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12 November 2012 15 December 2012

The clinical spectrum of frontotemporal dementia: A case of rapidly progressive dementia☆

El espectro clínico de las demencias frontotemporales: un caso de demencia rápidamente progresiva

Dear Editor:

Frontotemporal lobar dementias (FTLD) are a group of neurodegenerative disorders that are heterogeneous in their clinical expression, histopathological features, and genetic component. They affect frontal and temporal lobes and are associated with neuronal loss and gliosis. They are considered the third most common cause of dementia after Alzheimer disease (AD) and dementia with Lewy bodies. In patients younger than 65, they represent the second most common cause.[1] We have no incidence data but some autopsy series show that FTLD cases represent 10% to 15% of all neurodegenerative dementias.[2] The typical age of onset is usually younger than in AD, which manifests in patients older than 75 years. FTLD distribution is similar for men and women and we find a family history in 30% to 45% of cases, including cases with autosomal dominant inheritance.[1] Mean survival is 6 to 8 years, with a range of 2 to 15 years.[3]

Several groups have published consensus criteria on the clinical and histological changes that occur in FTLD.[4,5] The histopathology of FTLD cases is characterised by linear spongiosis in layers II and III of the cortex, with predominant neuronal loss and gliosis.[6] Furthermore, presence of aggregates or deposits in neurons or glial cells lets us classify these dementias into 4 groups: tauopathies, ubiquitinopathies, neuronal intermediate filament inclusion disease, and those with no data specifically pertaining to any of the above types.

☆ Please cite this article as: Castrillo Sanz A, Guerrero Becerra P, Duarte García Luis J. El espectro clínico de las demencias frontotemporales: un caso de demencia rápidamente progresiva. Neurología. 2014;29:384—385.

We present the case of an 80-year-old man with a history of high blood pressure who drinks one glass of wine a day and does not smoke. He requested a medical consultation due to having fallen several times in the preceding 6 months. The first neurological examination only revealed slow walking speed with a tendency to flex the trunk forward. At 5 months after the first visit, we observed rapidly progressive exacerbation of his gait disorder. Recent memory lapses and poor sphincter control were also observed. The patient was being treated with indapamide, piracetam, allopurinol, paracetamol, and mirtazapine. Examination showed that the patient was disoriented in space and time, with generalised muscular rigidity and unstable gait. He required help from 2 people in order to walk. The patient later presented rapid neurological exacerbation and became unable to walk, eat, or control sphincters. His level of consciousness was impaired, with excessive daytime drowsiness, disorientation, and poverty of speech which evolved to no speech. He also showed intense axial hypertonia at all levels, as well as generalised muscular rigidity, predominantly in the upper limbs which exhibited cogwheel rigidity. We observed a few intermittent and subtle myoclonic jerks when the patient held up his arms. We decided to admit him to the hospital to complete the study, after which he underwent the following complementary tests: full blood count, coagulation test, baseline arterial blood gas analysis, general and liver blood tests, ammonia test, creatinine kinase level, metal ion levels, PSA blood test, and electrophysiological study. All results were normal. Negative results were obtained in the screening for vasculitis, analysis of protein 14-3-3 in cerebrospinal fluid, and syphilis serology test. Levels of vitamin B_{12}, folic acid, and thyroid hormones were normal, as were results from the CSF study. The electroencephalogram showed slower background cerebral activity with frequent bilateral paroxysmal bursts (frontal regions) of slow waves. Brain MRI showed only significant cortical and subcortical atrophy, predominantly located in the temporal lobes and with ventricular dilation secondary to atrophy. The patient's condition progressively worsened and he died one week after.

Anatomical pathology study: external examination revealed global atrophy with a moderate dilation of the ventricular system. In the histological study, we observed mild-to-severe gliosis in the cortical grey matter, especially in the lower layers, and patchy areas of microvacuolation

in layers I and II. Gliosis and neuronal loss were more pronounced in the anterior entorhinal cortex and in region Ca2 of the hippocampus. Black matter showed patchy neuronal loss with gliosis. After staining with tau, we observed astrocytic plaques, tufted astrocytes, globose neurofibrillary tangles, granular cytoplasmic tau immunoreactivity, oligodendroglial cytoplasmic inclusions (coiled bodies) and striatal neuropil threads and aggregates.

We found no positive structures after α-synuclein staining and no prion protein deposition after PrP immunohistochemical staining. Vascular walls do not show amyloid deposits.

In summary, this was a case of tauopathy with a disease profile of corticobasal degeneration and argyrophilic grain disease.

Primary neurodegenerative diseases of the central nervous system are a complex group of conditions that are difficult to classify. There is an increasing tendency to base disease classifications on immunohistochemical features; however, diagnosis is significantly limited because different conditions show overlapping traits.[7] We know that at least one abnormal protein is present in every case of dementia, and it influences a series of processes that cause neuronal death. This may be due to a misfolded protein or one with tendency to form aggregates and deposits that might be toxic.[8] An interaction between the different proteins can also take place, leading to different conditions with overlapping neuropathological and clinical traits, as in the case of FTLD.

Since the clinical presentations are diverse, neurologists should consider the FTLD group of disorders when performing differential diagnosis of any rapidly progressing form of dementia. In such cases, anatomical pathology diagnosis and immunological and histochemical findings might help in identifying the correct phenotype of the disease.[9]

Our case is an elderly patient who presented a gait disorder that was progressively associated with parkinsonian symptoms, such as bradykinesia and rigidity. In less than 3 months, he presented rapidly progressing cognitive decline and later died. After performing differential diagnosis, doctors thought that the entity would most likely be classified as a corticobasal syndrome. However, after reviewing the literature, we observed that our patient's first symptom, gait apraxia, is one of the least frequent. There were no other typical signs of corticobasal syndrome, such as alien limb syndrome or asymmetric rigidity at onset. Unlike other cases, our patient rapidly developed cortical dysfunction symptoms that, according to published studies, normally appear at a later time, at 2 to 3 years after onset. Age of onset was atypical, since patients are normally younger, and so was survival. While survival is estimated between 6 and 9 years in other series, it was a few months after onset in our case.[3]

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