AMYOTROPHIC LATERAL SCLEROSIS WITH FRONTOTEMPORAL DEMENTIA

Corina Roman-Filip[1], C. Rociu[1], A. Ungureanu[1]
[1]Department of Neurology, Faculty of Medicine, University of Sibiu
[2]Neurology Clinic, Emergency Clinical County Hospital, Sibiu

ABSTRACT

We present the case of a 64 years old male admitted to our neurological clinic for progressive limb weakness associated by memory impairment and behavioral changes. This case is a particular association between amyotrophic lateral sclerosis (ALS) and dementia, association that is found in 5% from all cases of ALS. Such cases can be misdiagnosed in early stages when the motor neuron signs are discrete. The present case is such an example, the patient being diagnosed and treated for Alzheimer dementia.

Key words: amyotrophic lateral sclerosis, frontotemporal dementia, neurodegenerative dissease

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relatively rare disorder with an incidence of 0.4 – 1,76 per 100,000 habitants (1). The onset of this disease is known to be more frequent after the 5th decade of life, with a sex ratio – M:F=2:1. The most of the cases of ALS are sporadic, but in 10 percent there is an autosomal dominant form with inconstant penetrance (types 1, 4 and 8). The genetics are till unclear, but were described in the latest years a series of genes and mutations involved as ALS2, SETX, SOD1, VAPB genes located on the chromosome 2, 9, 20, 21. New research on the genes of highly conserved ribonucleoproteins as TDP-43, FUS/TLS suggests the selectivity of the degenerating process in a subset of neurons (2,3). Pathophysiology is characterized by the degeneration of motor neuron in the spinal cord and degeneration of pyramidal neurons in the cortex, leading to progressive loss of motor function. Accompaniment conditions are limited sometimes at frontotemporal dementia (FTD) or Parkinson disease.

CASE REPORT

We present the case of a 64 years old male, non smoker and a occasionally alcohol user, admitted in our clinic in January 2010 for memory impairment, behavioral changes, tremor and progressive weakness especially in lower limbs leading to gait and walk disturbance.

The neurologic symptoms began insidiously in the last year, in that time the patient was already diagnosed with Alzheimer disease and was in treatment with donepezilum. He was sent to our clinic for elucidate the progressive weakness associated to dementia. The patient is known with arterial hypertension and chronic obliterating arteriopathy.

Physical examination revealed a generalized muscular atrophy (see fig.1), fasciculation in proximal segment of both upper and lower limbs, pyramidal signs in all limbs (positive plantar cutaneous response, slight spasticity, hyperreflexia), dysarthric speech, logorrhea and echolalia, no sensory deficit, patient well orientated.

Author for correspondence:
Corina Roman-Filip, 10 Victoriei Av., Sibiu, Zip Code550024, Romania
email: corina.roman@ulbsibiu.ro

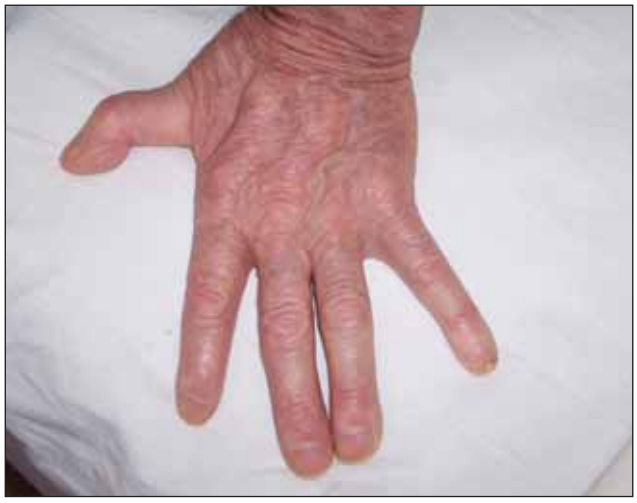

Figure 1. *Distal muscular atrophy in superior limbs*

We have proceeded to a series of paraclinical exams as follows:

Electromyography (fig. 2) and nerve conduction studies revealed neurogenic changes in both upper and lower limbs, proximal and distal segments and also in the genioglossus muscle (spontaneous activity, high amplitude and polyphase MUP). Conduction velocities are mildly reduced in lower limbs (about 35 to 40 m/sec). No conduction block detected.

A cranial CT scan was made to rule out other conditions and it revealed a cortical atrophy especially in frontal lobes. Spinal MRI showed a L4 – L5 discopathy without clinical significance. Laboratory findings: CPK = 299U/l, Cholesterol = 291mg/dl, PSA, VDRL – in normal ranges, no modifications in haemoleucogram, serum ions,

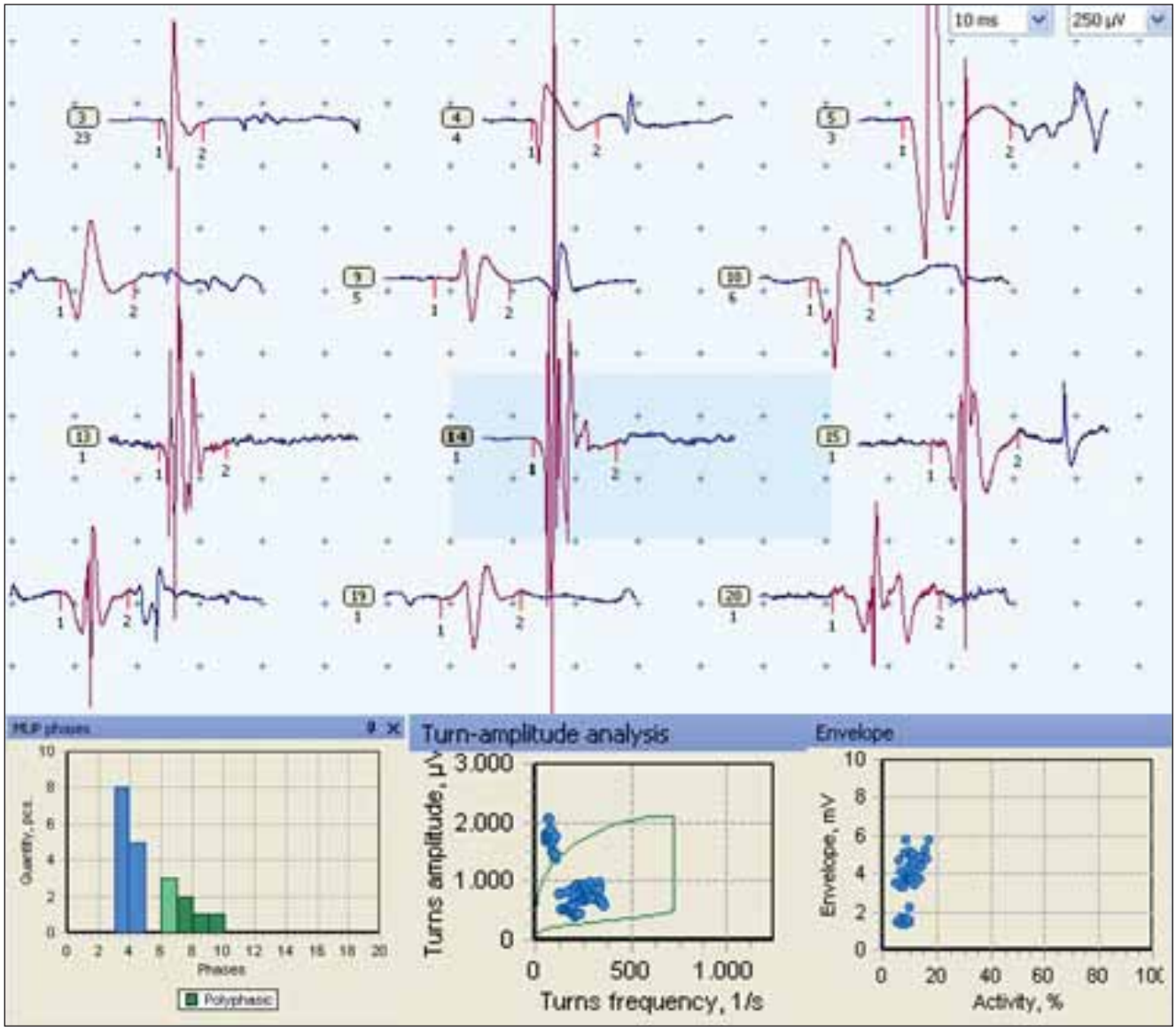

Figure 2. *EMG showed high amplitude polyphasic MUP in all tested muscles – deltoid, vastus lateralis, tibialis anterior, genioglossus*

LDH, ALAT, ASAT, bilirubin. Normal thoracic X-ray is found.

Psychological evaluation showed an MMSE score of 19, short time memory impairment, dyscalculia, executive dysfunction (difficulties in solving problems, difficulties to organize and planning activities).

Diagnosis: Amyotrophic lateral sclerosis with frontotemporal dementia, based on El Escorial criteria (we have found central and peripheral motor neuronal signs in more than 3 muscular region) and on psychological evaluation showing frontal lobe dysfunction. The diagnosis of Alzheimer disease was excluded (exclusion criteria in El Escorial consensus for ALS).

Differential diagnosis is principally made for the motor neuron disease and this includes the followings: a motor neuropathy with multiple blocks is to be ruled out as the EMG/NCS shows no conduction block. No other specific findings support the spinal amiotrophy, Guillain – Barré syndrome, CIDP, poliomyelitis, progressive bulbar palsy, paraneoplastic syndrome. The differential diagnosis between Alzheimer dementia and frontotemporal dementia is very important because the first excludes ALS and the latter supports it. All the psychological tests showed a representative impairment of frontal lobe functions and in consequence the Alzheimer disease was excluded.

There is no effective treatment for ALS. Riluzole only extends life with 2-3 months. Supportive treatment as physical procedures and psychological therapy must be done in order to improve the quality of life. In terminal stages mechanical ventilation is to be considered, but patient and family should consider all the factors when deciding this option.

The prognosis of ALS in general is a poor one and we deem that in our case the patient will develop progressive muscular weakness leading to respiratory failure, death may occur within 3 years.

DISCUSSIONS

This case is a particular association between ALS and FTD. About 5% of patients with ALS could develop dementia, especially frontotemporal type suggesting that neuronal degeneration in this patient is not limited to pyramidal and lower motor neurons (1). Such cases could be misdiagnosed in early stages when muscular atrophy and weakness are discrete (present case is such an example being diagnosed and treated like an Alzheimer dementia) (4), his medical history showing that in the time of Alzheimer dementia diagnose there were no motor neuron signs.

FTD also known as Pick's disease is characterized by loss of inhibition, impulsivity, loss of social awareness, neglect of personal hygiene, mental rigidity, stereotyped behavior and utilization behavior. Language abnormalities such as reduced speech output, echolalia and perseveration may be present.

Some propose that ALS associating FTD is nosologically distinct by a pure motor neuron disease. Others suggest that the FTD and ALS make part of a range of degenerative diseases each one being situated at the edges. As we said in the introduction lines, a recent discovery of pathological transactive response DNA-binding protein 43 (TDP-43) in both ALS and FTD with ubiquitinated inclusions (5) shows that these are closely related conditions which can occur separately or simultaneously and denominates a new biochemical class of neurodegenerative disease, demonstrating that the name TDP-43 proteinopathies which include ALS/FTD is just. TDP-43 is a common protein found in the nucleus of the neuron and some known functions are represented by binding DNA and RNA, inhibiting retroviruses, RNA splicing. In patients with ALS/FTD, this protein is redistributed from nucleus to cytoplasm and forms insoluble aggregates (7) that may become toxic for neurons.

Also related to TDP-43, FUS mutations (fused in sarcoma) were found in the anterior horn neurons in all cases of sporadic or familial ALS except SOD1 mutation ALS type and were reactive with antibodies to TDP-43 and ubiquitin (8).

All these neurogenetic, neurochemical and clinical facts as associations between ALS and FTD imply maybe a shared or partially shared pathogenic pathway underlying neurodegenerative disorders.

Our diagnosis were sustained only on clinical and paraclinical methods (neurophysiological, psychological and imagistic),but in order to have a complete diagnosis a neurogenetic analysis to conclude or to exclude it may be necessary due to nowadays diagnostic trends. In early stages such cases can be misdiagnosed when the motor neuron signs are discrete. The present case is such an example, the patient being diagnosed and treated for Alzheimer dementia.

REFERENCES

1. **Ropper AH, Brown RH.** Adams and Victor Principles of Neurology. 9th ed. Boston: McGraw-Hill; 2009
2. **Huang C, Xia PY, Zhou H.** Sustained Expression of TDP-43 and FUS in Motor Neurons in Rodent's Lifetime. *Int J Biol Sci* 2010; 6:396-406. Available from http://www.biolsci.org/v06p0396.htm
3. **Valdmanis PN; Daoud H; Dion PA; Rouleau GA.** Recent advances in the genetics of amyotrophic lateral sclerosis. *Curr Neurol Neurosci Rep.* 2009; 9(3):198-205
4. **R. J. Perry and J. R. Hodges.** Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease, *Neurology* 2000;54;2277-2284
5. **Avants B, Khan A, McCluskey L, Elman L, Grossman M.** Longitudinal cortical atrophy in amyotrophic lateral sclerosis with frontotemporal dementia. *Arch Neurol*. Jan 2009;66(1):138-9.
6. **Rohrer JD, Lashley T, Holton J, Revesz T, Urwin H, Isaacs AM, Fox NC, Rossor MN, Warren J.** The clinical and neuroanatomical phenotype of FUS associated frontotemporal lobar degeneration, *J Neurol Neurosurg Psychiatry*. 2010
7. Material provided by Gladstone Institutes for sciencedaily.com/releases/ 2010/01/ 100112171809
8. **Han-Xiang Deng et al.** FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis. *Ann Neurol* 2010;67:739-748