Clinical aspects of motor neurone disease

Richard W Orrell
Roberto J Guiloff

Richard W Orrell BSc MB ChB MD DCH FRCP FAAN is Associate Professor in Clinical Neuroscience at UCL Queen Square Institute of Neurology, and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, and Royal Free Hospital, London, UK. He has clinical and research expertise in motor neurone disease, and other neuromuscular and neurodegenerative diseases. Competing interests:

Dr Orrell has received a fee for speaking from Biogen. He has acted as an expert witness related to motor neurone disease, and participates in clinical trials related to motor neurone disease. He has received fees from NICE for consulting. Roberto J Guiloff LMSSA LPhil MD FRCP is Professor of Neurology and Emeritus Honorary Consultant Neurologist at Faculty of Medicine, University of Chile and Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK. He has clinical and research expertise in clinical trials, motor neurone disease and other neuromuscular diseases. Competing interests: none declared

Abstract
Motor neurone disease (MND), or amyotrophic lateral sclerosis (ALS), is a progressive, fatal neurodegenerative disease affecting upper and lower motor neurones. It eventually causes widespread weakness and wasting, spasticity, dysarthria, dysphonia, dysphagia and respiratory failure. The diagnosis is clinical, and it is important for management to establish this early. It presents with upper and lower motor neurone signs affecting the bulbar, cervicothoracic and lumbosacral regions (ALS), only lower motor neurone signs affecting one or more limbs (progressive muscular atrophy), purely bulbar region symptoms and signs (bulbar onset), or only upper motor neurone signs in the (usually lower) limbs (primary lateral sclerosis). Imaging, electrophysiological and other tests help the differential diagnosis of mimics, including potentially treatable conditions. The underlying cause remains uncertain. Only 5–10% of patients have a demonstrable genetic cause. There is no cure, and the greatest advances have been in improving multidisciplinary supportive management. This includes gastrostomy and nutritional support, respiratory monitoring and management, including provision of non-invasive ventilation, and communication aids. Drugs for symptomatic relief of excessive salivation and spasticity can help. Riluzole and edaravone (restricted acceptance) are used although their disease-modifying effects are said to be mild and are controversial. Genetic therapies are currently being trialled for *C9orf72*-and *SOD1*-related MND/ALS.

Keywords
Amyotrophic lateral sclerosis
diagnosis
genetics
motor neurone disease
MRCP
riluzole
spinal muscular atrophy
treatment

Key points
•Motor neurone disease, also known as amyotrophic lateral sclerosis, is a progressive, fatal degenerative disease affecting upper and lower motor neurones
•The diagnosis is clinical, based on progressive denervation in muscles and pyramidal signs. These cause wasting, weakness and spasticity in bulbar, cervicothoracic and lumbosacral regions, in varying combinations, that cannot be explained topographically by a single lesion or other causes
•Differential diagnosis includes inflammatory motor neuropathies, mimics with combined upper and lower motor neurone signs (e.g. combined spinal cord and multiple root involvement in degenerative spine disease), spinal muscular atrophies and muscle diseases (e.g. polymyositis and inclusion body myositis)

•Established risk factors are older age, family history of motor neurone disease and male sex. Around 5–10% of patients have an identified genetic cause, usually with autosomal dominant inheritance, although with incomplete age-dependent penetrance. The most frequent genetic causes relate to *C9orf72* and *SOD1*
•Treatment is palliative multidisciplinary care, including speech, feeding and respiratory support and daily life adaptations

Definition and incidence

Motor neurone disease (MND), also called amyotrophic lateral sclerosis (ALS), is progressive and fatal, usually within 4 years. Degeneration of both upper and lower motor neurones causes the key pathology and clinical signs. The cause is unknown. The incidence is 1.5 per 100,000 per year, and the prevalence 6 per 100,000 population. Approximately 50% of individuals die within 3–4 years, 20% live >5 years, 10% >10 years, and occasional patients 20 or more years. Risk factors for ALS are increasing age, a family history of ALS and male sex. MND affects individuals of all countries and racial backgrounds.

The 5–10% of patients with a family history of ALS are referred to as having familial ALS, and those without a family history as having sporadic ALS. A small proportion of 'sporadic' cases show the same genetic changes as familial ALS.

Pathogenesis

The pathogenesis of ALS is uncertain, but a key pathological feature is TDP43 (TARDBP; TAR DNA binding protein)-containing inclusions in the motor neurone cytoplasm. Aggregates of disease-causing proteins could disturb normal protein homeostasis. Oxidative damage, intracellular mitochondrial dysfunction, glial cell pathology, glutamate excitotoxicity and defects in axonal transport, growth factors and RNA metabolism may also be involved.

Over 20 genes have been recognized in patients with ALS. Inheritance is usually autosomal dominant. A gene mutation is identified in around 75% of patients with a family history of ALS, and around 10% of apparently sporadic ALS. The most frequent gene abnormality in familial ALS (40%) is a GGGGCC hexanucleotide repeat expansion in *C9orf72*; this is also found in patients with fronto-temporal dementia (FTD) without ALS – 25% of patients with familial FTD, and 6% of 'sporadic' FTD. Mutations in the copper zinc superoxide dismutase gene (*SOD1*) (20%), first identified in 1993, and *TARDBP* (5%), and FUS (5%) follow. The causative mechanism of the mutations remains uncertain. However, about 90% of patients diagnosed with ALS do not have these gene changes.[1]

Clinical features

Essential clinical features are upper and lower motor neurone symptoms and signs, a progressive course and a lack of sensory involvement; however, some patients have sensory symptoms or changes on investigation. Symptoms and signs can start in the legs, arms or bulbar muscles, around one-third in each region. A smaller proportion have a respiratory presentation. The motor signs are asymmetrical and do not follow a nerve or root distribution.

Upper and lower motor neurone features are summarized in Table 1. There is a wide range of clinical presentations, especially in the early stages.

Amyotrophic lateral sclerosis – both upper and lower motor neurone signs are present. Typical features are foot drop, hand-wasting and weakness, and/or speech and swallowing difficulties. (Figure 1).

Progressive muscular atrophy – it only has lower motor neurone features that can obscure upper motor neurone signs, this can be confused with spinal muscular atrophy (SMA).

Progressive bulbar palsy – this presents with dysarthria and/or dysphagia caused by upper (pseudobulbar palsy), lower or upper plus lower motor neurone signs. If seen in isolation, brainstem or brain pathology must be ruled out (Figure 1, Table 1).

Primary lateral sclerosis – only upper motor neurone features are present. If denervation is not evident after 5 years, a diagnosis of primary lateral sclerosis can be made, with a much better prognosis.

Cognitive dysfunction is variable and may appear as behavioural alteration. There is an overlap between ALS and FTD.

Diagnosis

The diagnosis should only be made clinically, by close attention to the history, examination findings and clinical interpretation of investigation results. Over-reliance on investigations can be misleading.

Expert clinical examination is usually sufficient to define the presence, nature and extent of upper and lower motor neurone involvement.

Electromyography (EMG) and nerve conduction studies (NCSs) – EMG may identify denervation in muscles of regions with early or no clinical involvement. NCSs exclude motor and other polyneuropathies (particularly multifocal motor polyneuropathy).

Central motor conduction time – measurement may identify corticospinal tract involvement but is very rarely useful or needed.

Other investigations eliminate other possible causes of upper and lower motor neurone involvement:

•**Magnetic resonance imaging** of brain and spinal cord helps to exclude pathology in the brain, spinal cord and roots.

•**Cerebrospinal fluid** (CSF) examination is not required for diagnosing ALS but may exclude other conditions. In ALS the CSF is normal except that 20% of patients show protein increases of up to 1.5 g/litre.

•**Blood tests** are not diagnostic but may determine other causes of treatable neuropathy or myelopathy.

•Muscle biopsy is not needed to diagnose ALS but can be performed if there is concern of a myopathic condition

•**Genetic testing**, in terms of DNA analysis, is currently not usually considered a diagnostic investigation for ALS.

Differential diagnosis

Multifocal motor neuropathy can mimic a lower motor neurone presentation of ALS. NCSs demonstrate focal conduction blocks related to demyelination. It can be treated with intravenous immunoglobulin.

Cervical and lumbosacral degenerative disease with disc spinal cord compression in the cervical region and multiple cervical and lumbosacral radiculopathies can give combined pyramidal signs, limb wasting and weakness, show progression and be helped by surgery.

Inclusion body myositis can be confused with a lower motor neurone presentation of ALS.

Primary inflammatory myopathies can be suggested by raised serum creatine kinase and evidence of mixed myopathic and active denervation features on EMG.

Important differential diagnoses of ALS include other diseases that affect lower but not upper motor neurones:

•**Spinobulbar muscular atrophy (SBMA)**, or Kennedy's disease is an X-linked lower motor neurone disease of male patients; there is gynaecomastia, diabetes mellitus, infertility and abnormal sural sensory action potentials.

•SMA shows symmetrical clinical features in the classical forms (types 1, 2 and 3). Type 1 presents around birth, and types 2 and 3 later in childhood, adolescence and adulthood.

Management

Many patients miss out on early support and therapy for the condition because of a delay in diagnosis.[2]

Disease-modifying therapy

Riluzole is recommended by the UK National Institute for Health and Care Excellence (NICE),[2] although its benefit in slowing progression of MND/ALS is controversial.[3] Edaravone is used in many countries but is not available in the UK (see Further reading). The FDA has recently approved Relyvrio (a combination of sodium phenylbutyrate and taurursodiol).

Symptomatic therapies[4]

Management of patients with ALS involves a coordinated multidisciplinary palliative care approach that meets the changing physical and psychosocial needs of patients, families and carers throughout the disease course. Physical, occupational, and speech and language therapies are important components (Figure 2).

Dysphagia and nutrition: in the early stages, nutritional supplements can be helpful. Percutaneous endoscopic gastrostomy or radiologically inserted gastrostomy is used for nutritional and food support when feeding is significantly disrupted, with danger of aspiration or loss of weight.[4] Complications of these procedures are more likely if there is respiratory involvement.

Dysarthria: assessment of the clinical features of dysarthria by the neurologist and speech and language therapist determines the management of communication deficits. This varies from antispastic agents for spastic dysarthrias, and speech therapy techniques for mild dysarthrias, to simple aids for written communication and computerized devices with speech production.[5]

Salivary problems: sialorrhoea is a major problem in patients with advanced disease. Anticholinergics, including hyoscine patches and atropine, and drugs with anticholinergic action such as amitriptyline and glycopyrrolate, can help. Botulinum toxin injection of the salivary glands may need to be repeated every 3 months. A suction device can also be provided

Respiratory failure: this is the most frequent cause of death in ALS. It relates to denervation and weakness of the diaphragmatic, intercostal and accessory muscles of respiration, worsened by the likelihood of aspiration pneumonia as a result of bulbar palsy. An expectant management approach dependent on patient preference is preferred. Non-invasive respiratory support or ventilation is increasingly used, with the goal of reducing symptoms related to nocturnal hypoventilation (morning headache, fatigue), and later respiratory distress from respiratory insufficiency.[4]

The need for invasive ventilation (tracheostomy) can often be discussed in advance. Management of patients with tracheostomy and ventilation is demanding for community services, patient and family, and many patients decide not to proceed. Other patients have prolonged survival with tracheostomy and home ventilation (Figure 3).

Pain, cramps and spasticity: immobility, loss of muscle, and general debility can lead to pain. Analgesics and non-steroidal agents should always be tried first. Oral morphine or transdermal fentanyl patches can help in severe cases but caution is needed if respiratory function is poor. With spasticity, baclofen, dantrolene and tizanidine can be used and physiotherapy may be helpful. Quinine sulphate is given for cramps.

Advance care-planning and emotional support: advance care-planning is important. This includes decisions on how to proceed, with or without gastrostomy, non-invasive ventilation or tracheostomy, and what to do in the event of severe illness such as chest infection. It is important that any advance care plan is known to relatives, carers, therapists and medical staff.

Depression can be a normal reaction to the diagnosis and situation. However, It can also be a manifestation of the neurodegenerative process, as can emotional liability.

Genetic advice: this is well established for patients with SMA and SBMA. Advice is more complex for ALS as a range of genes is involved, penetrance is incomplete and the genetic mechanism is not clear.

Future developments

The most significant recent advances in clinical care of ALS have been multidisciplinary team involvement and agreed management guidelines.

The prognosis of childhood-onset (type 1) SMA has recently changed dramatically. ~~Two~~ Three gene therapies reverse the disease process here, and babies who would otherwise have died may now develop and progress to walking. ~~Both~~ The therapies are approved by the US Food and Drug Administration, and ~~one~~ by NICE in the UK, although with varying indications, including adults with SMA. It remains to be seen how this approach might translate to ALS, where the disease processes are not clear. Clinical trials in genetic forms of ALS including *C9orf72* and *SOD1* related disease are underway. (see Further reading)

Upper and lower motor neurone signs by regional symptoms

Region	Symptom	Upper motor neurone signs	Lower motor neurone signs
Bulbar	Dysarthria	Tongue/facial spasticity and poor movements	Tongue/facial fasciculations, wasting and weakness
		Slow slurred speech and voice	Weak/nasal voice, dysphonia
		Poor palatal elevation with brisk gag reflex	Poor or absent palatal elevation with absent gag reflex
		Brisk jaw jerk	Absent jaw jerk
			Poor articulation, nasal emission of air during speech
	Dysphagia	Tongue/facial spasticity, weakness and poor movements	Tongue/facial fasciculations, wasting, weakness, poor movements
		Poor palatal elevation with brisk gag reflex	Poor or absent palatal elevation with absent gag reflex
		Brisk jaw jerk	Absent jaw jerk
		Slow oral phase (mastication)	Slow oral phase (mastication), nasal regurgitation of fluids
Cervical	Arm weakness	Arm/hand spasticity and weakness	Arm/hand/neck muscle fasciculation, wasting and weakness
	Neck weakness	Brisk arm/hand reflexes	Depressed/absent arm/hand reflexes
	Dyspnoea and Orthopnoea		Diaphragmatic weakness (paradoxical movement)
Thorax and abdomen	Dyspnoea	Muscle weakness	Muscle fasciculation, weakness and wasting
	Orthopnoea	Absent abdominal reflexes	
Lumbar and sacral	Leg weakness	Leg spasticity and weakness	Leg muscle fasciculation, wasting and weakness
		Brisk reflexes	Depressed or absent leg reflexes
		Extensor plantar responses	

Source: Adapted from Tomic and Guiloff (2010).[5]

Table 1.

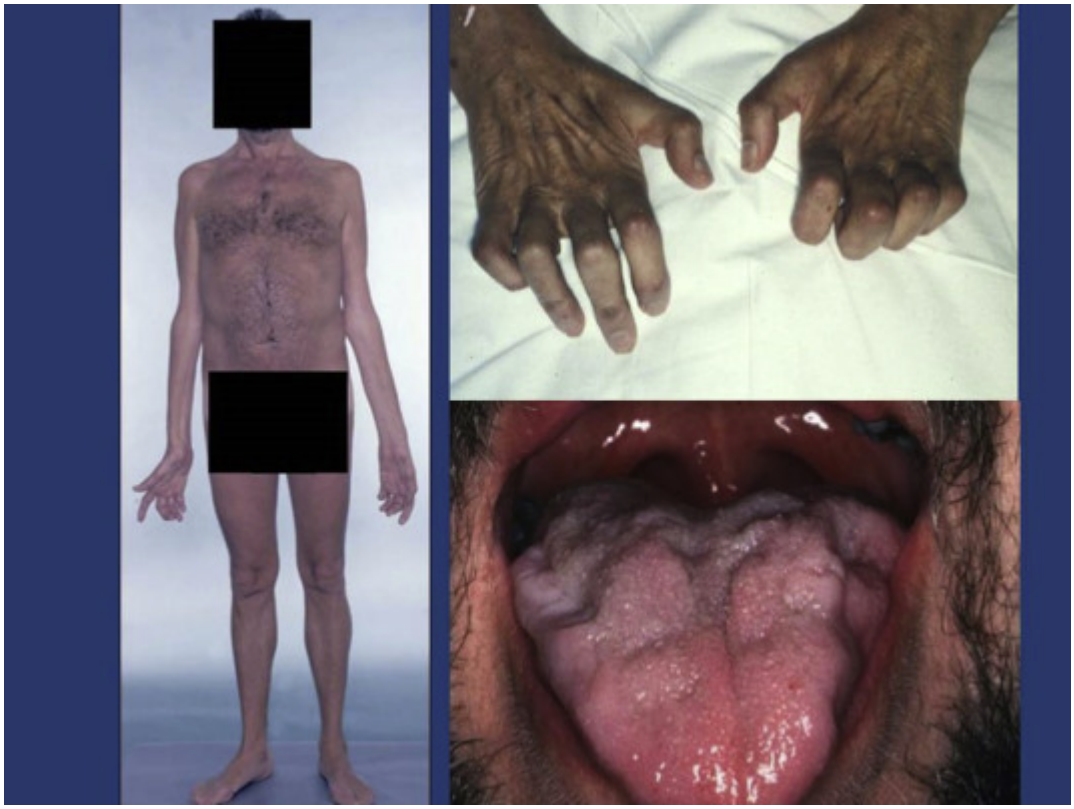

Figure 1. A patient with motor neurone disease, illustrating wasting in the muscles of the limbs and tongue.

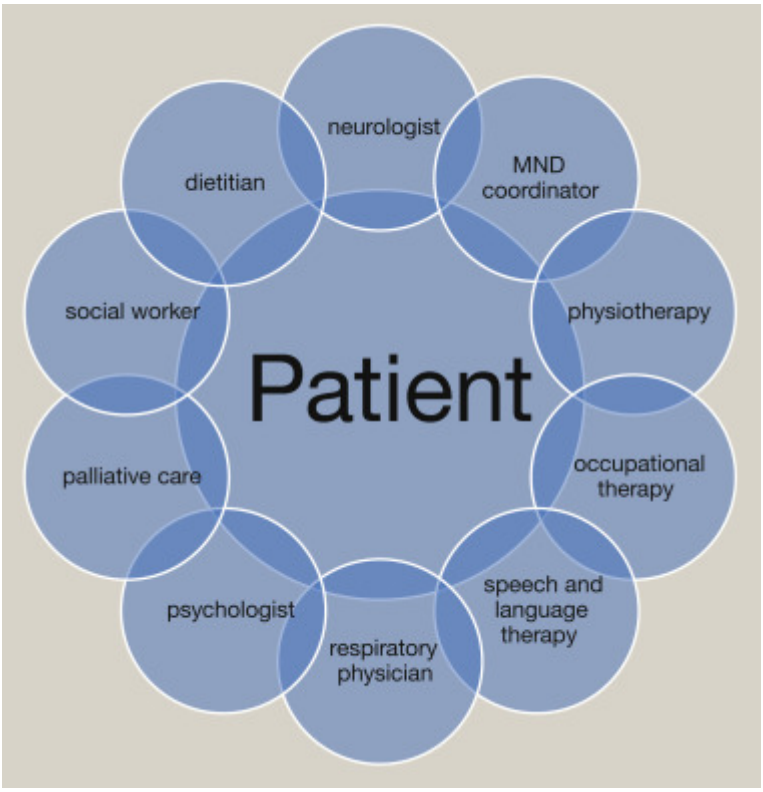

Figure 2. Multidisciplinary care of motor neurone disease (MND).

Figure 3. A patient requiring full support, including gastrostomy, tracheostomy ventilation, and eye gaze communication device.

KEY REFERENCES

1 Morgan S, Orrell RW. Pathogenesis of amyotrophic lateral sclerosis. Br Med Bull 2016; 119: 87e97.
2 National Institute for Health and Care Excellence. Motor neurone disease: assessment and management. 2019. NG42. www.nice. org.uk/guidance/ng42 (accessed ~~14 May 2020~~3 February 2023).
3 Sandercock J, Burls A, Hyde C, et al. Riluzole for motor neurone disease. More trials are needed. Br Med J 2001; 322: 1305.
4 Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on clinical management of amyotrophic lateral sclerosis (MALS) e revised report of an EFNS workforce. Eur J Neurol 2012; 19: 360e75.
5 Tomic B, Guiloff RJ. Dysarthria in amyotrophic lateral sclerosis. A review. Amyotroph Lateral Scler 2010; 11: 4e15.

FURTHER READING ~~Jackson C, Heiman-Patterson T, Kittrell P, et al. Radicava (edavarone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. Amyotroph Lateral Scler Frontotemporal Degen 2019; 20: 605e10.~~

Lejman J, Panuciak K, Nowicka E, Mastalerczyk A, Wojciechowska K, Lejman M. Gene therapy in ALS and SMA: Advances, challenges and perspectives. Int J Mol Sci 2023;24:1130.
Witzel S, Maier A, Steinbach R, et al. Safety and effectiveness of long-term intravenous administration of edaravone for treatment of patients with amyotrophic lateral sclerosis. JAMA Neurol 2022;79:121-130.

~~**AUTHORS: PLEASE CAN YOU SUBMIT 3 NEW SELF-ASSESSMENT QUESTION BASED ON YOUR ARTICLE**~~

Q1. A 45 year old salesman with well controlled Type 2 diabetes mellitus was referred to outpatients with progressive weakness in the limbs for 15 years and difficulty with speech and swallowing for five years. He lost 1 stone in weight in the last 5 years. Cognitive function preserved. He is married for 20 years. He has no children; his wife attended a gynaecology clinic but nothing abnormal was found. No family history of neurological disease.
His gait showed distal weakness in the legs. He had dysarthria. The tongue was wasted with fasciculations also seen in the face. Gag reflex was normal. There was wasting and fasciculations and weakness in upper and lower limbs. Tone was reduced. Tendon reflexes depressed. Plantar responses were flexor. Coordination and Sensation were normal.
Which is the one most useful initial investigation to support the suspected final diagnosis.

A.MRI brain
B.MRI spine
C.Autoantibody screen
D.Electromyography
E.Nerve conduction study

Answer. E is correct, Slowly progressive lower motoneurone syndrome affecting the bulbar region and limbs, no upper motorneurone or sensory features, with diabetes and likely infertility suggest bulbarspinal muscular atrophy (Kennedy's disease). An abnormal sural sensory nerve action potential distinguishes Kennedy's disease from other forms of spinal muscular atrophy and from a progressive muscular atrophy presentation of ALS/MND.

Q2. A 56 year old female teacher, previously healthy, was referred to outpatients with progressive wasting and weakness in flexion and elevation of the right arm for 3 months and difficulty walking. There had been no weight loss. She had a spastic gait, normal cranial nerves, moderate wasting,

fasciculations and weakness in the right deltoid and biceps, and in the left gastrocnemius. She had spasticity in the legs. Right biceps and left ankle reflex were absent . Other tendon reflexes in the limbs were pathologically brisk. Plantar responses were extensor. Vibration sense was absent in the lower limbs. Other sensory testing was normal. The following had been done and were normal: ESR, CRP, CK, Renal, liver and thyroid function, Hematology

Which of the following initial clinical diagnoses is more likely.

A.Amyotrophic Lateral Sclerosis

B.Progressive Muscular Atrophy

C.Multifocal Motor Neuropathy

D.Cervical cord Compression and Multiple radiculopathies

E.Spinal Muscular Atrophy

Question 2. D is correct. Fasciculations are not specific to MND. The absent reflexes . with *focal* wasting, weakness and fasciculations in the right C5-C6 and left L5-S1 terriories indicate denervation in those territories. The bilateral brisk reflexes in left arm and knees and right and the extensor plantar responses indicate pyramidal tract involvement in the cervical cord. A site of cord compression related to the cervical radiculopathy is likely.

Q3. A 48 year old male electrician is admitted via A&E in acute respiratory distress and is diagnosed with type 2 respitatory failure. Previously healthy, for six months he has had dysnoea on exertion, and minor weakness in upper and lower limbs. He has lost 6 kg in weight in the last 3 months. Appetite was normal. He was able to walk and had tongue fasciculations. There was mild generalised wasting and weakness in neck, shoulders, arms, hands and lower limb muscles. Fasciculations were seen in trapezii, arms and legs. Tendon reflexes in the limbs were brisk. Plantar responses were flexor. Sensation was normal. ESR, CRP, Haematology, Liver, Renal and Thyroid function all normal.

What is the most likely diagnosis with this presentation.

A.Cervical myelopathy and acute pneumonia

B.Lung cancer with metastasis

C.MND

D.Spinal muscular atrophy adult form

E.Polymyositis

Answer C is correct. An aggressive presentation of the progressive muscular atrophy form of MND. The widespread clinical signs of denervation in bulbar region upper and lower lims and the rapid evolution to respiratory failure are against an adult forms of SMA. The neurological signs and the initial blood tests do not support A, B, and E.