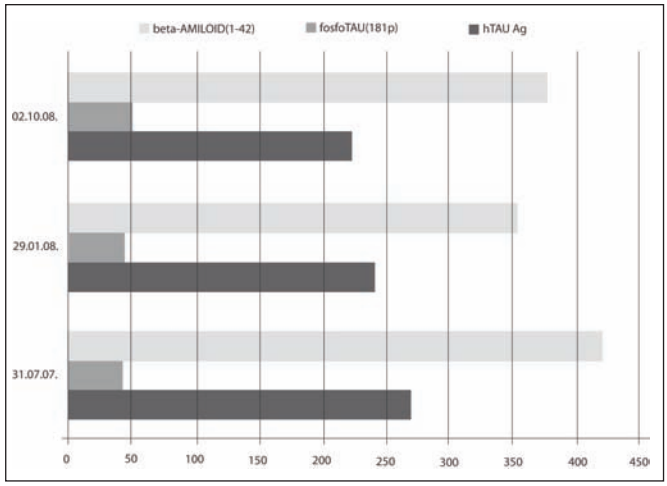

Figure 2: *Cerebrospinal fluid levels of β amyloid, phospho TAU and hTAU Ag over time.*

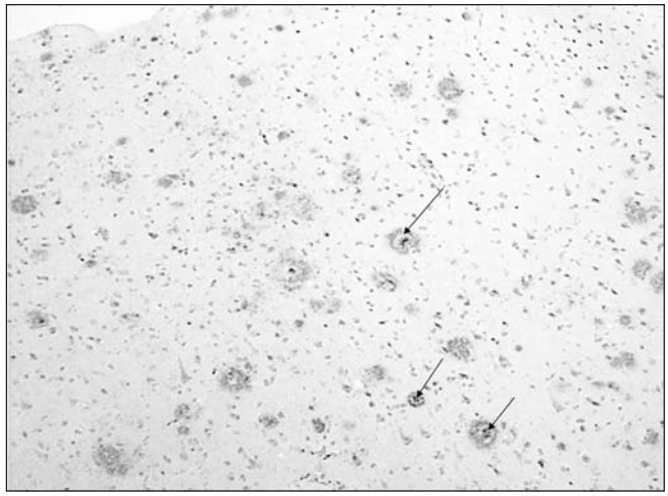

Figure 3: *Plaque cores were composed of extracellular β amyloid deposit (arrows) (magnification X100).*

Brain magnetic resonance imaging (MRI) revealed diffuse atrophy with bilateral enlargement of lateral ventricles and periventricular fluid attenuated inversion recovery (FLAIR) hyperintensities (Figure 1). Brain single photon emission computed tomography (SPECT) with ^{99m}Tc-ECD showed diffuse hypoperfusion, predominantly in the parietal and occipital lobes. Cerebrospinal fluid (CSF) analysis revealed elevated proteins with positive oligoclonal bands. Cerebrospinal fluid hTAU Ag, phosphoTAU(181P) and beta-amyloid (1-42) were 270 ng/L, 43 ng/L and 420 ng/L, respectively (normal values <300; <50; >500, respectively) (Figure 2). Protein 14-3-3 was negative. We did extensive search for infectious (serology for viruses, syphilis, fungi and parasites), immune (ANA, ANCA), metabolic (vitamin B12, thyroid hormones) and tumor/ paraneoplastic (Hu, Yo and Ri) causes, all with negative findings.

Brain biopsy (a part of the frontal lobe) yielded three needle cores of grayish tissue. Hematoxylin and eosin stained sections of paraffin-embedded tissue showed cortical tissue with a high density of senile plaques. Plaque cores were composed of extracellular β amyloid deposit (Figure 3), peripherally circumscribed by tau-immunoreactive neurofibrillary tangles (Figure 4), GFAP immunoreactive astrocytes and CD68 immunoreactive microglia. Around the amyloid cores senile plaques showed tau-immunoreactive neuritis (Figure 3). In cortical neurons, neurofibrillary tangles were also tau immunoreactive. Ubiquitin immunoreactivity was present in some tau-like distribution. The biopsy sample was free from β amyloid angiopathy.

Based on clinical presentation, neurologic examination, brain imaging, CSF analysis and brain biopsy, the diagnosis of frontal variant of Alzheimer's disease (AD) was made.

Discussion

FvAD is an unusual form of AD, which can mimic an fvFTD syndrome. Johnson et al identified a subgroup of patients with pathologically confirmed AD that presented clinically with early and disproportionate frontal lobe impairments on neuropsychological tests and exhibited an unusually high degree of frontal tangle pathology at autopsy[1]. The authors concluded that the most distinctive clinical feature of patients with frontal AD in this study was the severe impairment on frontal lobe functioning tests during mild stages of dementia. It is interesting that fvAD patients had an increase in tangles but not plaques in frontal lobes, suggesting that tangles may contribute to the atypical clinical presentation of fvAD patients. Other authors have reported that these patients show additional deficits in mnestic and visuospatial function on cognitive testing, indicative of dysfunction extending beyond the frontal lobes and hence falling outside diagnostic criteria for FTD but fulfilling diagnostic

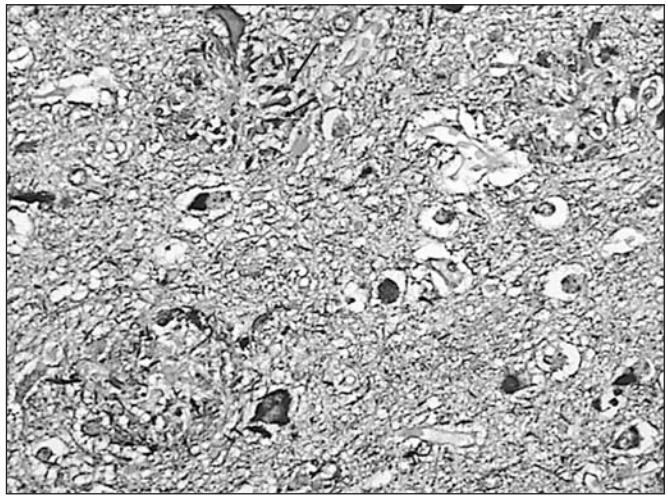

Figure 4: *Senile plaques around amyloid cores showing tau-immunoreactive neuritis (arrows) (magnification X400).*

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criteria for AD[2]. It is important to note that fvAD patients do not differ from typical AD patients on nonexecutive neuropsychological tests of intelligence, language, verbal and nonverbal memory and visual-spatial abilities, but they do show more severe neuropsychiatric symptoms, impaired activities of daily living and greater caregiver distress than typical AD patients[3].

Voxel-based morphometry studies suggested the neuropsychiatric symptoms seen in early AD to be associated with atrophy of well-defined brain structures[4]. For example, apathy that is commonly seen in early AD as well as in FTD is associated with gray matter atrophy of inferior frontal and orbitofrontal regions of both hemispheres.

Current longitudinal clinical data show that fvAD may be distinguished from fvFTD by the concurrence of signs of a genetic predisposition for AD (including positive family history and presence of an APOE ε4 allele) and episodic memory impairments early in the course of the disease[5]. However, diagnostic uncertainty remains when these genetic factors are absent, as in our patient.

CSF β amyloid (1-42) (Aβ42), total tau (tau) and phospho-tau (p-tau) have emerged as potential biomarkers to differentiate AD from normal controls, AD and FTD. The combination of these three biomarkers has a specificity of 85% in differentiating AD from FTD[6]. Based on literature data, guidelines issued by EFNS recommend that CSF tau, p-tau and Aβ42 can be used as an adjunct in cases of diagnostic ambiguity (Level B)[7]. It remains to be investigated whether CSF biomarkers can differentiate fvAD from FTD.

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