ATYPICAL PRESENTATIONS IN AMYOTROPHIC LATERAL SCLEROSIS – DISCUSSION BASED ON THREE CASE OBSERVATIONS

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ABSTRACT

Diagnosis of ALS is based on clinical examination and electromyographic tests which are used to confirm the clinical suspicion and to exclude alternatives. Atypical presentations may delay the diagnostic and subject the patient to unnecessary tests and procedures. We discuss here three cases with atypical features: head dropping, highly focal weakness and amyotrophy and the last case with surgery for lumbar stenosis.

Key words: amyotrophic lateral sclerosis, weakness, amyotrophy, electromiography, motor unit potential

Amyotrophic lateral sclerosis (ALS) is considered as a progressive neurodegenerative disorder involving upper and lower motor neuron affecting limb, trunk and bulbar musculature. Other brain functions are relatively spared though cognitive dysfunction is seen in 20-50% and 3-5% develop frank dementia of frontotemporal type (Abrahams, 1996).

Death due to respiratory failure follows on average 2-4 years, but a small group may survive a decade or more (Forsgren et al., 1983).

The annual incidence varies between 0.2 and 2.4 per 100,000 population and it has a tendency of increasing probably due to better case recognition (Bobovick, 1973, Brooks, 1996).

Diagnosis of ALS is based on clinical examination and electromyographic tests which are used to confirm the clinical suspicion and to exclude alternatives.

When diagnosing and managing a patient with ALS it is important to recognize that ALS is a heterogenous syndrome that overlaps with a number of other conditions (Ince 1998, Brugman et al 2005).

Clinical, electrophysiologic and pathologic diagnosis is actualy based on so called „El Escorial set of criteria“ which are mainly used for selection of patients in clinical trials. Definite ALS implies that features of upper and lower motor neuron involvement are present in at least three separate central nervous system regions. Probable ALS refers to presence of signs in only two regions and upper motor signs lie rostral to the lower motor signs.

Probable laboratory supported ALS if only one region is affected or upper motor signs are seen alone together with electromiographic evidences of lower motor involvement in two regions (Murray, Mitsumoto, 2002). Also the clinician should use neuroimaging and clinical laboratory testing to exclude other disorders that may mimic ALS.

Electrodiagnostic studies are an indispensable part of the ALS evaluation, an extension of the clinical examination beeing most useful in identifying lower motor neuron dysfunction and disclosing asyptomatic areas of involvement (Cintas, 2006).

Conduction studies are generaly used to exclude alternative diagnoses. Caracteristically SNAP (sensory nerve action potential) amplitudes are normal. With significant axon loss, low compound muscle action potential (CMAP) with modest degree of slowing may be found. On needle EMG in the affected muscles, features of both active and chronic denervation should be documented (Sonoo, 2006).

Even when the clinical picture and the accompaning EMG are highly suggestive of the diagnosis, magnetic resonance of the brain and spinal cord is important to exclude structural lesion and this is of particular value in the setting of an atypical presentation (Pradat, 2006, Mitchel, 2007).

These 3 case-reports are unususal presentations and are discussed because the atypical features delayed the diagnosis of ALS.

Presentation of Case 1

A 70 year-old woman, Mrs R.C. was admitted to the hospital in mars 2007 because of symptoms including head dropping accompanied by pain in the dorsal cervical region and also in the arms and shoulders bilaterally.

The first symptoms had appeared approximately 6 months before when she experienced pain in the back of the neck accompanied by dropping of the head. She reported that at times she had to hold her head up with her hands. Weakness was worse in the evening and aggravated by phisical activity. The pain was of medium to high intensity and was unresponsive to pain medication. These symptoms were later accompanied by a loss of strength in the arms. Following investigation of these symptoms she had been diagnosed with myasthenia gravis in September 2006 after finding a decremental activity in deltoids around 40% (figure 1).

Consequently she had started treatment with Miostin 5 mg three times a day. For the first 6 weeks the treatment showed promising results, with remission of neck-muscle weakness. The pain was treated with Lyrica 75 mg twice daily and diminished in intensity. After the first 6 weeks the symptoms reappeared progressively and in January 2007, after 5 months of monotherapy with Miostin, Mestinon was added to the treatment regime, in a dose of 2 mg twice a day. However this didn't improve the patient's condition which seemed to be worsening. During this period of 6 months other symptoms emerged including a tremor of the distal extremities of the arms, painful muscle cramps in the legs bilaterally accompanied by painful curling of the toes, and fasciculations in the shoulders, forearms, forelegs and upper back. Fasciculations were thought to be associated with the acetilcholinesteraze inhibitors treatment and she continued to take mestinon.

The patient had a history of thyroid nodules and hypothyroidism and was receiving treatment with 25 micrograms of Euthyrox daily. She also had Ischemic Heart Disease and was undergoing treatment with Isodinit and Preductal. After giving birth she experienced a degree of urinary incontinence due to perineal rupture. She also had a history of gastric discomfort and was found to be suffering from non-erosive esophagitis and Gastro-Esophageal Reflux Disease after a routine endoscopy of the upper digestive tract.

At the time of admission to the hospital (mars, 2007) the patient had normal vital signs, a BP of 120/70 mm Hg, her heart rate was 76 bpm (sinus rhythm), and she was alert and well oriented. Mental-status testing was normal. The cranial nerve exam revealed bilateral hypoacousia, difficulty in swallowing for both liquids and solids but more severe for solids (she was able to eat and drink normally but was sometimes gagging and had developed the habit of eating slowly to prevent that from happening), mild dysphonia occurring mainly in the evening and fasciculations of the tongue.

Bilateral atrophy of the deltoids was noted.

Motor examination showed weakness in the proximal muscles of the arms and shoulders. Neck extensors were the most affected.The patient sometimes had to hold her right hand with her left in order to brush her teeth. She experienced fatigue in the neck muscles and was occasionally unable to lift her head (figure 2).

Tests for dysmetria and dexterity in the upper extremities were performed slowly but accurately. These tests were normal in the lower extremities.

Sensory examination was normal but the patient reported occasional bilateral upper arms paresthesias. She had globally diminished osteotendinous reflexes (more predominantly in the upper arms) and the abdominal cutaneous reflexes were absent. Babinski signs were absent. Occasionally fasciculations could be noted at the level of the atrophied deltoid muscles and the tongue.

The complete blood count was normal and also the results of the lumbar puncture.

Blood Chemical and Enzyme Values were normal excepting CK level moderately increased (326U/L).

Hematological Laboratory Values – normal, no anemia, white blood cells count – normal values.

Biological thyroid function is normal.

The screening for a possible neoplasm did not uncover any significant findings. The Chest X-ray showed sequellar perihilar bands of fibrous tissue in

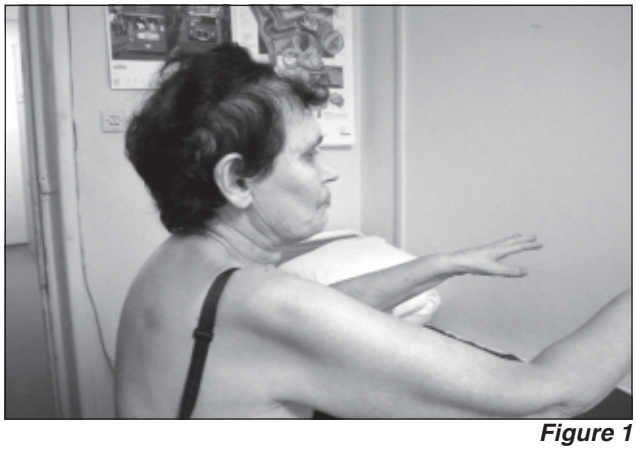

Figure 1
Patient fighting with the weakness of neck extensors

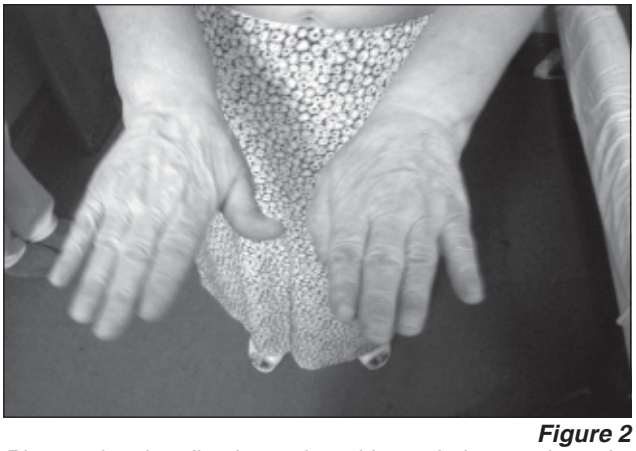

Figure 2
Picture showing distal muscles without obvious amiotrophy

the right lung but the aspect was not concordant with any malignancy. The Ob-Gyn exam was normal.

Cerebral and spinal MRI examination failed to reveal changes that might be at the origin of clinical signs.

An electromyography was performed. The diagnostic procedure included nerve-conduction studies and needle electromyography. The results of sensory-nerve conduction studies were normal. Motor-nerve conduction studies yielded normal conduction velocities.The first electromyographic study was normal for these muscles: tongue, short abductor first finger and Ist interosseux dorsal, there was no decrement. For the 2nd examination, 4 months later, electromyographic study showed fasciculations in the trapeze at rest, and poor recruitement in the masseter and in Ist interosseux dorsal (figure 3, 4).

Differential Diagnosis: although dropped head is reported as a feature of various neuromuscular disorders, specific for older patients is the isoleted neck extensor myopathy (INEM) (Suarez GA, 1992). The youngest patient described was 61 years old. The weakness may develop between 1 week and as long as several month. Pain often accompanies the progressive phase. Weakness is essentialy restricted to the neck but mild deltoid deltoid weakness coul be present. (Katz, Barohn, 2002)

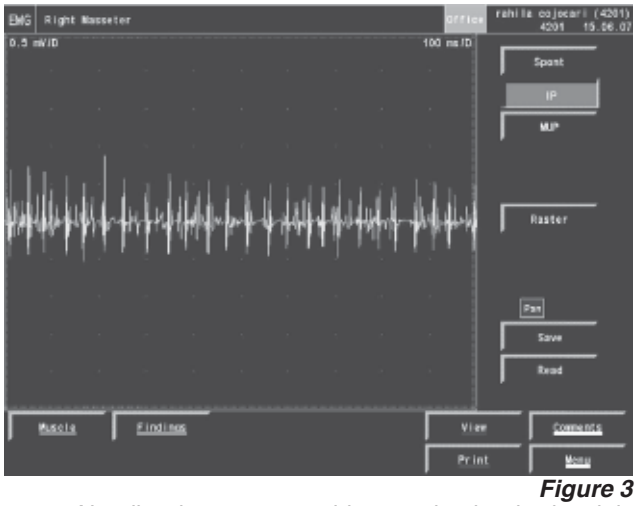

Figure 3
Needle electromyographic examination in the right masseter muscle with low recruitment but no giant MUP's(motor unit potential) probably because of the rapid progression of denervation (Sonoo, 2006)

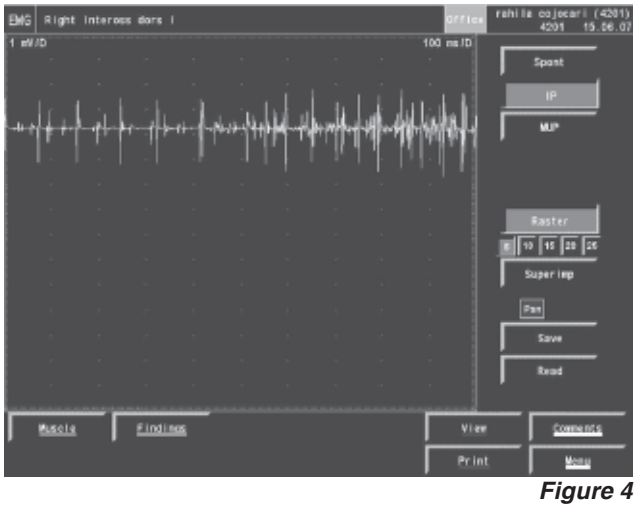

Figure 4
Denervation in the right interosseux muscle outside the area of clinical changes

The presence of weakness in regions other than neck and trunk suport the diagnosis of a generalized neuromuscular disorder which frequently are mysthenia gravis or amyotrophic lateral sclerosis. Head dropping has also been noted in hypothyroid myopathy, polymyositis, CIDP (chronic inflammatory demyelinating polyneuropathy) and Parkinson disease.

Treatment and Outcome at Three Months after Discharge:

The initial treatment with Miostin and Mestinon has been stopped following the diagnosis of ALS. The patient received corticotherapy for one month, consisting in 16 mg of Medrol daily. The weakness of the neck muscles and the consequent „head-drops" stopped occurring after 1 week of treatment with Medrol. However dysphonia was still present at times, especially in the evening. After 1 month of Medrol the patient started taking Rilutek and at the moment of the last examination she had been taking it for 3 weeks. She reported the absence of muscle cramps and fasciculations, but stated that the weakness of her arms is slowly becoming worse. The pain in the dorsal cervical region, the upper back and shoulders is still present and she is still using Lyrica to control it (75 mg twice a day), but she complains that the medication is aggravating the muscle weakness (probably due to the sedative effect of the drug).

Presentation of Case 2

A 60 year-old woman Mrs R.M was admitted to the hospital for left crural monoparesis, impaired ability to stand and walk, atrophy of the left thigh and fasciculations in both lower limbs, predominantly in the left thigh.

She had been admitted to the hospital on several occasions in the last year due to repeated subluxations of the left ankle which happened while walking normally. Shortly after she had experienced increased difficulty in raising the left leg and in lifting herself up from a crouched position. In the following weeks she had noticed instability in her left leg and a thinning of her left thigh. Some time later fasciculations had appeared in the left thigh and then progressed bilaterally in the lower limbs. Following the repeated injuries to the left ankle, the joint was swollen and slightly painful upon admission in our clinic.

The patient's history included duodenal ulcer which was controlled by the use of medication (Omeprazol, 20 mg daily). A routine endoscopy of the upper digestive tract showed hyperemic gastric mucosa but no other problems. She also had systemic homogenous osteoporosis.

At the time of admission to the hospital the patient had normal vital signs, a BP of 120/60 mm Hg, her heart rate was 80 bpm (sinus rhythm), she was alert and well oriented. Mental-status testing was normal. The cranial nerve exam revealed no pathological findings.

Motor examination showed hypotonia in the left thigh and a left crural monoparesis. The patient could walk only with the aid of a crutch but was able to stand on her own for a short period of time. She could not perform dorsiflexion of the left foot and was only able to lift her left leg off the bed for a few centimeters (figure 5).

She had no motor deficit in her right leg but reported occasional fasciculations in both legs, although these symptoms were more obvious on the left. The patient's left thigh muscles were significantly atrophied (especially the cvadriceps muscle). No other muscle atrophies were noted.

Tests for dysmetria and dexterity in the upper extremities were performed accurately. The same was true for the right lower limb but the tests could not be performed on the left lower limb because of the paresis.

Sensory examination was entirely normal.

The abdominal cutaneous reflexes were present. Babinski signs were absent. The osteotendinous reflexes were normal bilaterally in the upper limbs. They were significantly exagerated in the right leg.

Fasciculations were noted in the left thigh and on occasion in the right thigh.

Blood Chemical and Enzyme Values were normal

Hematologic Laboratory Values – slight anemia

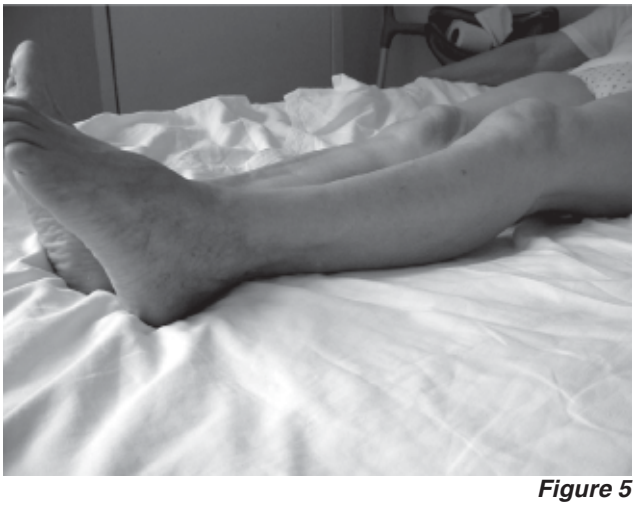

Figure 5

The Ob-Gyn exam was normal, screening for neoplasm negative and no thiroid dysfunction.

An electromyographic examination was performed. The diagnostic procedure included nerve-conduction studies and needle electromyography.

There is a severe decrease of the motor amplitudes for nerves: left tibialis, left peroneus and left femoralis with motor velocities, distal latencies and latencies of Fwawes quite conserved. No conduction block was observed.Sensory amplitudes and sensory velocities were normal. The muscle detection shows fasciculations for the right gastroc caput lat, the left abd dig min and for the left deltoide, fibrillations potentials in the tibialis anterior at the rest and with action, there is a poor recruitement with a high frequency, potential of motor units have a big ampplitude with a high duration and without stability for all these muscles (figure 6, 7, 8).

Differential Diagnosis. We eliminated a radiculopathy L4 severe, a monotruncopathy crural linked by an articular problem of the left ankle, a monoparsis crural caused by a stroke.

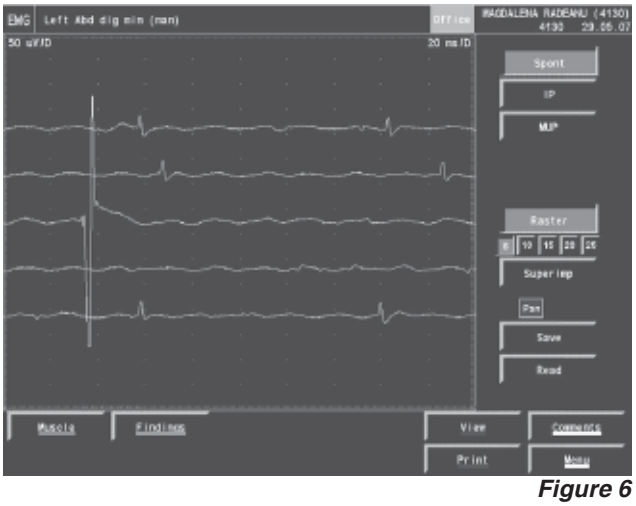

Figure 6

Fasciculation recorded in the left abductor digiti minimi which was not affected on clinical examination

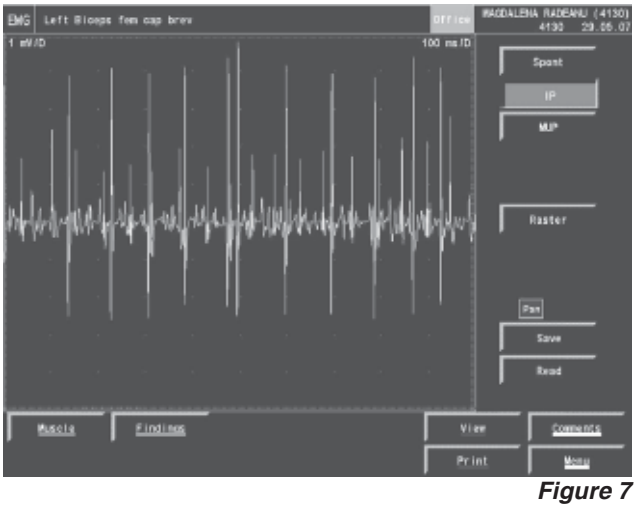

Figure 7

High amplitude MUP's and low recruitment in the left biceps femori muscle on needle examination

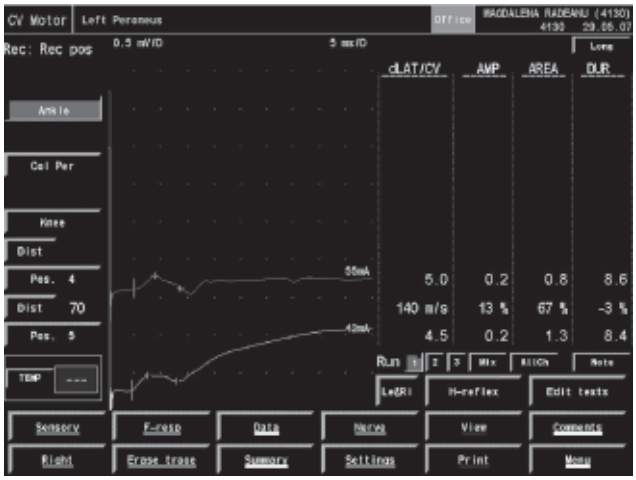

Figure 8
Low amplitude of left peroneal CMAP in the tibialis anterior muscle due to axonal loss

Presentation of Case 3

A 63 year-old woman Mrs E.P. was admitted to the hospital for complaints including lumbar pain accompanied by pain in the posterior and lateral sides of the thighs (especially in the left thigh) and calves bilaterally, inability to stand and walk without proper support, fasciculations in the thighs and dysphonia.

The patient had had a long history of recurrent lumbar pain dating back approximately 10 years. The pain had been initially responsive to pain medication (namely, Piafen). In 2005 the patient noticed that walking was becoming increasingly tiring and that she had to stop very frequently (sometimes after only 100 or 200 meters of walking). The fatigue was not particularly related to weakness in the muscles of the legs but rather to a general sensation of weakness. She did not have any particular cardiac pathology at the time.

In April 2006 the pain in the lower back started to descend in the left thigh, affecting the posterior and lateral aspects, and also in the left calf. She noticed that it was increasingly difficult to walk and that she could no longer stand on the toes of her feet or on her heels. These complaints have been investigated and an MRI of her lumbar spine diagnosed lumbar vertebral canal stenosis and foraminal stenosis at the levels L3, L4, L5 and S1. She was referred for a surgical intervention which took place in August 2006.

After the operation the patient postponed the start of physical therapy for about 10 months. She started wearing a specially made lumbar prop to support her lower back when she was in an upright position. The pain didn't disappear completely but regressed to a low bearable level and did not cause any particular distress for about 3 months. However, after the surgical procedure the patient experienced difficulty and instability in walking. The pain later increased in intensity and at the moment of the presentation to our clinic its distribution included the lateral and posterior aspects of both the thighs and the calves bilaterally. The pain in the thighs was a constant presence while the pain in the calves was present only on occasions, without a clearly defined pattern of appearance.

Three weeks before she was admitted to our clinic she had started physical therapy and she had done waking exercises using a walking frame. In the last week however she noticed that walking was no longer possible even in these conditions. She had lost all confidence in her abilities and she had become depressive, often crying at the slightest attempt of discussing her disease. She also had a history of difficulty in swallowing, a symptom which had first appeared roughly 18 months before and became more severe in emotional circumstances. She also reported coughing at times and „an increase in salivation", described as the feeling that „saliva is building up in the back of her throat" making her gag, possibly a consequence of impaired ability to swallow.

About 6 weeks before admission she had noticed a change in her voice. The ENT exam showed an „old" laryngeal paresis. Around the same time the change in the voice appeared she also noticed fasciculations in her left thigh, followed by similar symptoms in the right thigh and sometimes in the upper arms bilaterally. About one month before admission she had noticed atrophy of her left thigh and at the first dorsal interosseous muscles of the hands bilaterally.

The patient also suffered from an E. coli infection of the urinary tract and heartburn. She had followed several prescriptions of antibiotics and at the moment of admission to the clinic she had no sign of infection on urine analysis but Giordano's maneuver was positive bilaterally. She had no medication for her heartburn and the symptoms subsided after administration of Omeprazol 20 mg daily.

At the time of admission to the hospital the patient had normal vital signs, a BP of 130/70 mm Hg, her heart rate was 88 bpm (sinus rhythm), and she was alert and well oriented. Mental-status testing was normal but the patient showed marked emotional instability, anxiety and depressive tendencies. She would easily cry when talking about her symptoms and she was very concerned that what had happened to her legs could happen to her arms and hands as well.

The cranial nerve exam revealed the following: a general decrease in visual acuity (the patient reported wearing glasses which she had bought without a prescription and no prior ophthalmologic exams), a left eye scotoma, impaired swallowing associated sometimes with dryness of the mouth and dysphonia.

Motor examination showed hypotonia and weakness of the quadriceps muscles bilaterally,

predominantly on the left. The left quadriceps muscle also showed visible atrophy. There was no atrophy at the level of the calves or the tibialis anterior muscles but she had obvious amyotrophy of the first interosseux muscle on both hands (figure 9, 10).

She was able to stand for brief periods of time and she could walk for short distances with proper support. However, if asked if she could walk she consistently declined, showing a serious lack of confidence in her motor abilities.

Tests for dysmetria and dexterity in the lower extremities were performed slowly but accurately. These tests were normal in the upper extremities.

Sensory examination was normal. The abdominal cutaneous reflexes were absent. The plantar cutaneous reflexes could not be obtained. The osteotendinous reflexes were present and stronger in intensity in the upper limbs than those of the lower limbs. The left knee jerk reflex was weaker than the right one.

Figure 9

The patient was unable to perform plantar flexion or dorsiflexion of the feet. She could not lift her legs from a fully extended position on the bed. However she could flex her knees and from this position she was able to lift her legs from the bed at a 90 degree angle.

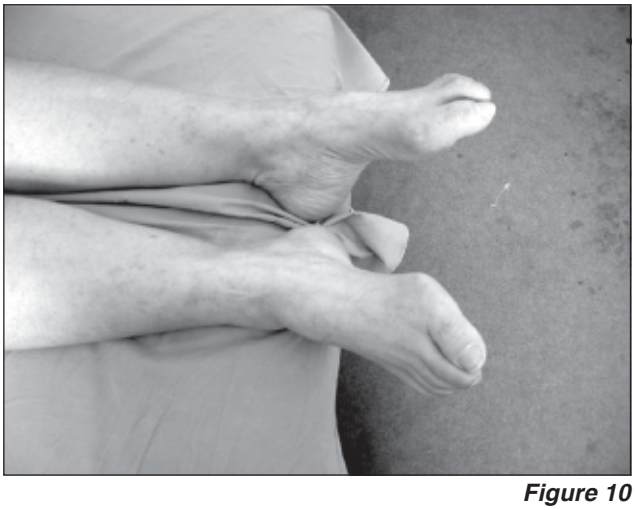

Figure 10

Weakness of the left leg in peroneal and tibial teritory but no important amyotrophy.

Fasciculations could be noted in the left quadriceps muscle.

The screening for a possible neoplasm did not uncover any significant findings. The Ob-Gyn exam was normal. An endoscopy of the upper digestive tract did not find any pathological changes. The abdominal ultrasound showed a hyperechogenic liver with homogenous structure and a sclero-atrophic right kidney (dimensions of 70/30 mm). The Chest X-ray showed no pathological findings.

Blood Chemical and Enzyme Values normal (table 1).

An electromyography was performed. The diagnostic procedure included nerve-conduction studies and needle electromyography.There is a severe decrease of the motor amplitudes for nerves: left medianus and milder for left ulnaris, severe for right and left peroneus and left tibialis with motor velocities, distal latencies and latencies of F waves quite conserved. No conduction block was observed. Sensory amplitudes and sensory velocities were normal except for the left medianus where the sensory velocity is a little bit decreased. The muscles detection shows fibrillations potentials for the left interosseux dorsal, slow potentials of reinervation for the right tibialis, left glossus at the rest and with the action, there is poor recruitement with a high frequency, motor units potentials have a big amplitude with a high duration and without stability almost for all these muscles (figure 11).

Differential Diagnosis: The main differential diagnosis is lumbar vertebral canal stenosis and foraminal stenosis at the levels L3, L4, L5 and S1

Diagnosis: Amyotrophic Lateral Sclerosis

DISCUSSION

ALS is the most frequent motoneurone disease. The diagnosis is almost a clinical diagnostic. And these is delayed for at least 3 reasons : the disease is not well-known by the doctors, the clinical presentation

Table 1

Pulmonary Function Tests showed respiratory dysfunction

Parameter	Measured	Predicted	%
FVC (L)	1.07	2.31	46.3
FEV*O.5 (L)	0.36		
FEV*1 (L)	0.84	1.92	43.7
FEV*O.5/FVC (%)	33.6		
FEV*1/FVC (%)	78.5	76.9	102.0
PEF (L/sec)	1.54	5.49	28.0
FEF*25-75% (L/sec)	1.11	2.68	41.4
FEF*75% (L/sec)	1.54	4.99	30.8
FEF*50% (L/sec)	1.31	3.3	39.1
FEF*25% (L/sec)	0.59	1.13	52.2
FET (sec)	1.99		
MTT (sec)	0.74	1.03	71.8

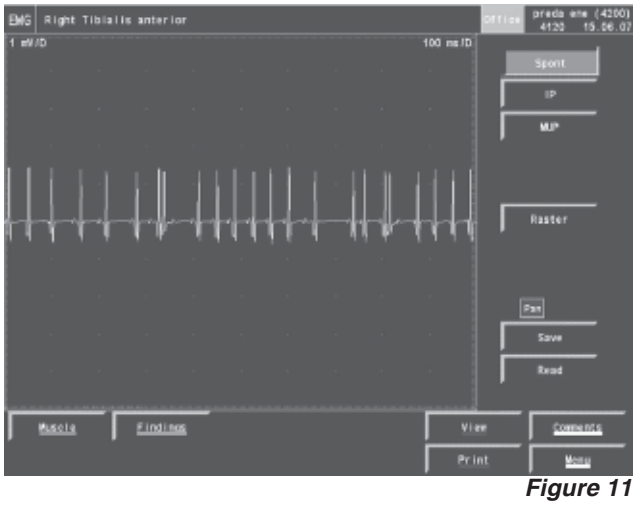

Figure 11
Low recruitment in tibialis anterior muscle on the left side on needle examination.

is often poor and sometimes misleading and there are no specific markers that is why you have to perform a complete clinical examination and to chose the main complementary examination which is the electromyogram.

(French Conscensus conference, 2005). The symptoms progression during the time is considered as an essential criteria (Brown and al., 2000).

Discussion of the Case 1

The particular aspect of this case resides in the unusual pattern of the early stages of the disease. The neck muscles were significantly affected from the beginning, enough to cause the head-dropping, but dysphonia has not become a clinical reality until recently, approximately 9 months after the initial symptoms, and the patient does not show any sign of dysphagia yet. The head-dropping was apparently connected (at least in the beginning) with the degree of effort to which the neck muscles were subjected. Another particular feature is the absence of amyotrophies in the distal muscles of the arms while the proximal ones are visibly affected. An axial deficit could be an early manifestation of ALS. A cervical extensors muscles attack with a dropped head is been reported for 1.3% of the ALS patients (Gourie-Devi and al., 2003). The axial deficit could be at the origin of a camptocormia (Van Gerpen, 2001).

The first electromyographic examination performed after symptom onset noted a decrement based on which the initial diagnosis of myasthenia was formulated. But electromyogram could be in default because it exists a decremnt of global muscular action potential with the repetitive stimulation in ALS as in myasthenia. (Denys and Norris, 1979). Single fibers EMG shows also the same abnormalities than in the myasthenia (jitter exaggerated and neuromuscular blocks) linked with the instability of the neuromuscular transmission of new junctions established by collateral reinnervation (Cui and al., 2004). It could exist acetylcholine anti receptors antibodies in patients with ALS without no myasthenia clinical signs (Okuyama and al., 1997)

Another interesting clinical fact is the initial response to corticotherapy. The treatment with Medrol for one month prior to the start of Rilutek has produced significant improvement in the motor function of the affected muscles.

Discussion of the case 2

This patient was particular because of monomyelic form. This could evocate us even a motor mononeuropahy This is very misleading if this clinical isolated symptom remains for a long time. (Singh and al., 1980). Monomyelic amyotrophy is described for the first time in japon (Hirayama and al., 1959). It exprimes with a distal weakness, amyotrophy, fasciculations and cramps for young man. This affection concerns the upper limb in general but also for the lower limb. It is an exclusion diagnostic after it is eliminated a motoneuron disease, motor neuropathy, radiculopathy or radiculoplexopathy or focal myopathy (Myoshi's myopathy).

Discussion of the case 3

This case was particular because of the pain and the initial symptoms which were understood as radiculopahies and vertebral canal stenosis. As we write before, successive clinical examinations and the following would be useful to correct the diagnosis with the presence of motoneuronal suffering in another place than in the radicular territory. For example, we can search tongue fasciculations. When the imagistic (MRI) can not help us, we can perform motor evoqued potentials because the cortico-nuclear and cortico-spinal conductions are disturbed (Truffert and al., 2000).

Respiratory dysfunction associates a poor prognosis and needs close monitoring for further deterioration and respiratory tract infection (Chetta, 2007).

Also emotional instability might be a manifestation of the syndrome of involunatry emotional expression disorder (IEED) frequently described in neurodegenerative conditions (Duda, 2007).

ALS is a singular affection in her classical clinical presentation that we can suspect it. To confirm the diagnosis is more difficult. Some elements can miss because of the variants of beginning, frontier forms and atypical symptoms and at the end, we do not have a specific test. The existence of 4 degrees of diagnostic confidence (El Escorial) shows that we have to do steps. Some studies show that the delay between the outcome of symptoms and diagnostic is from 12 to

24 months (Iwasaki and al., 2001). False positive are 10% and until 44% false negative (Brooks et al., 1999)

CONCLUSION

There are four reasons for making the diagnosis as early as possible: Psychological reasons: the progressive loss of motor symptoms causes anxiety and discomfort, impairing the patient's social and professional life

Ethical reasons: the patient can better plan the remaining part of her or his life

Economical reasons: a many patients go on a tour of the health care system undergoing series of unnecessary tests. Neurological reasons: be able to initiate neuroprotective medication before too many neuronal cells become dysfunctional and lost. Though no hard evidence exists on the kinetics of cell loss in ALS, it is reasonable to assume the earlier medication is started the greater the neuroprotective effect will be (Bromberg, 1999).

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