SHORT REPORT

Endplate dysfunction causing respiratory failure in a patient with prior paralytic poliomyelitis

A Truffert, P H Lalive, J P Janssens, M Sinnreich, M R Magistris

J Neurol Neurosurg Psychiatry 2003;**74**:370–372

A 56 year old man with late amyotrophic sequelae from poliomyelitis experienced progressive dyspnoea requiring intubation and artificial ventilation in the intensive care unit. Repetitive stimulation studies showed a marked decrement of the trapezius muscle response reversible with edrophonium. Ventilatory function considerably and lastingly improved under anticholinesterase treatment. In the absence of biological evidence for autoimmune myasthenia gravis, it is suggested that a mechanism implying endplate dysfunction related to postpolio syndrome. Repetitive stimulation procedure should be considered in postpolio syndrome patients as some of them may benefit from anticholinesterase treatment.

Breathing disorders are common in patients with prior poliomyelitis.^{1,2} Such complications may be associated with other manifestations of late motor deterioration in the so called postpolio syndrome (PPS), which can be defined as any late motor event occurring in a formerly poliomyelitic patient.³ Clinical manifestations of the PPS commonly include non-specific symptoms such as fatigue, muscle weakness, myalgias, and cramps. In PPS, respiratory insufficiency may be associated with the sleep apnoea syndrome.⁴ Patients who develop chronic alveolar hypoventilation several decades after acute poliomyelitis have been described,³ but it was not clear whether these patients had PPS, and respiratory insufficiency is usually not reported as the unique symptom of PPS, such as in the following observation.

CASE REPORT

A 56 year old man with limb amyotrophy attributable to polio sequelae presented with rapidly progressive breathing discomfort. At the age of 11, he had suffered from a severe form of paralytic anterior poliomyelitis, with tetraplegia and involvement of respiratory muscles requiring prolonged artificial ventilation. The disease was contracted in 1955 during the last epidemic polio outbreak in Geneva, just before introduction of vaccination. Progressive but partial recovery occurred, leaving the patient with severe paresis and amyotrophy of both lower limbs and of the distal muscles of upper limbs, but no conspicuous weakness of respiratory muscles. He was able to walk with braces and despite his motor handicap, could sustain a professional activity as a psychiatrist in private practice. He was a non-smoker and had no history of chronic obstructive pulmonary disease. One year ago, about 45 years after his acute polio, he began to notice progressive breathing discomfort. Recently, he developed over two weeks a severe dyspnoea that led him to seek medical assistance. Several weeks before his admission, he noticed headaches and difficulties in concentration, but no unusual fatigue, decrease in limb muscles force, or muscle pain. On admission in the emergency room, the P_{CO_2} was 7.2 kPa (54 mm Hg) and deteriorated to 17.2 kPa (129 mm Hg) after oxygen administration, requiring intubation and artificial ventilation.

On clinical examination, a severe amyotrophy of both legs and both hands with skeletal deformation and thoracic kyphoscoliosis were present. Manual testing of force showed a severe paresis of the most atrophic muscles, and a mild paresis (corresponding to M4 on the British Medical Council scale) of the limb girdle muscles including the trapezius. Pulmonary function tests (PFT) showed a restrictive disorder (total lung capacity: 3.45 litre, 54% of predicted) with markedly decreased inspiratory muscles strength (maximal mouth inspiratory pressure MIP: 53 cm H_2O , 61% of predicted).

A standard repetitive stimulation test was performed. Low frequency (3/s) repetitive pulses were applied to the right spinal nerve at the neck behind the posterior border of the sternocleidomastoid muscle. The amplitude of the motor response recorded over the right trapezius muscle was 3.1 mV and showed a 28% decrement on the fifth shock (fig 1A), which decreased to 15% 10 minutes after intravenous injection of 10 mg of edrophonium chloride (fig 1B). High frequency repetitive stimulation and single fibre EMG were not undertaken at this time. A muscle response of normal latency but decreased amplitude was recorded through surface electrodes from the diaphragm after a single electrical stimulus of the phrenic nerve at the neck. A thoracic CT scan showed no mediastinal mass suggestive of a thymoma. Antibodies directed against the acetylcholine receptor and against the muscle specific receptor tyrosine kinase (MuSK), anti-striated muscle, and anti-ganglioside antibodies were negative in blood samples.

In suspicion of an immune mediated myasthenia gravis (MG), a five days course of intravenous immunoglobulins (0.4 g/kg) was given without noticeable effect. The patient was then given increasing doses of pyridostigmine (up to 240 mg/day), which considerably improved breathing, permitting extubation after two weeks and transfer to a rehabilitation unit, from where he was discharged three weeks later with nocturnal non-invasive ventilatory support. On follow up examinations, one month and one year after his acute respiratory failure, the patient was free from respiratory symptoms. However, he was pyridostigmine dependent and reported relapses of breathing discomfort on attempts to reduce this treatment. Under anticholinesterase treatment, PFT showed improved values of all parameters (forced vital capacity: +15%, MIP: +45%) and the P_{CO_2} was normal at 5.8 kPa (43 mm Hg). Likewise, the 3 Hz repetitive stimulation test done one month and one year after his hospitalisation at the same recording site (right trapezius muscle) showed an increased initial amplitude (5.6 and 7.6 mV respectively) of the motor response and a marked reduction (to 8% and 11% respectively) of the decrement (fig 1C). No decrement was found in several other muscles (right abductor digiti minimi, gastrocnemius, and tibialis anterior) that were

Abbreviations: ALS, amyotrophic lateral sclerosis; EMG, electromyography; MIP, maximal mouth inspiratory pressure; MG, myasthenia gravis; MuSK, muscle specific receptor tyrosine kinase; PFT, pulmonary function tests; PPS, postpolio syndrome

Figure 1 Repetitive stimulation test (3/s) on the trapezius muscle. (A) At rest: 28% decrement of the response amplitude. (B) Ten minutes after injection of 10 mg of edrophonium chloride (Tensilon): reduction of the decrement to 15%. (C) One month later, under 240 mg/day of pyridostigmine (Mestinon), decrement is 8%. Note increased amplitude of the initial response.

previously affected by polio, but had not become weaker recently. A high frequency (20 Hz) repetitive stimulation test showed no significant increment of the trapezius motor response. A single fibre EMG was performed in two muscles (right trapezius and left extensor digitorum communis); the volitional technique permitted an overall analysis of only nine pairs of muscle fibres. However, in both muscles a clear increase of the jitter (62 to 139 μ s) without blockings was observed in all nine examined pairs.

DISCUSSION

Progressive breathing disorders developing insidiously over years, are common in patients with late polio sequelae.^{1,2,5} Proposed explanations for this progressive decline of respiratory function are usually unrelated to a new muscle weakness.⁶ They include musculoskeletal deformation with kyphoscoliosis causing a restrictive syndrome, pulmonary hypertension, and poor posture in the wheelchair bound patient. A central component is also suspected to contribute to hypoventilation in postpolio patients, when acute bulbar polio involved the reticular formation and the sleep regulatory centres,¹ with an increased incidence of the sleep apnoea syndrome.⁴ Additionally, respiratory decline with aging might be more marked in patients with prior poliomyelitis.³ In our patient, however, respiratory failure occurred over a short period, suggesting another pathophysiological mechanism.

Diagnostic criteria for the PPS include unusual fatigue, muscle or joint pain, new muscle atrophy, functional loss and cold intolerance beginning several decades after acute poliomyelitis.³ Although our patient experienced none of these symptoms, a PPS could nevertheless be considered, with new weakness of the respiratory muscles as the only manifestation. Such clinical

presentation of PPS seems uncommon, and a breathing problem was the least frequently (6%) new symptom reported in a series of 79 patients followed up in a postpolio clinic.⁷

In our patient, electrodiagnosis demonstrated a partial block of neuromuscular transmission. This was attested by (1) the low amplitude motor responses recorded over the diaphragm and trapezius muscles, (2) the decrement on repetitive shocks, and (3) the reduction of the decrement and the increased response under anticholinesterase treatment. Moreover, the absence of incremental response with tetanic stimulation suggests a post-synaptic, rather than a pre-synaptic disorder such as observed in the Lambert-Eaton myasthenic syndrome. The disorder could not be demonstrated in skeletal muscles that seemed spared by any recent weakness.

Clinically, the hypothesis that a neurotransmission defect played a significant part in the patient's respiratory symptoms, is further supported by favourable outcome and significant improvement of the restrictive syndrome with pyridostigmine, and by relapse of dyspnoea upon withdrawal of this treatment. Nocturnal ventilatory support probably also contributed to improvement of alveolar hypoventilation.

Disorders of neuromuscular transmission, and beneficial effects of anticholinesterase drugs have been recognised by early investigators in patients with poliomyelitis⁸ as well as in patients with other chronic loss of motor units such as ALS.⁹ In ALS patients, efficiency of this treatment is seldom lasting as it was in our patient. Anticholinesterase drugs have been shown to improve fatigue in some patients with PPS.¹⁰ However, a large randomised trial of pyridostigmine in 126 PPS patients¹¹ failed to demonstrate a significant benefit of this drug, suggesting that a defect of neuromuscular transmission was not the main mechanism for PPS symptoms in this group of patients.

Neuromuscular junction dysfunction is known to increase linearly with the time elapsed since acute polio.¹² These changes are believed to reflect inability of the enlarged motor units to sustain the metabolic demand of neurotransmission in an increased number of endplates over a prolonged period of time. Other possible mechanisms include permanent ongoing denervation and reinnervation of axons terminals resulting in immature endplates in a significant number of muscle fibres.^{12,13}

In our patient, an autoimmune myasthenia gravis (MG) cannot be completely ruled out. MG sometimes starts with acute ventilatory failure as the only manifestation.^{14,15} Antibodies directed against acetylcholine receptors were negative, as often reported in MG with predominant respiratory symptoms.¹⁶ Recently, Hoch *et al* demonstrated that 70% of these seronegative patients have serum autoantibodies directed against the muscle specific receptor tyrosine kinase, MuSK.¹⁷ In our patient, the anti-MuSK antibody assay was negative and intravenous Ig treatment was ineffective, rendering the hypothesis of MG unlikely.

In conclusion, this case report illustrates the possibility of acute respiratory events many years after an acute paralytic poliomyelitis. This may represent a particular form of PPS, perhaps related to exacerbation of chronic asymptomatic endplate dysfunction. Thus, PPS as a clinical entity shows a wide variety of manifestations and pathophysiological mechanisms. The practical conclusion is that repetitive stimulation tests in muscles affected by new weakness may help to identify patients with PPS who may benefit from an anticholinesterase treatment.

ACKNOWLEDGEMENTS

We wish to thank Dr Angela Vincent for having performed anti-MuSK antibodies assay in our patient. This observation has been presented as poster communication at the "XIIes Journées Francophones d'Electroneuromyographie" in Toulouse, France, on 5–7 June 2002.

Authors' affiliations

A Truffert, PH Lalive, M Sinnreich, MR Magistris, Clinique de Neurologie, Unité ENMG et des Affections Neuromusculaires, Hôpital

Cantonal Universitaire, Geneva, Switzerland

JP Janssens, Division de Pneumologie, Hôpital Cantonal Universitaire

Competing interests: none declared.

Correspondence to: Dr A Truffert, Clinique de Neurologie, Unité ENMG et des Affections Neuromusculaires, Hôpital Cantonal Universitaire, Rue Micheli-Du-Crest 24, CH-1211 Geneva 14, Switzerland; andre.truffert@hcuge.ch

Received 6 June 2002

Accepted in revised form 21 November 2002

REFERENCES

- 1 **Lane DJ**, Hazleman B, Nichols PJR. Late onset respiratory failure in patients with previous poliomyelitis. *Q J Med* 1974;**43**:551–68.
- 2 **Bach JR**. Management of post-polio respiratory sequelae. *Ann NY Acad Sci* 1995;**53**:96–102.
- 3 **Halstead LS**. Post-polio syndrome: definition of an elusive concept. In: Munsat TL, ed. *Post-polio syndrome*. Boston: Butterworth-Heinemann, 1991:23–8.
- 4 **Dean AC**, Graham BA, Dalakas M, et al. Sleep apnea in patients with postpolio syndrome. *Ann Neurol* 1998;**43**:661–4.
- 5 **Bach JR**, Alba AS, Bohatiuk G, et al. Mouth intermittent positive pressure ventilation in the management of postpolio respiratory insufficiency. *Chest* 1987;**91**:859–64.
- 6 **Dalakas M**, Illa I. Post-polio syndrome: concepts in clinical diagnosis, pathogenesis, and etiology. In: Rowland LP ed. *Advances in neurology*. Vol 56 *Amyotrophic lateral sclerosis and other motor neuron diseases*. New-York: Raven Press, 1991:495–511.
- 7 **Agre JC**, Rodriguez AA, Sperling KB. Symptoms and clinical impressions of patients seen in a postpolio clinic. *Arch Phys Med Rehabil* 1989;**70**:367–70.
- 8 **Hodes R**. Electromyographic study of defects of neuromuscular transmission in human poliomyelitis. *Arch Neurol Psychiatry* 1948;**60**:457–73.
- 9 **Mulder DW**, Lambert EH, Eaton LM. Myasthenic syndrome in patients with amyotrophic lateral sclerosis. *Neurology* 1959;**9**:627–31.
- 10 **Trojan DA**, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. *J Neurol Sci* 1993;**114**:170–7.
- 11 **Trojan DA**, Collet JP, Shapiro S, et al. A multicenter, randomized, double-blinded trial of pyridostigmine in postpolio syndrome. *Neurology* 1999;**53**:1225–33.
- 12 **Wiechers DO**, Hubbell SL. Late changes in the motor unit after acute poliomyelitis. *Muscle Nerve* 1981;**4**:524–8.
- 13 **Wiechers DO**. New concepts of the reinnervated motor unit revealed by vaccine-associated poliomyelitis. *Muscle Nerve* 1988;**11**:356–68.
- 14 **Dushay KM**, Zibrak JD, Jensen WA. Myasthenia gravis presenting as isolated respiratory failure. *Chest* 1990;**97**:232–4.
- 15 **Maher J**, Grand'Maison F, Nicolle MW, et al. Diagnostic difficulties in myasthenia gravis. *Muscle Nerve* 1998;**21**:577–83.
- 16 **Mossman S**, Vincent A, Newsom-Davis J. Myasthenia gravis without acetylcholine-receptor antibody: a distinct disease entity. *Lancet* 1986;**ii**:116–19.
- 17 **Hoch W**, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nature Med* 2001;**7**:365–8.