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ALS: pitfalls in the diagnosis

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A previously healthy man in his sixties presented with a 10-year history of progressive symmetrical and proximal lower extremity weakness, muscle atrophy, and fasciculations without any pain or sensory symptoms, which had spread gradually to his proximal upper extremities. Recently he had also noted weakness in his left hand causing difficulty clipping his nails. In addition, he had a five-year history of slurred speech without any difficulty swallowing. He had had mild dyspnoea on exertion and moderate low back pain for years. He denied any muscle pains or cramps, or any cognitive, cranial, bowel or bladder symptoms. He had been diagnosed with progressive muscular atrophy two years previously and came to our clinic for continuity of care. He had borderline diabetes and hypertension, but was otherwise well. There was no family history of any neuromuscular disorder, and he did not smoke or drink alcohol.

The abnormal neurological signs included mild bifacial weakness involving eye closure, mild dysarthria, and frequent perioral and tongue fasciculations with atrophy. There was mild weakness with atrophy in both lower extremities proximally and distally, the left hand, and neck flexion along with minimal weakness with atrophy in his proximal upper extremities with occasional fasciculations. He had depressed reflexes, no Babinski sign on either side, and sensation was normal. There was mild gynaecomastia.

Routine blood tests were normal, and urine heavy metal screen was negative. ANA was slightly raised at 1:160. Plasma CPK was raised at 2122 U/l (normal range 0–175 U/l). Nerve conduction studies (NCS) were normal. Electromyography (EMG) showed active denervation and reinnervation in the right arm and leg muscles proximally and distally, and spontaneous activity in the right thoracic paraspinal muscles. There were signs of reinnervation without active denervation in the right genioglossus. A spinal MRI was unremarkable. A left vastus lateralis muscle biopsy showed primarily neurogenic changes with angular atrophy without any signs of inflammation or myopathic features. Motor neuropathy profile (GM1, asialo GM1 and GD1B antibodies) and genetic studies for spinal muscular atrophy were all negative. However, genetic testing for Kennedy’s disease revealed increased CAG repeats in the androgen receptor gene, confirming the diagnosis.

This case highlights the importance of recognising the clinical features of Kennedy’s disease which can resemble amyotrophic lateral sclerosis (ALS), which brings us to reviewing some other pitfalls in diagnosing ALS—after first considering what ALS itself looks like.

EPIDEMIOLOGY OF ALS

ALS is a clinically and genetically heterogeneous neurodegenerative disorder which was first described by Charles Bell in 1830. The incidence is 1.5–2/100 000/year, the prevalence 3–8 per 100 000, and the mortality 1.9/100 000/year. There is a male predominance in younger onset cases. Most cases are sporadic, familial ALS occurring in 5–10%. The onset is generally in the late fifties and early sixties, although rarely symptoms can begin before 20 years of age (the youngest patient in our clinic was diagnosed at age 36).

THE ALS PHENOTYPE

Key features

The classical features of ALS are a combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs on examination and/or EMG without sensory, extraocular muscle or sphincter involvement (table 1).

Weakness presents first in the limbs (60–85%) or bulbar regions (15–40%). In the limbs, this occurs in an asymmetrical distal pattern, commonly either as a claw hand (fig 1) or foot drop. Early bulbar dysfunction frequently occurs particularly in older females with slow spastic dysarthria, dysphagia or pseudobulbar affect, or a combination of all three. The areas of weakness that are relatively specific for ALS include thoracic paraspinal, posterior neck, tongue (fig 2), jaw, first dorsal interosseous and tibialis anterior muscles.

Upper motor neuron involvement

Signs of bulbar UMN involvement include spastic dysarthria, dysphagia, excessive salivation, laryngospasm and pseudobulbar
Affect. Bulbar involvement is associated with emotional lability in up to 75% of patients with ALS. Isolated bulbar ALS can be difficult to diagnose; myasthenia gravis, oculopharyngeal muscular dystrophy and structural disorders like slow growing brainstem gliomas should be ruled out.

Asymmetrical UMN involvement is common in the limbs, especially early in the disease. There is a rare cortical hemiparetic, Mills’s variant; progressive unilateral weakness with both upper and lower motor neuron involvement. Deep tendon reflexes are invariably brisk. Babinski’s sign is present in 30–50% with ALS.

Lower motor neuron involvement

Cramps commonly affect the legs at night. These often resolve spontaneously with disease progression but may be severe. ALS rarely, if ever, presents with fasciculations without weakness.

Respiratory failure

Respiratory failure may occur in isolation in patients with ALS. In any possible case it is important to check for neck weakness and routinely ask about orthopnoea. The accessory muscles of respiration become flaccid over time. Morning headache may be an early symptom of hypoventilation. Interestingly, respiratory failure can be associated with loss of taste, weight loss and depression.

Other features

Up to one quarter of patients complain of minor sensory symptoms, which should not dissuade the clinician from making the diagnosis. Occasionally patients with ALS complain of pain, which is usually due to immobility or cramps. The association between ALS and frontal lobe dementia has been well described. Spastic bladder, dysautonomia and extraocular muscle involvement rarely occur.

Clinical course

The progression of ALS classically follows a segmental pattern, for example, first starting in the left arm, then left leg, then right arm, then right leg. There is no predictor of the time of involvement for each limb. Periods of symptomatic stabilisation may occur. Strength can be assessed by various scales and techniques (table 2); we routinely score our patients with the revised ALS-functional rating scale which monitors the progression of disability in ALS patients (table 3). The mean survival ranges from 3–4 years, with survival after diagnosis being approximately two years. Longer survival (>10 years) is seen.

### TABLE 1 Revised El Escorial criteria for the diagnosis of ALS

- **Definite ALS:**
  - progressive with UMN and LMN signs (such as fasciculations and/or atrophy) in 3 of 4 regions (brainstem, cervical, thoracic and lumbosacral spinal cord)
- **Probable ALS:**
  - progressive with UMN and LMN signs in 2 regions
- **Clinically probable—laboratory-supported ALS:**
  - UMN and LMN signs in only 1 region
  - UMN signs alone in 1 region
  - LMN signs in at least 2 limbs

with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

- **Clinically possible ALS:**
  - UMN and LMN signs in only 1 region
  - UMN signs found alone in 2 or more regions
  - LMN signs found rostral to UMN signs

in 4–10% of patients, mostly in younger patients with relatively pure UMN involvement. Respiratory failure is the most common cause of death. Depressed consciousness due to hypercapnia occurs, and death itself is usually peaceful and occurs in sleep. Choking to death is unusual in ALS.

**DIFFERENTIAL DIAGNOSIS OF ALS**

Among the mimickers of ALS, those that primarily present with UMN involvement include primary lateral sclerosis, human T-cell leukaemia virus (HTLV1) myelopathy, and hereditary spastic paraparesis. And those with LMN involvement include Kennedy’s disease (spinobulbar muscular atrophy), spinal muscular atrophy, multifocal motor neuropathy with conduction block, inclusion body myositis as well as other myopathies, HIV which may present as a progressive dysfunction of UMN s and LMNs with preferential involvement of LMNs or by causing an axonal polyradiculopathy, and oculopharyngeal muscular dystrophy. Primary lateral sclerosis and progressive muscle atrophy are considered as variants of ALS, the former with isolated UMN, the latter with LMN involvement (table 4).7

Many times, the initial presentation of ALS is with relatively sudden onset of dysarthria, leading to a (mis)diagnosis of stroke. The deficit is not however maximal at onset, and the continuing progression of symptoms typically leads the neurologist to eventually suspect ALS. Bulbar-onset ALS can even be mistaken for myasthenia gravis. Again here, there may be fluctuating symptoms initially, but the progressive nature of the condition helps the neurologist consider the diagnosis of ALS.

Cervical spondylotic myelopathy is usually diagnosed during the initial workup with neuroimaging, but it is important to be aware that severe cervical myelopathy with radicular involvement can create a clinical picture very similar to ALS, with spasticity and hyperreflexia in the lower extremities and muscle atrophy and fasciculations in the upper extremities.

While it is reasonable to consider these points in the differential diagnosis, it is important to recognise that sometimes it is very difficult to get the correct diagnosis of ALS at the first evaluation; one may have to follow the patient over time and wait for the disease to declare itself.

**SOME ALS MIMICS**

**Inclusion body myositis**

Inclusion body myositis (IBM) was first described in 1971 in a patient presenting with chronic polymyositis, cytoplasmic vacuoles and inclusions.3 IBM is most common in males older than 50 years, starting insidiously with asymmetric weakness in the quadriceps and deep finger flexors, leading to episodes of falling and tripping, and difficulty with gripping, pinching or buttoning. Mild dysphagia can occur but PEG tube placement is rarely indicated. CPK levels are mildly elevated (usually less than 1000 U). The combination of both neurogenic and myopathic features on needle electrode

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**TABLE 2 ALS assessment techniques**

- ALS global scales: revised ALS functional rating scale (table 3), ALS Severity Scale, Norris Scale, Appel Scale (forced vital capacity included), Schwab and England Scale, Ashworth Spasticity Scale
- Muscle strength: maximum voluntary isometric contraction, hand-held dynamometer, isokinetic muscle strength
- Electrophysiology: compound muscle action potentials, motor unit number estimates
- Quality of life assessment: SF-36, SF-12, Sickness Impact Profile

**TABLE 3 Revised ALS functional rating scale (4–0, 4 being normal and 0 being loss of useful activity)**

1. Speech
2. Salivation
3. Swallowing
4. Handwriting
5(a). Cutting food, handling utensils (without gastrostomy)
5(b). Cutting food, handling utensils (with gastrostomy)
6. Dressing, hygiene
7. Turning in bed, adjusting bedclothes
8. Walking
9. Climbing stairs
10. Dyspnoea
11. Orthopnoea
12. Respiratory insufficiency

examination during electromyography is highly characteristic. Here however, the predominant feature of the motor units is myopathic, that is, small amplitude, short duration units with early recruitment. The pathological hallmarks of IBM are rimmed vacuoles containing tau, prion, amyloid and 15–18 nm intranuclear or intracytoplasmic tubulofilamentous inclusions (which are pathognomonic for IBM) among non-necrotic muscle fibres. CD8 T-cell and B-cell endomysial inflammation can be seen, leading to the misdiagnosis of polymyositis. Patients with IBM should have hyporeflexia on examination; however, a coexisting cervical spondylotic myelopathy might mislead the clinician to the diagnosis of ALS.

Kennedy’s disease
Kennedy’s disease, otherwise known as spinobulbar muscular atrophy, elegantly described by Dr William Kennedy in 1968, occurs in males. There is late-onset proximal spinal and bulbar weakness, atrophy and fasciculations. Perioral fasciculations are frequently noted on examination and should raise the suspicion of this diagnosis. It is a triplet repeat disorder with expansion of polyQ repeats in the androgen receptor gene. Gynaecomastia and diabetes are classical non-neurological manifestations. Creatine kinase levels are often raised.

Multifocal motor neuropathy with conduction block
This is an acquired, immune-mediated, demyelinating motor neuropathy which classically presents with progressive distal asymmetrical weakness and atrophy of the intrinsic hand muscles in middle-aged patients. Fasciculations and cramps occur in more than 50% of cases, even outside the areas of affected nerves. Involvement of the median (anterior interosseous), ulnar, radial, musculocutaneous and occasionally tibial and peroneal nerves has been reported. Respiratory involvement is extremely rare. Minor sensory loss can occur in 20% of patients. Interestingly, there have been reports of patients having both ALS and multifocal motor neuropathy with conduction block. Despite being an LMN disorder, the deep tendon reflexes are normal or even brisk in 20–30%, making it even more difficult to distinguish from ALS clinically. Persistent, multifocal motor conduction blocks outside common entrapment sites with a normal needle examination of the thoracic paraspinals distinguish multifocal motor neuropathy with conduction block from ALS. Muscle or nerve biopsies are not helpful in making the distinction between these two disorders but CSF protein biomarkers might help in the future.

The electrophysiological demonstration of proximal patchy conduction blocks in motor nerves can be tricky and near impossible at times. The relative preservation of muscle bulk, weakness in named peripheral nerve distributions, and upper extremity involvement with very slow progression of weakness, and relative lack of active denervation on EMG are usually the tips for considering the diagnosis of ALS.

DIAGNOSTIC APPROACH TO ALS
If only LMN signs are present on initial examination, an EMG/NCS is mandatory to:

- exclude other possibilities, such as multifocal motor neuropathy with conduction block, spinal muscular atrophy, myopathies, polyradiculopathy/plexopathy and neuromuscular transmission disorders;
• delineate widespread clinical and subclinical involvement in myotomes;

• confirm the combination of active denervation and reinnervation, which is the hallmark of ALS.

If only UMN signs are present on initial examination without bulbar involvement, a brain and cervical spine MRI is indicated as cervical spondylotic myelopathy is common, especially in the ALS age group. If the imaging is negative an EMG/NCS should be performed to look for any subclinical LMN involvement.

If only bulbar signs are present on initial examination then a brain MRI should be performed to look for structural abnormalities like stroke, malignancy, vascular malformation, multiple sclerosis and CNS infection. A needle EMG of the genioglossus may be helpful to assess LMN involvement (see below).

The basic blood workup is shown in table 5. Blood tests for GM1 antibodies and parathyroid hormone levels can be helpful. HTLV-1 should be tested in patients with bladder involvement24 and HIV in young patients with pure LMN involvement. 25 If the patient is less than 40 years of age, hexosaminidase A levels could be of value to diagnose adult Tay-Sachs disease26 which may be quite difficult to distinguish from ALS on clinical examination. Urine screening for heavy metals is indicated if there is a possibility of exposure.27 If there is a family history, genetic testing for the superoxide dismutase-1 (SOD-1) mutation might be useful for counselling purposes. Serum CK levels range from normal to mildly elevated, but not exceeding 10 times the upper limits of normal—that is, less than 2000 IU/l.

**ELECTRODIAGNOSTIC PITFALLS**

Nerve conduction studies of the sural, peroneal, median and ulnar motor and sensory nerves are commonly performed, the focus being to look carefully for clear sensory abnormalities, or more importantly, any signs of conduction block or temporal dispersion that might support the diagnosis of multifocal motor neuropathy with conduction block (table 6). Minor sensory abnormalities should not necessarily preclude the diagnosis of ALS, and it is not uncommon to find minor abnormalities in motor responses, such as slightly small compound muscle action potential amplitudes or mild slowing.28 EMG should be performed in at least two limbs and three muscles each, proximally and distally, looking for the combination of acute denervation with florid fibrillation potentials (fig 3) and positive sharp waves, and very large amplitude motor

### TABLE 5 Diagnostic workup

**Basic:** full blood count, erythrocyte sedimentation rate, glucose, urea and electrolytes, liver function, thyroid function, B12, ANA, rheumatoid factor, serum protein immunofixation and electrophoresis

**EMG/NCS**

**Most patients:** brain and/or cervical spine MRI (depending on clinical syndrome) with gadolinium enhancement

**Rarely:** nerve-muscle biopsy, CSF analysis

If age <40: hexosaminidase A levels for adult onset Tay-Sachs disease

If history of early bowel/bladder involvement: consider HTLV-1 testing

If possible exposure: urine heavy metal screening panel

If family history of ALS: genetic testing (SOD1 mutation)

### TABLE 6 Quick checklist for ALS when reviewing the EMG/NCS report

Check the actual numbers and waveforms rather than relying on the summary of the report; make sure the cursors for the nerve conduction studies were placed correctly.

**Nerve conduction:**

- Are the sensory responses fairly normal? If not, think of Kennedy’s disease or vitamin B12 deficiency. Note: the patient might have other medical comorbidities such as diabetes which can affect the sensory responses as well.

- Is there evidence of partial conduction block in the motor responses at non-compressible sites (ie outside of a median neuropathy at the wrist, ulnar neuropathy at the elbow, or peroneal neuropathy at the fibular head)? If so, think of chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block.

**Note:** if there is evidence of a partial conduction block in the forearm on ulnar motor studies, make sure that a Martin-Gruber anastomosis variant was ruled out.

**EMG:**

- Which muscles (proximal v distal, arm v leg) were tested? Were the thoracic paraspinals, genioglossus or even sternocleidomastoid muscles tested?

- Which areas (right arm, left leg, tongue, etc) had the combination of acute denervation and chronic reinnervation suggestive of ALS? Was the spontaneous activity florid as expected in ALS?

- Did the patient have UMN signs on examination in these areas as well? Remember, it is the combination of UMN and LMN findings in the same area that defines ALS.

- Was there evidence of acute denervation (and possibly chronic reinnervation) in proximal muscles such as the deltoids, or those that were not clinically involved, which would support a more widespread disease such as ALS?
units with markedly decreased recruitment (fig 4) which are the electrodiagnostic signature of ALS. Fasciculations that are missed on clinical examination are occasionally detected electrophysiologically, but these can also occur in polyradiculopathies; the absence of fasciculation potentials does not exclude the possibility of ALS.\(^3\) EMG of the thoracic paraspinal muscles should be routinely performed to look for spontaneous activity; lumbar paraspinals are not helpful in differentiating between ALS and a lumbo-sacral polyradiculopathy.\(^3\)

In early cases where there is no tongue atrophy and maybe rather uncertain fasciculations, needle examination of the genioglossus, revealing fibrillation potentials and positive sharp waves, can be very helpful in establishing the cause of a diffuse LMN process. This is especially helpful in situations where there is a concomitant cervical spondylotic myelopathy complicating the analysis of the extremity abnormalities. A needle examination through the chin with a 26 or 30 gauge concentric or monopolar needle is surprisingly well tolerated.

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