Dementia, Amyotrophy, and Periodic Complexes on the Electroencephalogram

A Diagnostic Challenge

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Background: The clinical diagnosis of neurodegenerative diseases is a challenge to the neurologist. In many cases the diagnosis becomes neuropathological only after the autopsy. Several consensus criteria have been defined for the clinical diagnosis of different neurodegenerative diseases, among them the various types of dementia as well as prion-induced diseases. When compared with neuropathological findings, these criteria have proved to be reasonably accurate for regular practice, research, and epidemiological studies. The problem arises when a combination of complementary and clinical data are obtained that do not easily match these diagnostic criteria.

Case Description: We describe a patient with dementia and periodic complexes on an electroencephalogram, suggesting a diagnosis of sporadic Creutzfeldt-Jakob disease.

Results: When the condition progressed, signs and symptoms of a motoneuron disease appeared. Thus, 2 different diagnoses were proposed: (1) an amyotrophic variant of a prion-induced disease; or (2) an ELA dementia syndrome with periodic complexes on the electroencephalogram, a finding that previously has not been described.

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In addition to memory loss, his family observed a striking psychological change in the patient. He did not take part in conversations and refused to socialize at all. No other behavioral disorders were observed.

The results of the neurological examination were unremarkable. The patient’s cognitive status as determined by the Mini-Mental State Examination was in the lower-normal limit for his age and cultural level (23/30). The patient was partially oriented with regard to time and had evidence of short-term memory impairment as well as delayed retrieval. Verbal fluency was moderately reduced. He was unable to subtract 7 from 100 and made errors in simple arithmetic calculations and when reciting backward the months of the year. Ideomotor and constructive praxis (cube and clock drawing) were normal. In contrast, he was unable to follow simple hand motor sequences. His insight was poor, and he could not interpret a common proverb. His mood was dysphoric, slightly moric, and disinhibited. His thought was perseverant and disturbed by hypochondriac and paranoid ideas.

A blood cell count and routine biochemical analysis yielded normal results. A very mild dilatation of the anterior frontal and temporal sulci was observed on the computed tomographic scan and magnetic resonance imaging study of the brain. A striking bilateral frontotemporal hypoperfusion was detected with single-photon emission computed tomography (Figure 1).

No significant clinical changes were observed in the next 6 months. His family noted apathy, bradypsychia, and sporadic aberrant behavior. In September 1999, slurred speech and amyotrophy of both hands caused re-admission. The patient’s cognitive level had deteriorated. A gross impairment in attention and concentration precluded a detailed neuropsychological evaluation. Results of the neurological examination were unchanged (Mini-Mental State Examination score, 20/30); other neuropsychological tests were impossible to perform because of severe dysarthria and early fatigue. Dysphagia appeared, so he could swallow only soft foods. Decubitus intolerance forced the patient to sleep in an armchair. His cough was feeble, and secretions accumulated in the oropharynx. Amyotrophy had spread to the scapular girdle and cervical muscles; both arms were pendulous, and the patient was wearing a cervical collar because of a bent head. Muscle reflexes were weak in both arms but brisk in the legs, with ankle clonus. No Babinski sign was observed. A serial EEG depicted a progressive slowing of background activity but no periodic complexes. A gastrostomy was performed, but the patient refused artificial ventilation. He died on February 22, 2000, 18 months after the disease began.

Following the safety rules proposed by experts for performing high-risk autopsies in patients with possible prion diseases, only the brain was removed. The uppermost segments of the spinal cord were retrieved through the foramen magnum. After formalin fixation, the brain was cut following the coronal plane while the brainstem and cerebellum were cut following the horizontal plane. Representative fragments were selected from all areas of the central nervous system. They were preventively decontaminated in formic acid and embedded in paraffin. Histological sections of 5 μm were stained with hematoxylin-eosin, cresyl violet, and luxol fast blue and immunostained for ubiquitin, τ-protein, and proteinase K-resistant prion protein following standard methods and using commercially available monoclonal antibodies (anti-prion protein: DAKO Clone, 1/30; DAKO Diagnosticos SA, Barcelona, Spain; antiubiquitin: DAKO...
A macroscopic examination of the brain showed nothing remarkable. A microscopic examination found histological lesions in 2 sets of central nervous system structures: first in the frontotemporal neocortex, the amygdala, and the hippocampus and second in the bulbar and anterior horn motor neurons.

The frontotemporal neocortex showed moderate laminar spongiosis of the second cortical layer. This spongiosis was unevenly distributed from one circumvolution to the other. In the most severely affected zones, mild neuronal loss and gliosis were observed; in general, however, the neuronal density and cytoarchitectonic structure of the neocortex were not conspicuously altered. In the primary motor cortex, the Betz cells maintained their normal characteristics in the cresyl violet stain.

In the amygdala, a moderate to severe neuronal loss with associated gliosis was evident. The basolateral nuclear complex was more severely involved than the corticomedial complex. The parahippocampal gyrus and entorhinal cortex showed superficial spongiosis that increased in intensity toward the subiculum. The presubiculum exhibited dense focal laminar gliosis and neuronal depletion. In the hippocampal formation, both the pyramidal and molecular layers remained undamaged.

The motoneurons in the anterior horn of the spinal cord were abnormal, exhibiting retracted angulus cytoplasmic profiles and pycnotic nuclei. The same signs were observed in the neurons of the ambiguous nuclei in the medulla. In the hypoglossal nuclei there was a marked neuronal loss, and the remaining cells showed atrophic features. No Bunina bodies were observed in motoneurons at any level.

There was no demyelination in the sections stained with luxol fast blue, neither in the cervical corticospinal tracts nor in the bulbar pyramids. No evident histological abnormalities were observed in the basal ganglia, thalamus, or cerebellum. Minor lesions were present in the substantia nigra, with some neuronal loss, free and phagocyted pigment, and a few hyaline intracytoplasmic inclusions. However, no Lewy bodies were found. Neither neurofibrillary tangles nor amyloid plaques were observed in any examined area.

The neocortex, the amygdala, and the hippocampus underwent ubiquitin-positive immunostaining. The neocortical areas showed both intraneuronal and intraglial cytoplasmic inclusions; they were predominantly distributed in superficial layers following the laminar microspongiosis. However, in some gyri a striking deposition was observed in the otherwise histologically undamaged fifth and sixth cortical layers. Scattered neurons in other layers also had ubiquitin-positive inclusions that were of varying shape and size: either triangular, rounded, or curvilinear surrounding the nuclei. Some neuronal perikaryons were completely decorated by ubiquitin, whereas others harbored a particularly dense inclusion. In the amygdala, the ubiquitin deposition roughly followed the severity of histological damage. In the hippocampal gyrus, there were plenty of small, rounded inclusions in the molecular layer (Figure 3). In contrast, only some granular inclusions were observed in a few pyruvate neu-

rons. Outside of the frontotemporal cortex and hippocampus, very few ubiquitin-positive inclusions were found in the larger neurons of the caudate nuclei and putamen. Findings from ubiquitin immunostaining were negative in the substantia nigra, in the motor nuclei neurons in the brainstem, and in the anterior horn of the spinal cord. The neuropathological diagnosis was frontotemporal degeneration with motoneuron disease and associated ubiquitin-positive inclusions.

The patient we describe had cognitive impairment and behavioral disorders suggesting frontal or frontotemporal lobe dysfunction. Secondary symptomatic dementia was ruled out by an extensive work-up. Neuroimaging studies indicated the absence of a macroscopic structural lesion in the frontotemporal lobes. In contrast, a profound anterior brain hypoperfusion was observed with single-photon emission computed tomography, in correlation with the clinical picture. Thus, a frontotemporal type of dementia was our first clinical diagnosis for the patient. However, focal deficits of perfusion have been described in early stages of CJD. This hypoperfusion is detected at the frontal level in some patients. Unexplained, the polysomnographic EEG detected bursts of periodic sharp biphasic or triphasic waves, resembling the typical pattern observed in sporadic CJD. According to the current diagnostic criteria developed in Europe, the association between rapidly evolving dementia and a periodic EEG pattern supports the clinical diagnosis of probable sporadic CJD if 2 of the following neurological abnormalities are also present: pyramidal, cerebellar, or extrapyramidal signs, myoclonus, abnormal vision, or akinetic mutism. Such presumed cases of CJD should be reported to the respective National Prion Disease Registry following the recommendations of the European Concerted Action Project. Our patient fulfilled various clinical criteria for possible or probable CJD.

Many studies have been conducted to establish the sensitivity and specificity of EEG abnormalities in the diagnosis of CJD. Because the EEG complexes vary with the patient’s level of attention, sensitivity depends on factors such as the number, length, and time of the proce-
Specificity of the EEG was 86%. Periodic EEG complexes have been introduced as a useful tool to endorse the diagnosis of sporadic CJD (it often produces spinal fluid characters that have not been described in frontotemporal dementias such as Alzheimer disease and dementia with Lewy bodies, although they have not been described in degenerative dementias such as Alzheimer disease and dementia with Lewy bodies, although they have not been described in frontotemporal dementia.

Recently, an assay of 14-3-3 protein in the cerebrospinal fluid has been introduced as a useful tool to endorse the diagnosis of sporadic CJD (it often produces a negative result in hereditary cases). The sensitivity and specificity of the 14-3-3 test have been estimated to be as high as those of the EEG. In our patient this test result was negative, in contrast with the positive EEG finding.

Later in the course of his illness, our patient had fully developed lower motor neuron disease. He had severe, widespread weakness and amyotrophy in both arms, prominent fasciculations, bulbar palsy, tongue atrophy, and diffuse signs of denervation on the electromyogram with normal nerve conduction velocity. He also had a pyramidal syndrome with ankle clonus and brisk muscular reflexes in his legs. This upper motor neuron syndrome is common to both CJD and amyotrophic lateral sclerosis. In contrast, the characteristic lower motor neuron involvement of amyotrophic lateral sclerosis has been disputed in CJD. Although some authors have proposed an amyotrophic variant of CJD, other experts have rejected such a clinicopathologic phenotype, holding that amyotrophy in CJD is just a terminal phenomenon in emaciated patients with dementia. However, in a recent and exhaustive review of the literature, Worrall et al found 50 cases of sporadic or familiar prion disease positively confirmed, in which clinically significant amyotrophy and electromyographic denervation were well documented. They concluded that "amyotrophy is occasionally a prominent feature of Creutzfeldt-Jakob disease and underscores the importance of documenting lower motor function and the crucial role of examining the spinal cord in cases of prion diseases." This proposal differs from the current recommendation that only the brain should be removed in the autopsies of patients with suspected prion diseases. In cases of frontal dementia plus amyotrophic lateral sclerosis, a complete autopsy can be performed following the routine safety measures; the literature data continue to support the validity of this conclusion even if transient periodic EEG complexes are observed, provided the 14-3-3 test of the cerebrospinal fluid yields a negative result.

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