SHORT REPORT

Dysphagia as the sole manifestation of myasthenia gravis

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Three patients are described who had dysphagia as the sole manifestation of myasthenia gravis. Severity ranged from the need to be fed by nasogastric tube to moderate dysphagia requiring only diet change. Oesophageal manometry was carried out in two patients and showed generalised weakness of peristaltic contractions which included the smooth muscle part of the oesophagus. These disturbances worsened with repeated swallows. They were partly reversed by intravenous edrophonium and by rest. Repetitive nerve stimulation was normal in all three patients, but stimulated single fibre EMG of the frontalis muscle showed that all had impairment of neuromuscular transmission. Anti-AChR antibodies were found in only one patient. The most affected patient was treated with pyridostigmine, plasmapheresis, and high dose prednisone. The remaining two patients received only oral anticholinesterases.

D ysphagia is a frequent symptom in myasthenia gravis and it eventually occurs in 15–40% of patients with the generalised form.[1][2] In contrast, it is very uncommon for dysphagia to be the sole manifestation of the disease.[1][3][4] Diagnosis in these patients may be difficult, especially if acetylcholine receptor (AChR) antibodies are not present or if there is not a clear clinical response to the parenteral administration of anticholinesterases.

In myasthenic patients with dysphagia, oesophageal manometric studies have shown a progressive deterioration in the amplitude of pharyngeal contractions with repeated swallows. Peristalsis recovered after rest or following the administration of edrophonium.[3] Besides dysfunction of the upper oesophageal sphincter, which is formed of striated muscle, Huang and coworkers found a decrease in the amplitude and an increase in the duration of peristaltic waves in the entire oesophagus, together with augmentation of abnormal oesophageal contractions.[2] These results are surprising as the middle and lower thirds of the oesophagus are composed entirely of smooth muscle.[5]

We describe three patients with myasthenia gravis and dysphagia as a sole symptom. The oesophageal motility and its response to the administration of edrophonium were studied in two of them by oesophageal manometry.

METHODS

Electrodiagnostic procedures

Conventional EMG was carried out using standardised techniques.[6] Neuromuscular jitter was measured in the frontalis muscle with a single fibre EMG electrode (Teca, Old Woking, Surrey, UK) using the axonal microstimulation technique.[7] In brief, intramuscular facial nerve branches were stimulated through a monopolar steel needle placed above the eyebrow, using rectangular current pulses of 50 µs duration and a variable intensity of around 20 mA. The stimulation rate was 2 Hz when searching for optimal action potentials and 10 Hz during jitter measurements. Special care was taken to maintain supramaximal stimulation for each single fibre action potential studied. A study was considered abnormal if the mean difference between consecutive discharges (MCD) of two muscle potentials exceeded 33 µs (upper normal limit in our laboratory) or when the mean MCD of 20 muscle potentials or more exceeded 22 µs (upper normal limit in our laboratory), or both. Studies were done using a Premiere Plus or a Synergy electromyograph (Medelec®, Oxford Instruments, Oxford, UK).

Oesophageal manometric study

Recording of intraluminal pressure was done using a single catheter assembly consisting of four fluid filled tubes bonded together with lateral openings placed 5 cm apart. The catheter assembly was connected to a pressure recorder and its output fed into a personal computer equipped with a digitising board (Synectics Medical, Stockholm, Sweden). Two manometric studies were carried out in patients 2 and 3 on different days. First, oesophageal peristalsis was studied according to the recommendations of the Spanish Society of Digestive Pathology.[8] Second, the response of the oesophageal musculature both to repetitive swallows and to the administration of edrophonium was explored.

RESULTS

Case summaries

Clinical details of the patients are given in table 1.

Patient 1 was a 28 year old woman with a four month history of progressive dysphagia accompanied of frequent choking episodes and weight loss. She was initially admitted to another hospital where a cranial magnetic resonance imaging study, lumbar puncture, conventional EMG examination, and laryngoscopic exploration were undertaken with no abnormal findings. A fluoroscopic study showed passage of contrast into the trachea, and oesophagogastroscopy revealed acute lesions of the gastric mucosa. On admission to our hospital, the patient had to be fed through a nasogastric tube and her voice was hypophonic. She was receiving antibiotics because of aspiration pneumonia. There was a generalised loss of muscle bulk, but muscle strength and cranial nerve functions were preserved. There was no response to either 10 mg of edrophonium or 5 mg of neostigmine. Repetitive nerve stimulation at 2 Hz was normal. However, stimulated single fibre EMG showed a marked neuromuscular transmission defect. Anti-AChR antibodies were negative and thyroid hormones were normal. Thoracic computed tomography showed a 2 cm diameter small mass in the anterior mediastinum of doubtful nature, and an extensive alveolar infiltrate in the left inferior lung lobe with associated loss of volume and the remains of digestive contrast.

After the diagnosis of myasthenia gravis had been made through the single fibre EMG study, plasmapheresis and oral pyridostigmine were started with marked improvement in swallowing that allowed the withdrawal of the nasogastric tube. However, dysphagia reappeared 10 days after the last plasmapheresis. The patient was then treated with

intravenous immunoglobulins without response. Eventually, she had to be mechanically ventilated owing to massive atelectasis. Daily plasmapheresis was then carried out for 10 days followed by oral prednisone (90 mg/day). Her state improved again but, unexpectedly, she developed a cerebral infarct in the deep territory of the left middle cerebral artery eight days after the last plasmapheresis. In the days following this she again required mechanical ventilation because of atelectasis of the left lobe of the lung. After extensive diagnostic evaluation, no cause for the stroke was found and it was attributed to a complication of the plasma exchanges. She was finally discharged to her referring hospital on prednisone and pyridostigmine, with a right hemiplegia but able to swallow soft food.

The remaining two patients presented with a more protracted and less severe dysphagia. Stimulated single fibre EMG was abnormal in both, and anti-AChR antibodies were found in one of them (table 1). Treatment with pyridostigmine restored swallowing almost to normality in both (table 1).

Oesophageal manometric studies

The amplitude of peristaltic contractions was markedly decreased in the patients 2 and 3 along the entire oesophagus (fig 1, panels A and B). The pressure of the lower oesophageal sphincter was normal in both cases, while there was a slight reduction in the pressure of the upper oesophageal sphincter in patient 3. Successive swallows caused a greater than expected reduction in the amplitude of peristaltic contractions in patient 3, given the interval between swallows

(fig 1B, I and II). In patient 2, repetitive swallows eventually led to complete suppression of oesophageal motility, preceded by a progressive reduction in contraction of the upper oesophageal sphincter. Oesophageal peristalsis was partial and was temporarily restored by intravenous edrophonium chloride in that patient (fig 1C, I and II), whereas the response in patient 3 was equivocal.

DISCUSSION

The work of Huang et al[2] and our results show that in myasthenia gravis there is a profound alteration in the motility of the oesophageal segments that are composed solely of smooth muscle. This dysfunction is unexpected as neuromuscular transmission in smooth muscle is mediated by muscarinic acetylcholine receptors.[9] It might be simply a result of weakness of the striated muscle portion of the oesophagus, which could decrease afferent feedback in the distal oesophagus. In the rat, curarisation causes a marked alteration in reflex activity in both the nucleus of the tractus solitarius (which receives the central projections of sensory vagal afferents) and in the oesophagomotor portion of the nucleus ambiguous.[10] Nevertheless, in baboons curarisation does not suppress primary peristalsis of smooth muscle despite paralysis of the oropharynx and cervical oesophagus, suggesting that primary peristalsis does not depend on receiving afferent feedback in the primate.[5]

Alternatively, the smooth muscle dysfunction might reflect a blockade of neurotransmission between the neurones of the dorsal motor nuclei of the vagus nerve and the neurones of the oesophageal myenteric plexus; this transmission is

Table 1 Clinical details of the patients

	Patient 1	Patient 2	Patient 3
Age (years)	28	25	28
Sex	Female	Male	Female
Date of diagnosis	October 2000	May 2001	December 2001
Approximate time until diagnosis	4 months	24 months	12 months
Grade of dysphagia	Need for nasogastric tube; aspiration pneumonia	Solids	Solids and liquids
Weight loss	Severe	None	Moderate
Oesophageal fluoroscopy	Contrast passage to airway	Normal	ND
Endoscopy	Acute lesions of gastric mucosa	ND	Normal
Oesophageal manometry	ND	Peristaltic contractions of low amplitude; frequent simultaneous contractions	Reduced UES pressure; peristaltic contractions of low amplitude
Conventional EMG	Normal	Normal	ND
2 Hz Repetitive stimulation	Normal in right abductor digiti minimi, right trapesius, and right nasalis	Normal in right abductor digiti minimi, right trapesius, and right nasalis	Normal in left nasalis
Stimulated SF-EMG	Mean MCD = 78 µs; 10 of 19 fibres with an increased MCD, three with blocking	Mean MCD = 26.3 µs; 10 of 37 fibres with an increased MCD, two with blocking	Mean MCD = 23.4 µs; 3 of 34 fibres with an increased MCD, two with blocking
Anti-AChR antibodies	Negative	Negative	Positive (5.7 nmol/l)
Thyroid hormones	Normal	Normal	Normal
Thoracic CT	2 cm diameter mass in the thymus compartment of doubtful nature	Normal	Normal
Edrophonium test	Absence of a clinically appreciable response	Absence of a clinically appreciable response but transient increase in amplitude of oesophageal peristaltic contractions	Equivocal response during the manometric study
Treatment	Pyridostigmine, plasma exchange (two courses), and prednisone (90 mg daily)	Pyridostigmine	Pyridostigmine
Date at last follow up	March 2004	April 2004	April 2004
Status at last follow up	Neither dysphagia nor other symptoms attributable to MG; right residual hemiparesis but able to walk	Decrease in speed of eating; occasional difficulties with foods of high consistency; no other symptoms attributable to MG	Decrease of speed of eating; frequent difficulties with foods of high consistency; no other symptoms attributable to MG
Treatment at last follow up	Prednisone (20 mg every other day) and pyridostigmine (240 mg daily)	Pyridostigmine (180 mg daily)	Pyridostigmine (240 mg daily)

Anti-AChR, anti-cholinergic receptor antibodies; CT, computed tomography; EMG, electromyography; MCD, mean difference between consecutive discharges; MG, myasthenia gravis; ND, not done; SF-EMG, single fibre electromyography; UES, upper oesophageal sphincter.
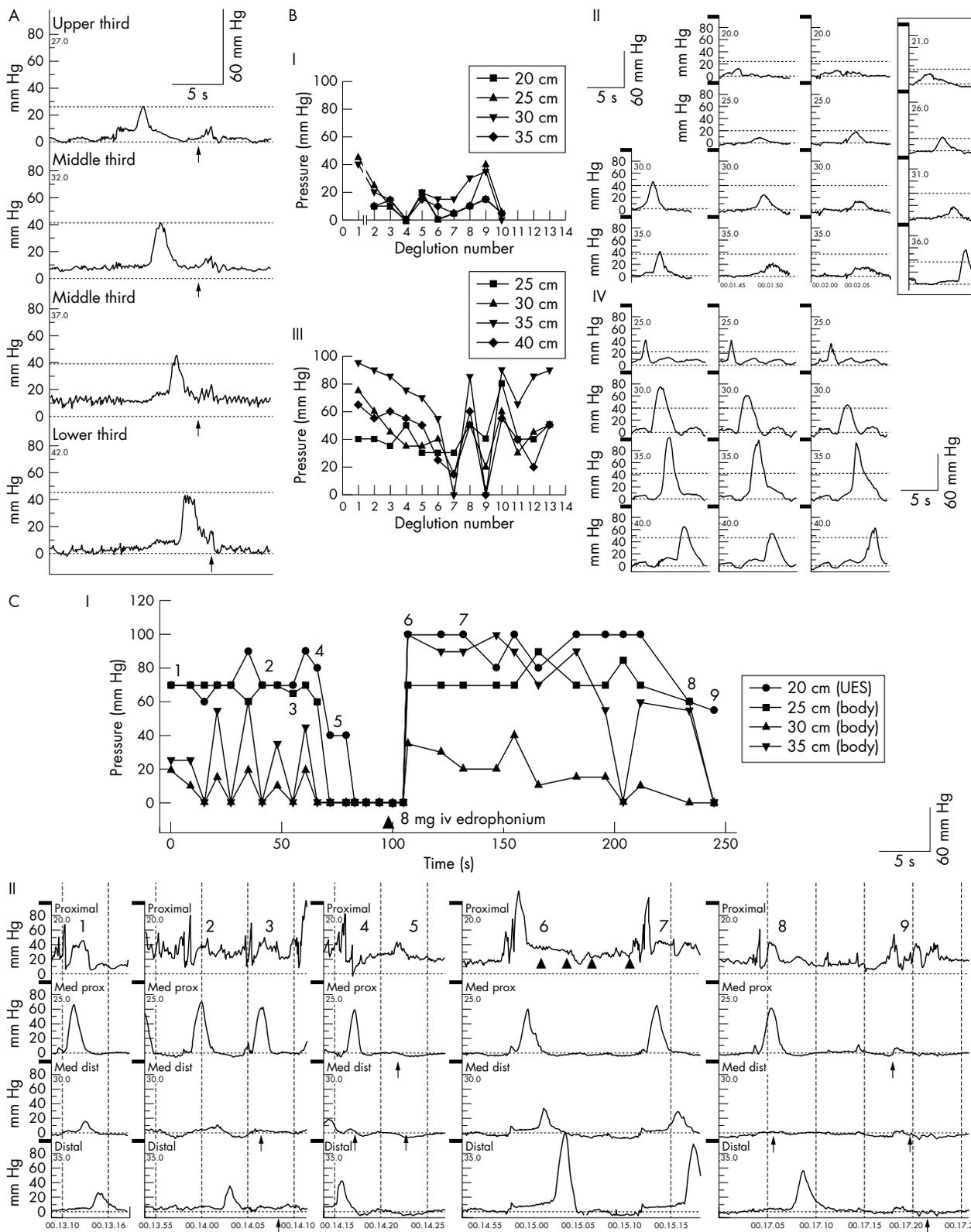
Figure 1 (A) Representative peristaltic contraction wave of low amplitude recorded during oesophageal manometry in patient 2. Note the presence of a simultaneous oesophageal contraction (arrows). (B) Oesophageal response to rapid swallowing in patient 3 (panels I and II) compared with a control subject (panels III and IV). *Panel BI*: Time course of the pressure of peristaltic waves with successive swallows in patient 3. The amplitude of the second swallow was about 50% lower that of the first although it occurred 68 s later (note the break in the x axis). At this interval no reduction in amplitude is expected. Successive swallows were delivered at 19 (9.3) s intervals (mean (SD)). *Panel BII*: Manometric recordings of the first three swallows of the series; a peristaltic wave recorded after 10 minutes of rest is shown in the inset. *Panel BIII*: Time course of the peristaltic wave pressure with successive swallows in a control subject. The interval between swallows was 15 (4.7) s. Note the first phase of progressive reduction in the amplitude of peristaltic waves (the amplitude of the second swallow was about 20% lower than that of the first), especially in the more distal segments, until a minimum value was reached. Afterwards, there was a period in which near normal swallows alternated with greatly inhibited contractions. This pattern of contraction

was also observed in our patients. *Panel BIV*: Manometric recordings of the first three swallows of the series. (C) Oesophageal response to rapid swallowing in patient 2 and the effect of edrophonium. *Panel CI*: Time course of the change in the amplitude of the oesophageal contractions. Interswallow interval was 6.8 (1.2) s before the administration of edrophonium and 12.5 (4.4) s after edrophonium. *Panel CII*: Sample recordings of the manometric study corresponding to the points identified by numbers in panel CI. Arrows mark the absence of propagation of the peristaltic wave along the corresponding oesophageal segment. Note that after a period of intermittent inhibition of peristalsis (similar to that observed in the control subject), there was compete abolition of oesophageal motility. After the edrophonium infusion, the amplitude of the oesophageal contractions (both in the upper oesophageal sphincter and in the oesophageal body) and the resting pressure of the upper oesophageal sphincter (arrowheads) transiently increased. In (A) and (B), dotted lines mark the limits of normality in our laboratory. During the study of the response of the oesophageal musculature to repetitive swallows and to the administration of edrophonium, patients were encouraged to maintain the same swallowing rate throughout. dist, distal; iv, intravenous; prox, proximal; UES, upper oesophageal sphincter.

mediated by nicotinic acetylcholine receptors, although of the ganglionic neural type.[5] In this respect, autoantibodies to human ganglionic acetylcholine α3 receptors have been found in patients with subacute autonomic neuropathy or Isaac's syndrome.[11] Moreover, some rat monoclonal antibodies to the main immunogenic region on muscle α1 receptors also react well with human α3 and α5 subunits.[9] Nevertheless, at present, autoantibodies in patients with myasthenia gravis have not been found to bind to human α3 acetylcholine receptors.[9]

Some seronegative patients with myasthenia gravis have serum IgG antibodies against the muscle specific kinase (MuSK) and it is thought that these antibodies impair neuromuscular transmission.[12] Bulbar involvement was the rule in an extensive series of anti-MuSK positive patients described by Evoli *et al*.[13] As the assay is not available in our geographical area, the anti-MuSK antibody status of our patients is unknown. Nevertheless, in contrast to our patients, weakness of bulbar muscles was accompanied by ocular disturbances and facial weakness in Evoli's series, and many of their patients did not respond to pyridostigmine.[13] Finally, to our knowledge, MuSK has not been identified in smooth muscle.

In healthy subjects, there is a decrease in oesophageal peristalsis ("deglutitive inhibition") along a series of closely spaced swallows, and this is more pronounced in the distal oesophagus and at interswallow intervals of less than 10 to 15 seconds.[14] A pause of 30 seconds is enough to restore peristalsis to its basal value.[14] This amplitude reduction was notably greater in patient 3 (fig 1B, I–II) than in a control subject (fig 1B, III–IV). Patient 2 experienced complete inhibition of oesophageal peristalsis with repetitive swallowing, which was transiently reversed by edrophonium (fig 1C).

In conclusion, isolated dysphagia may be a form of presentation of myasthenia gravis. Such patients may have a profound alteration in peristalsis in the smooth muscle portion of the oesophagus. Single fibre EMG appears to be indispensable in the diagnostic evaluation of seronegative patients with myasthenia gravis in whom repetitive stimulation is normal.[15]

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