AMYOTROPHIC LATERAL SCLEROSIS WITH DEMENTIA

CASE REPORT

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ABSTRACT - A patient is described in whom a profound and rapidly progressive dementia occurred in association with clinical features of amyotrophic lateral sclerosis. A magnetic resonance imaging showed signs of frontal and especially left temporal atrophy. The pattern of dementia indicated impaired frontotemporal lobe functions, evidenced by reduced tracer uptake in the frontotemporal lobes on brain single photon emission computed tomography. Neuropathological examination in this patient revealed mild frontotemporal atrophy with spongiform changes and neuronal loss affecting mainly layers II and III of the frontotemporal cortices. There was atrophy of the hypoglossal nuclei. The spinal cord changes were consistent with motor neuron disease. The patient showed an irreversible and progressive course. A review of the relevant literature was made.

KEY WORDS: dementia, amyotrophic lateral sclerosis, hypothyroidism, brain SPECT.

Esclerose lateral amiotrófica com demência: relato de caso

RESUMO - Demência de evolução rápida e progressiva associada com esclerose lateral amiotrófica ocorreu em uma paciente de 68 anos. A ressonância magnética mostrou sinais de atrofia frontal e, principalmente, temporal bilateral mais acentuada à esquerda. A demência se caracterizou como de tipo fronto-temporal, como sugere por hipoperfusão moderada nos lobos fronto-temporais através da tomografia cerebral computadorizada por emissão de fóton simples. O exame neuropatológico revelou atrofia leve fronto-temporal com alterações esponjiformes e perda neuronal afetando principalmente as camadas II e III dos córtices fronto-temporais. Havia importante perda de neurônios em ambos os núcleos do hipoglosso. A medula espinhal mostrou alterações consistentes com doença do neurônio motor. O caso teve curso de quatro anos até o óbito.

PALAVRAS-CHAVE: demência, esclerose lateral amiotrófica, hipotireoidismo, SPECT cerebral.

There has been considerable progress in the understanding of unusual dementias, often referred to as non-Alzheimer or rare dementias. These developments fall into three major areas: definition of clinicopathological entities, investigations into the cellular and molecular mechanisms, and genetic discoveries. Some of the unusual dementias have been previously considered to be subcortical, but now the widespread involvement of the cerebral cortex has been recognized. Most unusual dementia are associated with frontotemporal degeneration including Pick's disease, motor neuron disease (MND), corticobasal degeneration, frontal lobe degeneration of non-Alzheimer type, and the more recently defined frontotemporal degeneration with parkinsonism linked to chromosome-17. In MND, dementia is associated with ubiquitin-positive inclusions in the cortex and in the hippocampal formation. More recently it was recognized that neuronal loss affects not only the motor, but also non-motor cortical areas[1].

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Amyotrophic lateral sclerosis (ALS) is a fatal degenerative disease mainly characterized by signs of the first and second motor neuron (muscular weakness and atrophy, fasciculation and pyramidal signs), labio-glosso-pharyngeal paralysis and absence of sense and sphincteric disturbances. According to clinical symptoms at onset, three variants can be distinguished in ALS: 1) "classic" ALS, with cervical or lumbar onset; 2) bulbar ALS; 3) pseudopolyneuritic ALS (Patrikios' disease), characterized by distal muscular weakness mainly in the legs, and absence of achillean reflexes[2]. It progressively destroys the cells in the anterior horns of the spinal cord, the fibers of the pyramidal tracts and, terminally, the motor nuclei in the medulla. It is more common in men and mostly afflicts those in their 50s and 60s and sometimes those in their 70s[3]. About 5-10% of all MND cases are familial, with the majority of these showing a dominant pattern of inheritance. The features of most of these familial ALS cases, including age at onset, natural history, and clinical and pathological characteristics, are very similar to those of sporadic typical ALS. Thus, it is possible that both sporadic and familial ALS share common pathogenetic mechanisms[3]. The mean age at onset of ALS is 55 years and the incidence of new cases is approximately 1 per 100000 of the population. The total number of cases in the population is about 5 per 100000. In the United States, it is estimated that there are 20000 to 30000 cases[4].

It is traditionallly held that lesions of the nervous system in ALS are restricted to the upper and lower motor neurons and that clinical features of ALS do not include the loss of memory or the impairment of intellectual abilities. However rare, instances of neuropsychological disturbance have attracted special attention. These include disturbances in short-memory, and delayed memory. At issue is wheter such disturbances are concomitant features of a coexistent neurological disorder[5]. Cavalleri and De Renzi[6] presented a case with frontal dementia, another with a predominant aphasic, apraxic, amnesic syndrome, while the remainder showed cognitive decline in association with blunt affect. Motor signs were characterized by a precocious involvement of the upper motor system. Moreover, there are two distinct types of ALS with dementia (ALS-D), one characterized by juvenile onset and autosomal recessive inheritance, and the other by adult onset and autosomal dominant inheritance. In the adult type the age of onset is after 40 years, and not all those with motor disability are demented. This type of ALS is a very rare familial disorder[7].

Since we consider ALS with dementia to be a rare type of syndrome, we present our experience and review the literature on ALS with dementia of adult onset.

METHOD

A patient with a diagnosis of ALS-D made according to Neary[8] was studied. Neuropsychological assessment was made according to ANAD[9], token-test[10], and trail making test[11]. He was also submitted to neuroimaging studies, using both computed tomography (CT) and magnetic resonance imaging (MRI), and brain single photon emission computerized tomography (SPECT).

Post-mortem neuropathological examination of the brain and spinal cord of the patient was fixed in 10% formalin for four weeks. The paraffin-embedded coronal sections of the frontal, temporal, parietal and occipital lobes of the brain and serial sections at the cervical, thoracic, lumbar levels of spinal cord were stained with hematoxylin-eosin, Masson and Wölcke's myelin.

CASE REPORT

In the patient there was no previous psychiatric history. There had been no occupational exposure to chemicals, heavy metals, or previous family history of dementia.

A 68-year-old housewife, with five years of schooling, was admitted to hospital in December 1994, with affective symptoms of fixed ideation, delusion and fear that had started three years before. She also showed behavioural disorders and swallowing difficulty that had started two years earlier. In the previous six months she had had a gait difficulty, a severe worsening of her behavioural disorder and of her language disturbance. She had suffered from hypothyroidism for 32 years.

Neurological examination revealed affective symptoms (anxiety and excessive sentimentality), behavioural disorder (inappropriate jocularity, restless pacing, inflexibility, mannerisms such as clapping). There was also spastic crying. She was unable to keep her eyelids closed. The palatine and pharingeal reflexes were absent and there was hypomotility of the vellum and pharynx. There was atrophy of the thenar muscles and distal upper extremities. The small muscles of the hands were slightly hypotrophic and the strength of the adductor policis and abductor digiti minimi was mildly decreased. The snout reflex was present. She had increased bilateral palmomental and all deep tendon reflexes. Babinski's sign was absent bilaterally. Gait was slow and paretic. Fasciculation was absent.

Neuropsychological assessement showed desinhibited, impulsive, inappropiate, aggressive behaviour with an exaggerated and melodramatic emotional display. Her spontaneous speech was hard to evaluate because of the severe dysarthria. On the visual naming test, she scored at the lowest level of the normal range. Verbal comprehension of names and sentences (token test) was impaired. There was both an expressive and a receptive aphasia. She was severely apraxic, for both oral and limb movements. The trail making test for both A and B forms was wrong.

Routine biochemical, hematological and serological investigations were normal. MRI performed when she was 71 years old revealed bilateral atrophy of the frontotemporal lobes, especially the left temporal lobe (Figs 1 and 2). There was an abnormal hyperintense signal in the white matter of the left frontal lobe. A brain SPECT imaging performed when she was 72 years old showed bilateral severe hypoperfusion of the frontotemporal lobes (Fig 3).

She died aged 72 years, after a total clinical course of four years. The clinical diagnosis was dementia with motor neuron disease of the bulbar type.

Neuropathological findings - The weight of the brain was 1050 g before fixation. Macroscopical examination disclosed mild bilateral cortical atrophy, mainly of the frontal and temporal lobes, and there was moderate enlargement of the ventricles. There was major atrophy of the nerve roots of the spinal cord (Fig 4). Microscopic examination showed neuronal loss in the hypoglossal nuclei, frontal and temporal lobes. There was also status spongiosus and neuronal loss affecting mainly layers II and III of the frontotemporal cortices. The hippocampus showed no change, not even neurofibrillary tangles or senile plaques. There was marked neuronal loss in the anterior horn of the spinal cord, especially in the medial cervical segment.
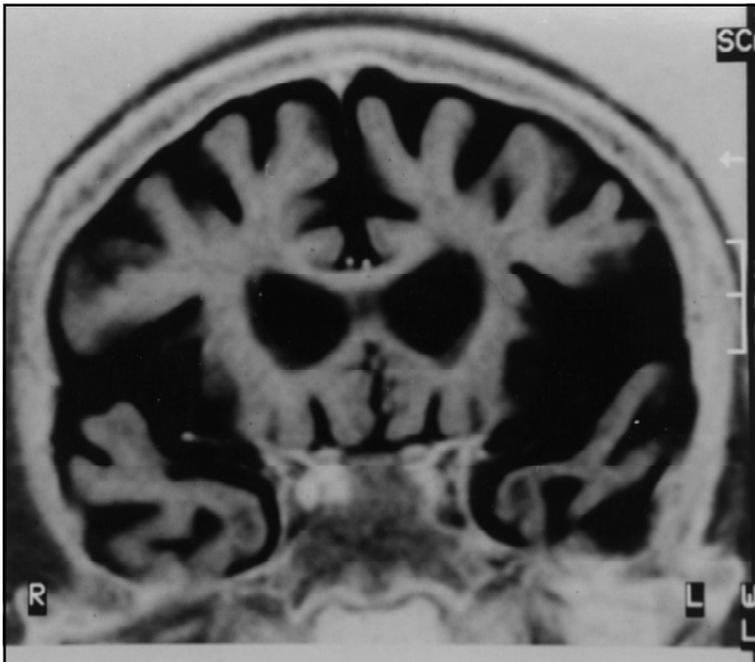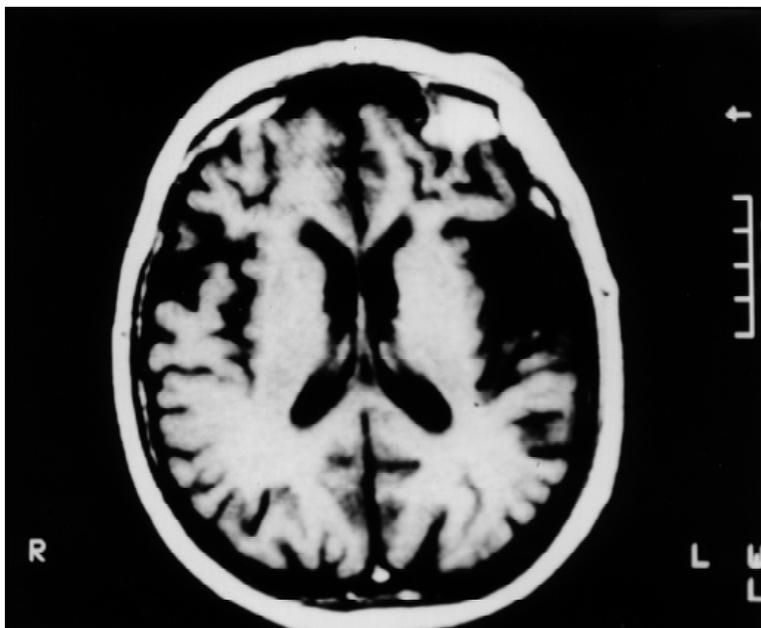

Fig 1. MRI coronal image showing bilateral frontal and temporal lobes atrophy, mainly on the left temporal lobe.

Fig 2. MRI transaxial image showing bilateral frontal and temporal lobes atrophy, mainly on the left temporal lobe

DISCUSSION

The patient reported in this study had presented with severe language disturbance, increased deep tendon reflexes, progressive weakness in all four limbs, atrophy of the muscle and distal upper extremities, and dementia. The diagnosis of ALS rested on the presence of signs of upper and lower motor neuron disease, involving bulbar, as well as limb function, and was confirmed by neuropathological findings in the spinal cord. Moreover, the patient presented a bulbar and spinal form of the ALS, from both the clinical and neuropathological viewpoints associated with dementia. However, most patients with ALS do not develop dementia, but various states of mild memory disturbance, mental insufficiency and even psychotic reactions may occur, making the clinical assessment more difficult[12]. Severe anxiety, inappropriate responses to questions, inability to make judgments and euphoria were present. Early involvement of the anterior temporal cortex together with the laminar selectivity of the cortical lesion may be responsible for the psychotic symptoms seen in some cases of ALS-D such as this one. A pathophysiological hypothesis for the hallucinations of ALS-D is the involvement of the supranuclear layers of the anterior temporal lobes that produces a state of desinhibition of infragranular neurons. Since corticocortical feedback projections arise predominantly from infragranular neurons, they may promote abnormal retroactivation of post-rolandic unimodal association cortices, causing hallucinations [13].

In our patient, language disturbance was characterized by progressive diminution in speech output and responses to questions becoming increasingly brief, stereotyped and echolalic, leading finally to mutism and frontotemporal dementia. The differential anatomical atrophy supports the view that clinical manifestations of lobar atrophy are dictated by the topographical distribution of a common underlying pathology, linking the syndromes of progressive aphasia to dementia of the frontal lobe and to ALS[14]. In this case, there were also spells of crying and bouts of laughter. In addition to clinical symptoms at onset of classic ALS, there were bouts of automatic laughter and crying, behavioral disorder
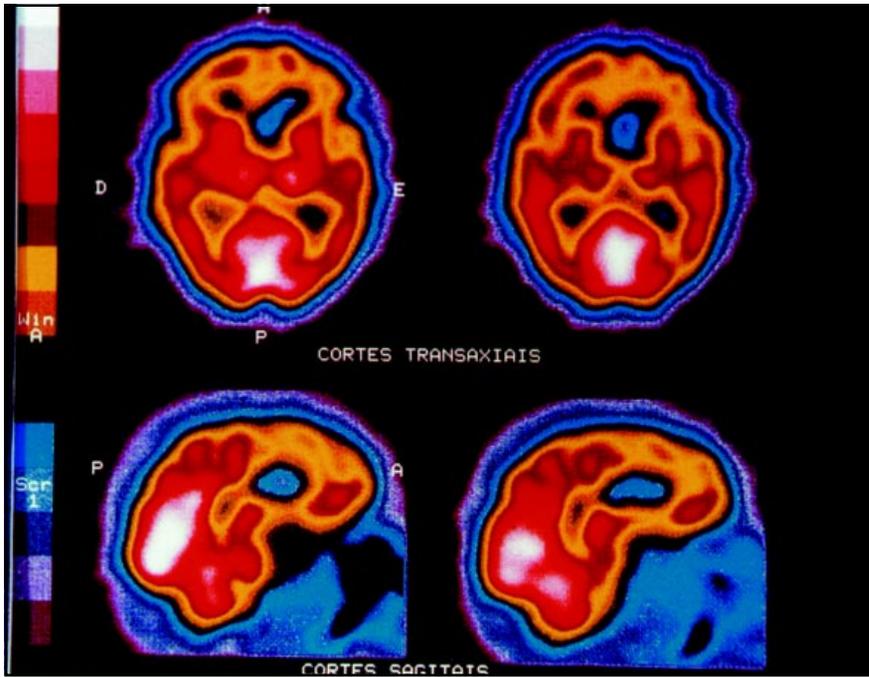
Fig 3. Brain SPECT using ^{99m}Tc HMPAO: transaxial and coronal images showing bilateral frontal and temporal hypoperfusion, mainly on the left side. Yellow regions represent decreased relative perfusion (see color scale on the left side).

Fig 4. The anterior spinal cord image showing marked atrophy of various nerve roots.

and dementia. They occur as explosive, unwanted and unexpected outbursts that are really attacks of pseudo-emotion. What is known is that with advancing age, fine degrees of emotional control become diminished. What is also known is that disease in frontal lobe, the temporal lobe, third ventricle, hypothalamus, putamen, caudate nucleus and, most of all, lesions in the brain stem can bring on bouts of unwanted laughter and weeping. Many clinicians feel that the existence of motor disease in the brain stem is a *sine qua non* for the onset of emotional speels in illnesses such as ALS[15].

In the patient reported in this study, MRI revealed bilateral atrophy of the frontotemporal lobes, especially the left temporal lobe, and brain SPECT showed bilateral severe hypoperfusion of the frontotemporal lobes. Brain SPECT is currently the great hope in the study of primary degenerative diseases of the brain such as ALS-D[16]. The lack of prospective clinical studies associated with the pathological data obtained from brain SPECT images limits its usefulness in the diagnosis of dementia in its mild phase. However, the pattern of dementia indicated impaired frontotemporal lobe functions, confirmed by reduced tracer uptake in the frontotemporal lobes on brain SPECT of this patient. According to Chang et al.[17], brain SPECT has been shown to be useful in the early diagnosis of frontotemporal lobe dysfunctions and should be performed in ALS patients suspected of having frontotemporal dementia.

The total course in this case was four years, and the main neurological findings were compatible with the diagnosis of ALS in addition to the psychotic symptoms and behavioural disorders and dementia. Macroscopically, pathological changes in the cerebral hemispheres showed a mild area of atrophy within the frontal lobes, affecting particularly the middle and superior frontal giri. The anterior spinal cord, particularly in the cervical region showed marked atrophy of various nerve roots. On microscopic examination the frontal cortex, and particularly the middle and superior frontal giri, showed moderate spongiform change affecting mainly layers II and III, and neuronal loss in the hypoglossal nuclei. Within the anterior horns there was important loss of neurons. On silver staining, no senile plaques or neurofibrillary tangles were observed in any region of the brain. The Lund and Manchester Groups[18] advocated the idea of frontotemporal dementia. They proposed clinical and neuropathological diagnosis with features of frontotemporal dementia, and they divided frontotemporal dementia into the three types: frontal lobe degeneration type, Pick type, and motor neuron disease type. These are the same as frontal lobe degeneration, although usually less severe, and there is also hypoglossal degeneration in some cases.

Conclusions: 1-hallucinations and delusion may occur in ALS-D, sometimes as early manifestations; 2- brain SPECT should be performed in ALS patients suspected of having frontotemporal dementia because it showed a bilateral hypoperfusion on frontotemporal lobes and spared the parietal and occipital lobes; 3- the spectrum of cognitive disorders in ALS-D is marked by an extensive involvement of language, gnosis, and praxis, as in Alzheimer's disease, and especially in forms that present with more selective deficits of the frontotemporal dementia type; 4- the differential anatomical atrophy supports the view that clinical manifestations of lobar atrophy are dictated by the topographical distribution of a common underlying pathology linking the syndromes of progressive aphasia to dementia of the frontotemporal lobes type and with ALS; 5- we believe that various types of cases with both dementia and ALS-D will be identified and that further continuous clinico-pathological studies are needed.

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