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Pathophysiological mechanisms of oropharyngeal dysphagia in amyotrophic lateral sclerosis

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Summary

We investigated the pathophysiological mechanisms of dysphagia in amyotrophic lateral sclerosis. Forty-three patients with sporadic amyotrophic lateral sclerosis were examined by clinical and electrophysiological methods that objectively measured the oropharyngeal phase of voluntarily initiated swallowing, and these results were compared with those obtained from 50 age-matched control subjects. Laryngeal movements were detected by a piezoelectric sensor and EMG of submental muscles, and needle EMG of the cricopharyngeal muscle of the upper oesophageal sphincter of both the amyotrophic lateral sclerosis and control groups was recorded during swallowing. Amyotrophic lateral sclerosis patients with dysphagia displayed the following abnormal findings. (i) Submental muscle activity of the laryngeal elevators, which produce reflex upward deflection of the larynx during wet swallowing, was significantly prolonged whereas the laryngeal relocation time of the swallowing reflex remained within normal limits. (ii) The cricopharyngeal sphincter muscle EMG demonstrated severe abnormalities during voluntarily initiated swallows. The opening of the sphincter was delayed and/or the closure occurred prematurely, the total duration of opening was shortened and, at times, unexpected motor unit bursts appeared during this period. (iii) During voluntarily initiated swallows there was significant lack of co-ordination between the laryngeal elevator muscles and the cricopharyngeal sphincter muscle. These results point to two pathophysiological mechanisms that operate to cause dysphagia in amyotrophic lateral sclerosis patients. (i) The triggering of the swallowing reflex for the voluntarily initiated swallow is delayed and eventually abolished, whereas the spontaneous reflexive swallows are preserved until the preterminal stage of amyotrophic lateral sclerosis. (ii) The cricopharyngeal sphincter muscle of the upper oesophageal sphincter becomes hyper-reflexic and hypertonic. As a result, the laryngeal protective system and the bolus transport system of deglutition lose their co-ordination during voluntarily initiated swallowing. We conclude that these pathophysiological changes are related mainly to the progressive degeneration of the excitatory and inhibitory corticobulbar pyramidal fibres.

Keywords: sporadic ALS; oropharyngeal dysphagia; pathophysiology of dysphagia; voluntarily initiated swallow; spontaneous swallow

Abbreviations: CP-EMG = EMG of the cricopharyngeal; SM-EMG = EMG of the submental muscle complex; UES = upper oesophageal sphincter

Introduction

Dysphagia is one of the most important clinical problems encountered in amyotrophic lateral sclerosis. It is not uncommon as an initial symptom in amyotrophic lateral sclerosis, but it appears typically several months after the onset of the disease. Most patients with amyotrophic lateral sclerosis ultimately show oropharyngeal involvement (Roller *et al*., 1974; Carpenter *et al*., 1978; McGuirt and Blalock, 1980). When amyotrophic lateral sclerosis presents predominantly with dysphagia, further investigation may reveal bulbar and/or pseudobulbar palsy. The presence of dysphagia can be diagnosed by videofluoroscopic/manometric methods even before the bulbar symptoms or swallowing difficulty appear clinically (Leighton *et al*., 1994; Briani *et al*., 1998). The dysphagia and related aspiration pneumonia are usually the major handicaps to the quality of life, in addition to the risk of poor nutrition and dehydration, which occur particularly in older patients (Hillel and Miller, 1989; Strand *et al*., 1996).

Although dysphagia can be frequent or very severe and may be life-threatening in amyotrophic lateral sclerosis

patients, the pathophysiological nature of dysphagia in amyotrophic lateral sclerosis has not been systematically studied and documented either clinically or by EMG, although a number of videofluoroscopic studies have been reported (Bosma and Brodie, 1969; Robbins, 1987; Leighton *et al*., 1994; MacDougall *et al*., 1995; Wright and Jordan, 1997; Briani *et al*., 1998). So far, neither clinical nor X-ray studies have been able to explain clearly the neurophysiological mechanisms of dysphagia in amyotrophic lateral sclerosis.

In this study, we investigated the pathophysiological mechanisms of dysphagia in amyotrophic lateral sclerosis by means of clinical and electrophysiological methods. The electrophysiological methods have been described by our group previously (Ertekin, 1996; Ertekin *et al*., 1995, 1996, 1997). The results of this study strongly indicate that the pathophysiological mechanisms of dysphagia in amyotrophic lateral sclerosis patients are primarily associated with the progressive degeneration of the excitatory and inhibitory corticobulbar pyramidal fibres that control the bulbar swallowing centre.

Patients and methods

We investigated 43 amyotrophic lateral sclerosis patients (16 female, 27 male), with a mean age of 54.6 years and an age range of 36–72 years. Amyotrophic lateral sclerosis was diagnosed according to the El Escorial criteria (Brooks, 1994). Bulbar involvement of the lower motor neuron type was absent in eight patients without dysphagia. Electrodiagnostic studies, including needle EMG, supported the clinical diagnosis in all patients.

The clinical duration of amyotrophic lateral sclerosis since the patient became aware of the first symptoms related to the disease varied from 1 to 36 months, with a mean of 14 months. At the time of investigation, signs of lower motor neuron involvement in the limbs were prominent in 13 patients, while signs of upper motor neuron involvement in the limbs predominated in 15 patients. Bulbar and suprabulbar signs other than dysphagia were also apparent in all of the patients except eight non-dysphagic patients. Among the dysphagic group of 35 patients, 18 had predominant pseudobulbar involvement. Their clinical picture was prominent, with spastic laughing/crying, an increase in brainstem reflexes and lingual motor dysfunction without clinical atrophy. In eight dysphagic patients, the bulbar lower motor neuron involvement was apparent, with fasciculations and atrophy in the tongue, normal or decreased brainstem reflexes and no hyperemotionalism. In the remaining dysphagic patients, pseudobulbar and bulbar symptoms and signs were present in almost equal amounts.

All patients were specifically questioned and examined with respect to their suprabulbar and bulbar involvement, including dysphagia and aspiration (Logemann, 1983; Splaingard *et al*., 1988; Linden *et al*., 1993; Hughes and Wiles, 1996*a*). After a complete neurological examination had been carried out, needle EMG and nerve conduction tests were performed. Some patients were also investigated by cranial and/or cervical MRI and by CT scanning.

The degree of dysphagia was graded as follows. Grade 1: no clinical signs and symptoms of dysphagia. Grade 2: very mild dysphagia was suspected by clinical examination, but the patient never complained directly of dysphagia. Grade 3: the patient complained of dysphagia, and this was supported by other clinical signs; however, non-oral feeding was not necessary at the time of investigation. Grade 4: the patient had obvious clinical signs and symptoms of dysphagia, including aspiration, and dysphagia was severe enough to necessitate non-oral feeding.

Electrophysiological methods for the evaluation of oropharyngeal swallowing

The methods that we used for the evaluation of dysphagia have been described previously (Ertekin, 1996; Ertekin *et al*., 1995, 1996, 1997; Pehlivan *et al*., 1996). In brief, during the examination, the seated patient was instructed to hold his or her head in a neutral upright position. Swallows were initiated voluntarily with the bolus (liquid) positioned on the tongue and the tip of the tongue touching the upper incisors (Dantas *et al*., 1990). Swallow signals were recorded following the delivery of 1 or 3 ml of liquid (water) through a graduated syringe. The patients were also investigated while performing dry swallows. Mechanical upward and downward laryngeal movements during swallowing were detected by means of a piezoelectric sensor designed in our laboratory. This was a simple piezoelectric wafer with a 4×2.5 mm rubber bung fixed to its centre. The rubber bung was placed on the coniotomy region between the cricoid and thyroid cartilages at the midline, this region being located by palpation. The sensor was taped onto the neck and its output signal was filtered (bandpass 0.01–20 Hz) and fed into one of the channels of the EMG apparatus (Medelec Mystro, MS-20, Surrey, UK). The submental EMG (SM-EMG) was recorded by bipolar silver chloride EEG electrodes taped under the chin over the submental muscle complex (mylohyoid, geniohyoid and anterior digastric muscles). Signals were filtered (bandpass 100 Hz to 10 kHz), amplified, rectified and integrated.

Cricopharyngeal muscle activity of the upper oesophageal sphincter (UES) was recorded with a sterile needle electrode (Medelec disposable needle electrode DMC-37, diameter 0.46 mm, recording area 0.07 mm^2) inserted through the skin at the level of the cricoid cartilage ~1.5 cm lateral to its palpable lateral border in the posteromedial direction. High-frequency tonic EMG activity and its cessation during swallowing served as the criterion for correct electrode penetration into the cricopharyngeal muscle. In this study, we refer to the cessation of tonic EMG activity of the cricopharyngeal muscle during swallowing as the 'CP-EMG pause'. The cricopharyngeal sphincter EMG (CP-EMG) was recorded together with the laryngeal movement sensor signal, under the same recording conditions as for the SM-EMG.

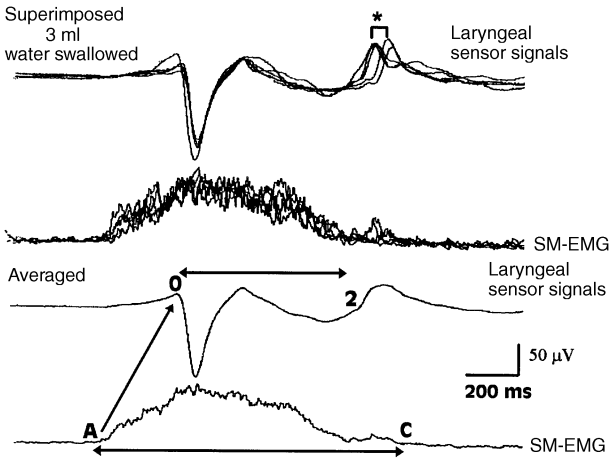

Fig. 1 Laryngeal sensor signals (upper traces in superimposed and averaged recordings) and integrated SM-EMG activities (lower traces in superimposed and averaged recordings) obtained from an amyotrophic lateral sclerosis patient without clinical evidence of dysphagia and bulbar involvement. 0 and 2 denote the onsets of upward and downward laryngeal movement deflections, respectively. A and C denote the onset and end of SM-EMG activity during the swallowing of 3 ml of water. The oblique arrow from A to 0 (referred to in the text as the A–0 interval) denotes the interval from the onset of voluntarily triggered swallowing to the onset of reflex swallowing, as demonstrated by the onset of upward movement of the larynx. The asterisk indicates the swallowing jitter.

The electrophysiological traces obtained from the piezoelectric laryngeal movement sensor and from the SM-EMG are illustrated in Fig. 1, in which the labels 0, 2, A and C indicate the points of measurement. The laryngeal sensor output shows two deflections during swallowing. The first deflection represents the upward movement of the larynx and the second deflection its downward movement (Fig. 1; upper traces of the superimposed and averaged recordings). The upward and downward deflections of the laryngeal sensor were sometimes diphasic or triphasic for technical reasons. Their shortest time with high amplitude at the beginning of deflexion from the baseline was important, and this was accepted as the point of onset. The midregion of the first deflection was stabilized on the oscilloscopic screen by using the delay-line technique, so that, throughout successive recordings, the deflections appeared at the same location of each sweep (~800 ms after the onset of the sweep). In this way, all electromechanical events were displayed synchronously. The onsets of the two deflections in the laryngeal sensor signal recordings are denoted as '0' and '2' (Fig. 1). The interval between the onsets of two deflections, indicated in Fig. 1 by '0⟷2', is thought to reflect the time necessary for the elevation, closure and upward relocation of the larynx (Ertekin, 1996; Ertekin *et al*., 1995), i.e. a physiological event that is one of the components of the swallowing reflex (Logemann, 1983; Donner *et al*., 1985; Jacob *et al*., 1989). Total analysis time was adjusted to between 2 and 5 s, and at least five successive sensor and SM-EMG traces were recorded. The individual traces were examined, superimposed and then averaged.

When the first deflection was stabilized on the EMG screen, the onset of the second deflection showed variability for the same subject for boluses of the same volume. This variability of the laryngeal downward movement was measured at the peaks of the second deflections (asterisk in the uppermost trace of Fig. 1). The interval between the earliest second deflection peak to the latest peak of the superimposed traces is called the 'swallowing jitter', and is a measure of the variation in swallowing response from one swallow to another, for boluses of the same volume (Ertekin *et al*., 1995, 1996, 1997).

Since the submental muscle complex (mylohyoid, geniohyoid and anterior digastric muscles) fire concurrently to initiate a swallow and function as laryngeal elevators, pulling the larynx upwards (Miller, 1982; Logemann, 1983; Donner *et al*., 1985; Jacob *et al*., 1989; Gay *et al*., 1994; Perlman and Christenson, 1997), the rectified and integrated surface EMG activity of the submental muscles (SM-EMG) gives a considerable amount of information about the onset and duration of the pharyngeal phase of swallowing. The onset and end of the SM-EMG activity are labelled 'A' and 'C' in Figs 1, 3 and 4 (e.g. the lower traces of the superimposed and averaged recordings in Fig. 1). The duration and the peak amplitude of the integrated EMG activities were also measured from the averaged traces.

We also measured another important parameter that is related to the triggering of the reflex swallow. This parameter is the interval between the onset of the SM-EMG and the first deflection of the laryngeal sensor signal reflecting the upward movement of the larynx, which is one of the first events of pharyngeal reflex swallowing (Miller, 1982; Logemann, 1983; Donner *et al*., 1985; Dodds *et al*., 1990). This interval, which we term the 'A–0 interval' (oblique arrow in the lower part of Fig. 1), can provide information about the temporal relationship between the instant of the voluntary activation of the submental muscle complex and the instant of reflex triggering of the swallowing response (Ertekin, 1996; Ertekin *et al*., 1998*a*).

The phenomena of piecemeal deglutition and the dysphagia limit have also been investigated using the same technique (Ertekin *et al*., 1996). Piecemeal deglutition refers to division of the bolus into two or three successive swallows (Logemann, 1983). To investigate this phenomenon, the same recording system was used, with the sweep duration set at 10 s and the delay line starting at 2 s. After a certain amount of water had been ingested, the effect of the bolus was followed for 8 s. The patients were given 1, 3, 5, 10, 15 and 20 ml of water and oscilloscopic traces were initiated at the examiner's order to swallow. The laryngeal sensor signals and the integrated activities of the SM-EMG and/or the CP-EMG were recorded from the beginning of these long sweeps. It was requested that the patient swallow all the liquid given in a single effort. Any swallowing-related recurrence of the EMG activity and the laryngeal sensor signal within 8 s after

the onset of the sweep was accepted as piecemeal deglutition or as a sign of a dysphagia limit. However, as piecemeal deglutition is observed physiologically in normal subjects when swallowing >20 ml of water, duplication or multiplication at or below 20 ml of water is referred to as the 'dysphagia limit' (Ertekin *et al*., 1996).

Normal values of electrophysiological parameters were obtained from 50 normal adult subjects (20 female, 30 male) with ages ranging between 30 and 75 years (mean 52.2 ± 14.4 years). The lower and upper limits of normal values for different swallowing parameters were compared with the results obtained from individual patients. The CP-EMG was performed in 21 normal subjects (11 female, 10 male) within the age range of 30–75 years (mean 46.2 ± 13.2).

This study was approved by the ethics committee of our university hospital, and informed consent was obtained from each subject.

Values of the mean ± standard error of the mean were calculated for all parameters measured and statistical analyses were performed to assess the differences in swallowing parameters using variance and correlation analysis as appropriate.

Results

Clinical findings associated with dysphagia in amyotrophic lateral sclerosis patients

Clinical symptoms and signs of dysphagia were common in patients with amyotrophic lateral sclerosis (35 out of 43 patients). In the dysphagic group, dysphagia was the first symptom in 11 patients, whereas in other patients dysphagia developed after a mean period of 11 months (range 1–33 months). At the time of investigation, the mean duration of dysphagia was ~6 months in the dysphagic group. In the majority of patients the primary symptom was difficulty controlling liquid and solid boluses in the oral cavity because of the weakness of the tongue. Other clinical observations were probably related to the delay in the triggering of swallows (i.e. accumulation of saliva in the mouth and delay in elevating the larynx). Subglottal aspiration often occurred in amyotrophic lateral sclerosis patients with pseudobulbar and bulbar signs, as evaluated by the following clinical observations: coughing during or after swallowing, a wet voice after swallowing water and a choking sensation when attempting to drink a 10–20 ml volume of water. Although it was difficult for these patients to swallow solid food, they were at much greater risk of aspirating liquid material. Therefore, most of the patients preferred to take semisolid food. Twenty-one out of 35 patients with dysphagia were aware of their recent weight loss.

In most patients with bulbar/suprabulbar involvement (26 out of 35), the perioral muscles, tongue and submental-suprahyoid muscles were often weak. The mandibular and gag reflexes were also brisk in the majority of cases (25 out of 35 patients) and weakness of the laryngeal and respiratory muscles was determined clinically by the presence of dysphonia and/or weak coughing (28 out of 35 patients).

On the basis of clinical evaluations, the grading of dysphagia was severe (grade 4) in three patients in whom non-oral feeding was necessary. Dysphagia was clinically evident in 21 patients with amyotrophic lateral sclerosis, but these patients could manage by measures other than non-oral feeding (grade 3). In 11 amyotrophic lateral sclerosis patients, dysphagia was probable (grade 2) and in eight patients no difficulty related to swallowing was detected. In all amyotrophic lateral sclerosis patients, the degree of dysphagia was more easily and objectively determined by evaluating piecemeal deglutition and the dysphagia limit.

Piecemeal deglutition and the dysphagia limit

The dysphagia limit was >20 ml of water in all of the normal subjects investigated, whereas it was definitely pathological and ⩽20 ml in all amyotrophic lateral sclerosis patients with dysphagia. At this volume the bolus was divided into two or more parts in all patients with amyotrophic lateral sclerosis suffering from different degrees of dysphagia, as determined by objective electrophysiological methods (Ertekin *et al*., 1996, 1998*a*). The dysphagia limits of the eight amyotrophic lateral sclerosis patients without dysphagia were normal (i.e. >20 ml water). Figure 2 shows the normal and pathological dysphagia limits for two patients with amyotrophic lateral sclerosis. The clinical severity of dysphagia was significantly correlated with the dysphagia limit in amyotrophic lateral sclerosis patients ($r = -0.86$, $P < 0.001$). The dysphagia limit ranged between 1 and 3 ml water in severely dysphagic patients, whereas in patients with mild dysphagia it ranged between 10 and 15 ml.

SM-EMG and reflex movements of the larynx during voluntarily initiated swallowing

In dysphagic amyotrophic lateral sclerosis patients, one of the prominent electrophysiological disorders was delay in the triggering of the swallowing reflex during the voluntarily initiated deglutition, as can be seen in Fig. 3. The oblique arrows indicate the A–0 interval in wet swallowing in a normal subject and two amyotrophic lateral sclerosis patients with moderate (grade 3) and severe (grade 4) dysphagia. The A–0 interval was significantly prolonged in the amyotrophic lateral sclerosis patient with moderate dysphagia (middle panel in Fig. 3). This interval was ~274 ms in control subjects but had a much longer mean value (482 ms) in amyotrophic lateral sclerosis patients with dysphagia during wet swallowing (Table 1) ($P < 0.01$ for both wet and dry swallowing). On the other hand, the duration of the laryngeal relocation time (the interval between points 0 and 2 in Fig. 3, referred to here as the '0–2 interval') was not significantly different between normal subjects and amyotrophic lateral sclerosis patients with mild or moderate dysphagia. Although

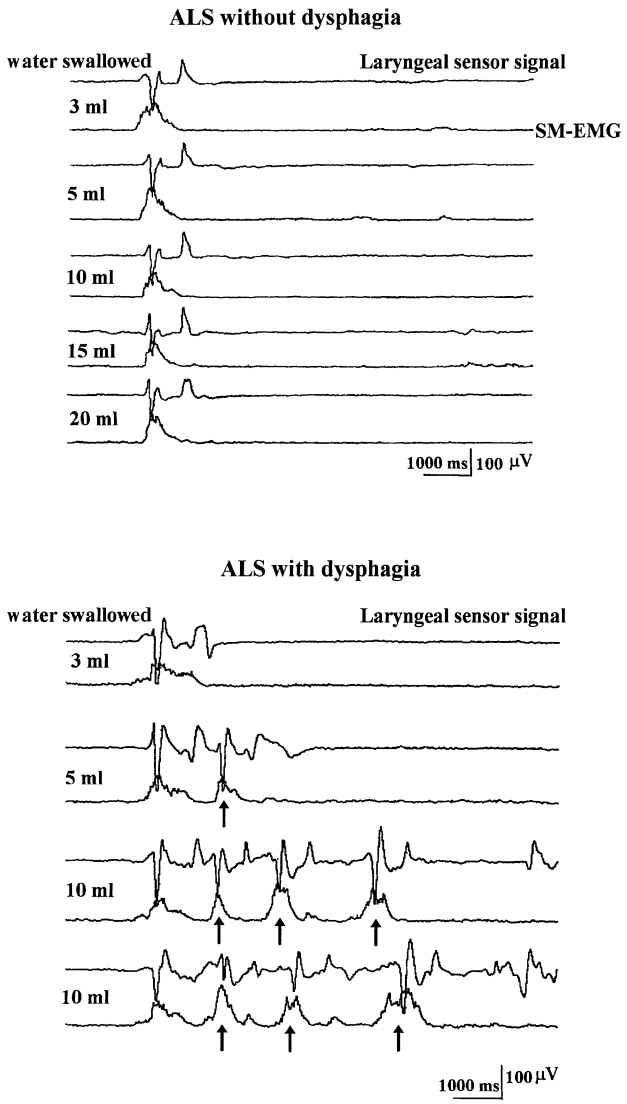

Fig. 2 Laryngeal sensor signals (top trace of each pair) and integrated SM-EMG activities (lower trace of each pair) obtained from two amyotrophic lateral sclerosis patients (ALS) during the swallowing of different amounts of water (3–20 ml). Note that the volume swallowed in a single attempt was up to 20 ml in the non-dysphagic patient, whereas in the amyotrophic lateral sclerosis patient with dysphagia the bolus was divided into two or more separate swallows during the swallowing of 5 or 10 ml water. Arrows denote the second and subsequent swallows. For this patient the dysphagia limit was 5 ml water. Amplitude calibration: 100 μV for SM-EMG traces. Time calibration: 1000 ms in all traces. (The amplitude of the laryngeal sensor signal is irrelevant.)

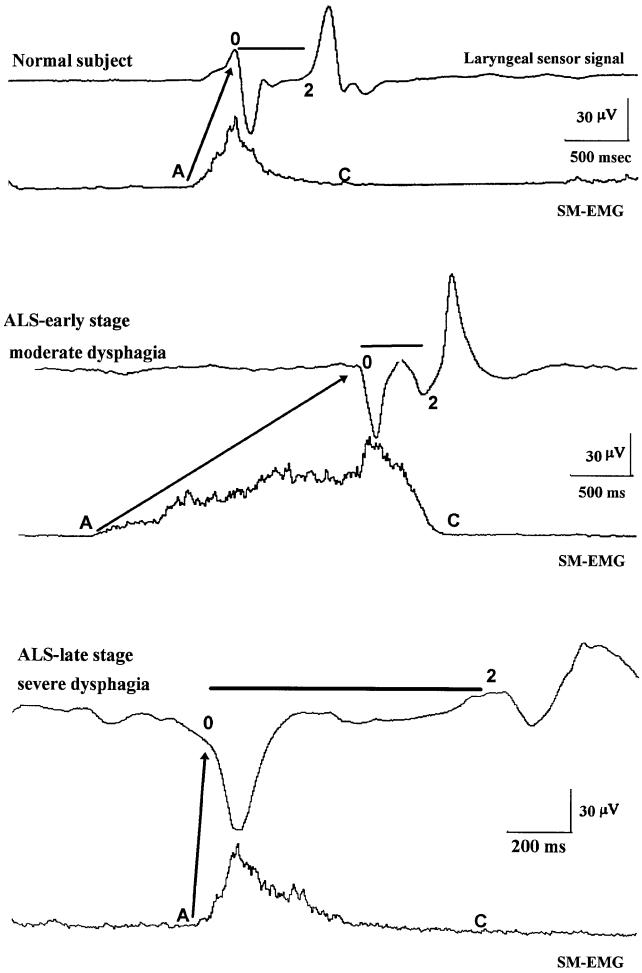

Fig. 3 Laryngeal sensor signals and integrated SM-EMG obtained from a normal subject and two dysphagic patients with amyotrophic lateral sclerosis (ALS) during water swallowing. Extreme prolongation of the A–0 interval (oblique arrow) or delay in the triggering of swallowing was observed in the amyotrophic lateral sclerosis patient with moderate dysphagia; there was also an increase in the total duration of SM-EMG (A–C interval). The laryngeal relocation time (0–2 interval) was not significantly different between the normal subject and this amyotrophic lateral sclerosis patient (upper horizontal line on the laryngeal sensor signals). For the amyotrophic lateral sclerosis patient with severe dysphagia, the A–0 interval was very short and the triggering of swallowing occurred only by the reflex mechanism. All traces are averages of five responses.

the 0–2 interval was slightly prolonged in some amyotrophic lateral sclerosis patients (nine out of 32 patients) when compared individually with the normal range, these individual differences were not statistically significant in either wet or dry swallowing. Collectively, these results indicate that, in amyotrophic lateral sclerosis patients with dysphagia, one of the prominent disorders is a delay or difficulty in triggering reflex swallowing during voluntarily initiated deglutition. However, once the swallowing reflex has been initiated, reflex swallowing can be carried to completion in these patients, just as in normal subjects.

When amyotrophic lateral sclerosis patients were severely dysphagic (grade 4 or a dysphagia limit of ~1 ml), voluntarily triggered swallows could not be completed and all swallows remained at the reflex or so-called 'spontaneous' stage, as can be seen in the bottom traces of Fig. 3. In this situation, the A–0 interval or reflex triggering time was very short (<50 ms). In practice, the SM-EMG activity and the upward deflection of the larynx almost coincided. In some patients

Table 1 *Summary of statistical analyses of swallowing parameters obtained from normal subjects and ALS patients during dry and wet swallowing*

Swallowing parameters	Wet swallowing			Dry swallowing		
	ALS with dysphagia* (n = 32)	ALS total* (n = 40)	Normal control (n = 6)	ALS with dysphagia (n = 15)	ALS total (n = 18)	Normal control (n = 39)
0–2 laryngeal relocation time (ms)	653.5 ± 19.4 109.8 410–885	654.7 ± 16.7 105.8 410–885	588.9 ± 10.3 69.8 450–712	593.6 ± 37.8 145.5 365–900	605.7 ± 31.9 135.6 365–900	553.4 ± 12.7 79.3 392–690
Swallowing jitter (ms)	101.6 ± 7.3 40.7 35–200	104.6 ± 6.8 42.4 35–180	82.1 ± 6.8 46.1 10–216	97.2 ± 12.2 43.8 30–170	102.7 ± 11.2 43.3 30–170	95.9 ± 7.2 45.0 24–250
SM-EMG duration (ms)	1268.4 ± 62.6 354 4 510–2250	1257.1 ± 63.7 402.7 510–2630	908.7 ± 19.5 132.4 650–1250	1701.2 ± 152.2 589.6 900–2715	1693.2 ± 137.6 583.7 900–2715	947.1 ± 33.9 212.0 580–1490
A–0 time interval (ms)	482.1 ± 48.2 272.5 110–1280	457.4 ± 43.0 272.2 94–1280	274.4 ± 15.9 107.6 70–480	836.3 ± 141.2 546.9 150–1995	859.2 ± 133.5 566.5 150–1995	325.6 ± 25.8 161.4 20–607
SM-EMG amplitude (μV)	76.8 ± 3.1 17.4 40–125	75.8 ± 3.0 18.8 40 40–125	63.7 ± 4.1 60.0 **2**22–144	73.1 ± 7.0 26.2 40–145	74.6 ± 5.9 24.5 40–145	79.7 ± 4.6 28.5 33–163

*Three patients with severe dysphagia (grade 4 and dysphagia limit at 1 ml) were excluded. Values are given as mean ± SEM, SD, range. ALS = amylotrophic lateral sclerosis.

with severe dysphagia it was possible to see both a prolonged A–0 interval for the initiation of the swallowing reflex during a voluntary attempt and spontaneous swallowing with almost the same initiation time of SM-EMG and upward relocation of the larynx. Spontaneous swallows with the same characteristics have been observed and produced in normal subjects under some special conditions or during sleep (Fig. 4) (Ertekin *et al*., 1998*b*).

The total duration of SM-EMG (A–C interval) was prolonged in dysphagic patients, partly because of an increase in the A–0 interval ($P < 0.001$). Other electrophysiological parameters, such as the amplitude of submental muscle activity and the swallowing jitter, did not deviate from normal values (Table 1).

The A–0 interval and the 0–2 laryngeal relocation time during the swallowing of 3 ml water were compared in two dysphagic groups of patients with amyotrophic lateral sclerosis. The two groups comprised patients with either clinically predominant upper motor neuron (suprabulbar palsy; 18 cases) or lower motor neuron (bulbar palsy; eight cases) involvement. Figure 5 shows such a comparison with the mean values of A–0 and 0–2 intervals. The A–0 interval was significantly prolonged in patients with predominantly suprabulbar symptomatology (mean ± SEM, 559.6 ± 72.7 ms versus 298.0 ± 37.7 ms, $P < 0.05$). On the other hand, the 0–2 laryngeal relocation time did not differ significantly between the two groups (mean ± SEM, 676.7 ± 26.1 ms for the suprabulbar group and 713.5 ± 37.7 ms for the bulbar

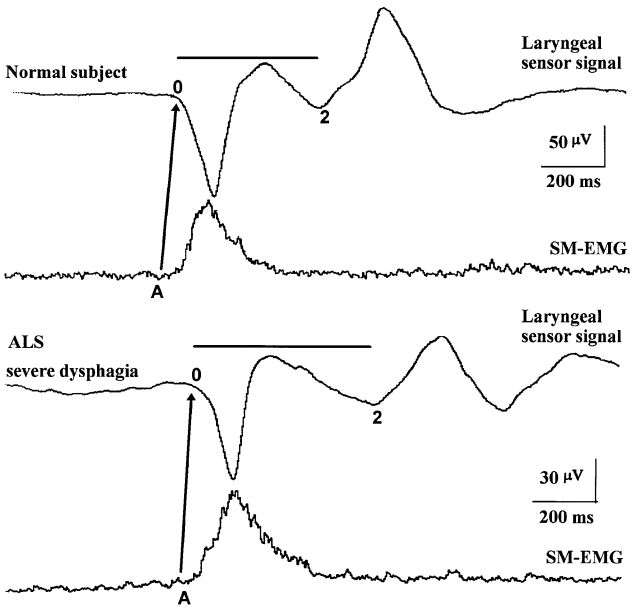

Fig. 4 Averaged laryngeal sensor signals and integrated SM-EMG traces obtained from a normal subject and an amyotrophic lateral sclerosis patient with severe dysphagia (ALS) during reflex or spontaneous swallowing. Note that in both cases the onset of the SM-EMG (point A) and the upward deflection of the larynx (point 0) appear almost at the same time and that the A–0 interval is very short.

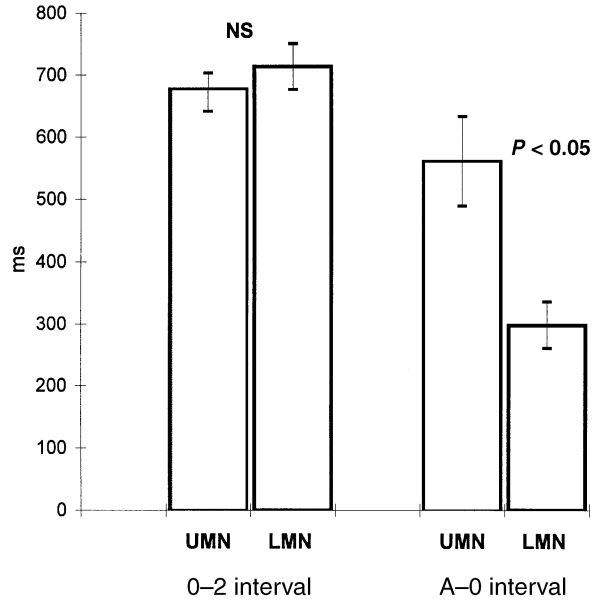

Fig. 5 Histogram representations of the mean values of the 0–2 and A–0 intervals during the swallowing of 3 ml water. Note that the A–0 interval was significantly prolonged in the predominantly suprabulbar palsy group (UMN, upper motor neuron) compared with the bulbar palsy group (LMN, lower motor neuron), while the 0–2 interval was not different in the two groups. NS = not significant. Vertical lines denote ±1 SEM.

group, $P > 0.05$). Other parameters, such as the total duration of the SM-EMG, the amplitude of the SM-EMG and swallowing jitter, were not significantly different between the two groups.

CP-EMG of the upper oesophageal sphincter during swallowing

The CP-EMG was investigated in 25 of 35 patients with amyotrophic lateral sclerosis, all of whom had dysphagia, and in four of eight patients without dysphagia. In amyotrophic lateral sclerosis patients with dysphagia, the most striking findings were found in the CP-EMG of the UES and in its relationship with laryngeal movements and the SM-EMG (Table 2). Figure 6 shows the CP-EMG and the sensor signals of laryngeal movements during wet swallowing in two amyotrophic lateral sclerosis patients with dysphagia and a normal control subject. There were some distinguishing features of the CP-EMG results obtained from amyotrophic lateral sclerosis patients compared with those of normal subjects. First, the duration of the CP-EMG pause associated with the passage of the bolus into the oesophagus from the UES was considerably shortened ($P < 0.001$) (Fig. 6). Secondly, the CP-EMG pause produced by a swallow ended too early before the onset of the laryngeal downward movement ($P < 0.05$) (oblique arrow in Fig. 6B). In other words, the cricopharyngeal sphincter closed prematurely while the larynx was still in its elevated position. Thirdly, during the elevation of the larynx the cricopharyngeal muscle of the UES was not completely silent and some unexpected motor unit bursts appeared (Fig. 6C). This was in contrast to the complete silence of the cricopharyngeal muscle in normal subjects (Fig. 6A). Fourthly, there was a mild but statistically significant delay in the onset of the CP-EMG pause in relation to upward movement of the larynx. Individual results indicating the late opening and premature closing of the cricopharyngeal sphincter of the UES with respect to laryngeal movements are depicted graphically in Fig. 7.

The last abnormality related to CP-EMG was encountered only in three patients with dysphagia who had other advanced bulbar and pseudobulbar clinical signs. In normal subjects, the SM-EMG normally begins earlier and ends later than the cricopharyngeal sphincter pause, whereas in these amyotrophic lateral sclerosis patients with dysphagia this activity ended almost in the middle of the CP-EMG pause (arrows in Fig. 8). Similarly, a mild but statistically significant delay in the onset of the CP-EMG pause was observed in these patients when compared temporally with the negative peak of SM-EMG activity (Table 2).

Shorter mean values were found for the CP-EMG pause in amyotrophic lateral sclerosis patients, probably as a result of the late opening and the premature closing of the UES. Unexpected extra motor unit bursts with an amplitude of >20 μV, occurring during the CP-EMG pause, must have been another factor that shortened the duration of the CP-EMG pause. Despite the pathological CP-EMG findings described above, individual motor unit potentials of the cricopharyngeal sphincter were similar to those of normal control subjects, and their values remained within the normal range for all amyotrophic lateral sclerosis patients at the different stages investigated. The incidences of all electrophysiological abnormalities are given separately in Table 3.

Electrophysiological abnormalities in relation to dysphagia

In normal control subjects, the CP-EMG pause significantly correlated with the 0–2 interval of the laryngeal sensor signal ($r = 0.71$, $P < 0.001$) (Fig. 9). In other words, at the onset of the swallowing reflex the tonic activity of the cricopharyngeal sphincter was switched off and remained silent during transport of the bolus to the oesophagus. The EMG pause of the cricopharyngeal sphincter has a very close temporal correlation with the upward repositioning of the larynx. This important correlation of the time of the closure and upward repositioning of the larynx with the opening time of the CP-EMG was lost in patients with amyotrophic lateral sclerosis ($r = -0.10$, $P > 0.05$) (Fig. 9). In normal subjects, this correlation may indicate that, during a swallow, the upper relocation time of the larynx clearly coincides with the CP-EMG pause or vice versa, whereas the significance of this time relationship is not preserved in amyotrophic lateral sclerosis patients with dysphagia. Such lack of co-

Table 2 *Results of the CP-EMG parameters obtained from normal control subjects and amylotrophic lateral sclerosis patients during wet swallowing*

Parameters	ALS with dysphagia (n = 25)	Normal control (n = 21)	$P\leqslant$
Duration of CP-EMG pause (ms)	359.2 ± 18.0 90.1	462.0 ±17.9 81.9	0.001
The interval between the onset of the upward deflection of the laryngeal sensor signal (‘0′) and the onset of CP-EMG pause (ms) (late opening)	171.2 ± 20.8 90.8	113.1 ± 17.7 70.8	0.04
The interval between the end of the CP-EMG pause and the onset of the laryngeal downward movement (‘2′) (ms) (premature closing)	208.4 ± 38.3 157.7	100.4 ± 19.0 60.1	0.02
The interval between the peak of the SM-EMG and the onset of CP-EMG pause (ms)	134.8 ± 19.3	84.0 ± 9.5 28.5	0.001
Interval between the end of SM-EMG and CP-EMG pause (ms)*	284.4 ± 66.8 176.6	105.1 ± 11.8 39.0	0.04

This is the earliest end of SM-EMG according to the end of CP-EMG pause. Values are given as mean ± SEM and SD.
ALS = amylotrophic lateral sclerosis.

ordination between the laryngeal elevators and the cricopharyngeal muscle of the UES during swallowing is proposed as an obvious cause, among others, of dysphagia and the source of aspiration in amyotrophic lateral sclerosis patients. The severity of dysphagia and the level of the dysphagia limit also correlate well with the shortening of the CP-EMG pause (Fig. 10) ($r = -0.56$ and 0.54 respectively, $P < 0.05$), and this may also be closely linked with the same pathophysiological mechanism.

Discussion

In this study, we obtained the following electrophysiological findings in amyotrophic lateral sclerosis patients: (i) abnormalities in the reflex initiation of swallowing and in the elevation of the larynx during oropharyngeal swallowing; (ii) abnormalities in the dynamic features of the cricopharyngeal sphincter EMG during swallowing; and (iii) lack of co-ordination between the laryngeal elevator muscles (including the submental muscles) and cricopharyngeal sphincter muscles during oropharyngeal swallowing.

Abnormalities in the initiation of oropharyngeal swallowing and in the elevation of the larynx

The interval between the onset of SM-EMG (voluntary onset) and the first deflection of the laryngeal movement signal (reflex onset) (the A–0 interval), is prolonged during attempts to swallow in amyotrophic lateral sclerosis patients. This is probably caused by the delay in the triggering of the swallowing reflex, which has also been shown by cinefluoroscopic and videofluoroscopic studies (Bosma and Brodie, 1969; Logemann, 1983; Robbins, 1987; Briani *et al*., 1998). This delay in reflex activation may be the result of poor tongue and submental muscle control due to involvement of either lower or upper motor neurons or both. As a result of difficulties in the triggering of voluntary swallows, the bolus in the mouth will escape into the airway before the swallowing reflex takes over, resulting in subglottal aspiration (Logemann, 1983).

In order to keep the larynx in the upward-suspended position, the laryngeal elevators, including the submental muscles, need to overcome their weakness during swallowing. The weakness of the tongue muscles and the muscles of the mouth floor, including the submental muscles in amyotrophic lateral sclerosis, must be similar regardless of whether these muscles are mainly affected by upper motor neuron or lower motor neuron disorders. We propose that an upper motor neuron type of weakness of the muscles of the tongue and the mouth floor is more important in the development of swallowing disorders in voluntarily triggered deglutition. In this type of weakness, it is more difficult to move these muscles voluntarily while reflex movements can still occur easily. However, in patients with pure lower motor neuron disorders, both voluntary and reflexive movements are expected to be similarly weak. There is evidence for this conjecture, as summarized in the following paragraphs.

(i) One of the important findings concerning dysphagia in amyotrophic lateral sclerosis is the difficulty in triggering a reflex swallow. This can be inferred from the significant prolongation of the A–0 interval, especially in patients with mild and moderate dysphagia (grade 2 or 3, or a dysphagia limit between 10 and 20 ml). Furthermore, dysphagic amyotrophic lateral sclerosis patients with predominant suprabulbar/corticobulbar involvement show significant prolongation of the A–0 interval in comparison with

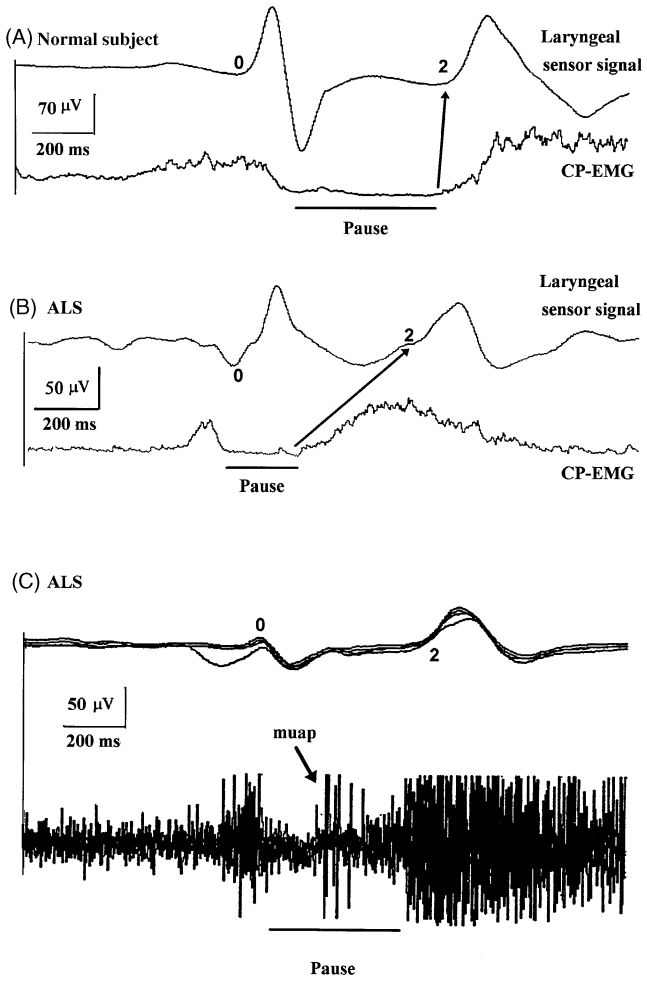

Fig. 6 Laryngeal sensor signals (top traces in each pair) and CP-EMGs (lower traces in each pair) recorded from a normal subject (**A**) and two amyotrophic lateral sclerosis patients with dysphagia (ALS) (**B** and **C**) during the swallowing of 3 ml water. The duration of the CP-EMG pause was shorter in the patient with amyotrophic lateral sclerosis (**B**) than in the normal subject (**A**). In the amyotrophic lateral sclerosis patient, the CP-EMG pause ended prematurely, before the larynx had descended from its superior position (oblique arrow, **B**). The unexpected burst of motor unit action potentials (muap) during the swallowing pause of the cricopharyngeal muscle is clearly seen in the recording for the amyotrophic lateral sclerosis patient (arrow, **C**). The first two traces are averages of five responses; EMG traces are rectified and integrated. The third trace is the superimposition of three responses. The EMG trace in **C** was obtained from conventional EMG recordings.

dysphagic patients with predominant bulbar lower motor neuron involvement. However, the laryngeal relocation time (0–2 interval) of the swallowing reflex does not differ between the two groups of patients (Fig. 5). Thus, the voluntarily activated submental and tongue muscle fibres that control the first part of the SM-EMG would be weaker and less responsive to a volitional onset of swallowing because of a lesser degree corticobulbar excitatory drive. The remaining intact excitatory corticobulbar fibres would first try to compensate for the weakness in these striated muscles by sending more descending impulses, which would be dispersed throughout a longer time period than normal. Therefore, the voluntarily triggered swallowing reflex would be delayed and the A–0 interval observed in our records would be longer than normal. However, once the reflex was triggered, the laryngeal elevator muscles would have a reflex contraction and the laryngeal relocation time (0–2 interval) would frequently be within normal limits, as we have found in our patients. The delay in triggering the swallowing reflex from the voluntary initiation of dry and wet swallows can thus be attributed to the progressive degeneration of excitatory corticobulbar fibres. In the advanced stages of amyotrophic lateral sclerosis with severe dysphagia, it would be expected that the A–0 interval should get progressively shorter because of further degeneration of the corticobulbar fibres associated with swallowing. When all corticobulbar control was lost, all swallows would be spontaneous and controlled by the bulbar swallowing centre (Miller, 1982; Ertekin *et al*., 1998*b*).

(ii) The observation that dysphagia is more often present in amyotrophic lateral sclerosis patients with prominent suprabulbar palsy has also been reported by other investigators (Buchholz, 1994; Leighton *et al*., 1994; Hughes and Wiles, 1996*b*).

(iii) The presence of lower motor neuron involvement in bulbar amyotrophic lateral sclerosis should not exclude the possibility of dysphagia. It is known that dysphagia is not rare in other disorders with pure lower motor neuron involvement associated with bulbar muscles, such as acute poliomyelitis, postpolio syndrome (Buchholz and Jones, 1991; Silbergleit *et al*., 1991; Jones *et al*., 1992; Sonies and Dalakas, 1995) and X-linked bulbospinal muscle atrophy (Kennedy *et al*., 1968; Harding *et al*., 1982; Sobue *et al*., 1989). However, dysphagia appears to be mild and the incidence is lower in such anterior horn cell disorders.

(iv) Using the same electrophysiological methods, we have shown that, in dysphagic patients with myasthenia gravis (Ertekin *et al*., 1998*c*) and polymyositis (Ertekin *et al*., 1998*a*), triggering of reflex swallowing is not very severely disturbed or may even be normal, as judged by the normality of the A–0 interval. However, in these patients the relocation time of the larynx (0–2 interval) is often prolonged. Further evidence about the importance of suprabulbar motor fibres comes from our previous results obtained from patients with suprabulbar palsy with lacunar states. In these patients also, the A–0 interval was found to be as prolonged as in amyotrophic lateral sclerosis patients (Ertekin, 1996; Ertekin *et al*., 1998*a*).

Therefore, we can reiterate that the major cause of dysphagia in amyotrophic lateral sclerosis, especially in relation to the triggering of the swallowing reflex, is due to the degeneration of the corticobulbar motor pathway.

Abnormalities in the dynamic features of the CP-EMG during swallowing

In amyotrophic lateral sclerosis patients with dysphagia, the most striking and common findings were obtained from

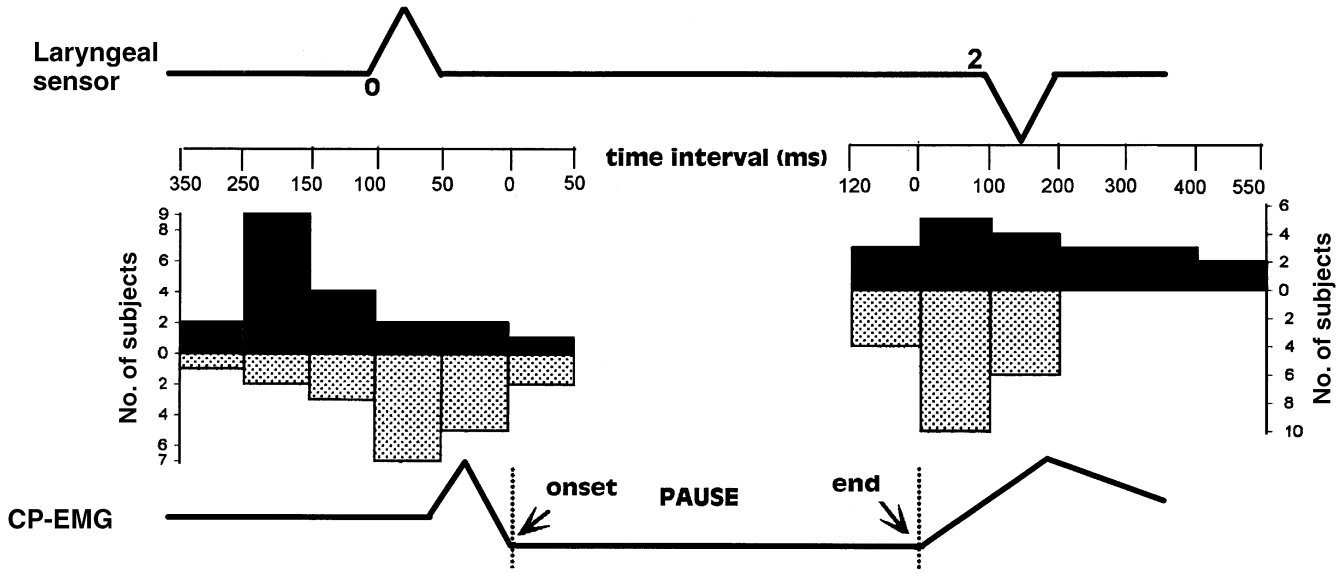

Fig. 7 Graphical representation of the temporal relationship between the laryngeal movement and the cricopharyngeal sphincter during swallowing. The individual intervals between the onset and end of the laryngeal upward movement (points 0 and 2) and the onset and end of the CP-EMG pause are shown along the time axis. Results were calculated by taking the onset and end points of the CP-EMG pause as the reference (zero) point. For example, a value of 100 ms on the *x*-axis of the graph on the left indicates the onset of the upward movement of the larynx (point 0) which occurs 100 ms before the onset of the CP-EMG pause. Each column represents the number of normal subjects (stippled, below the zero line) and amyotrophic lateral sclerosis patients (black, above the zero line). In amyotrophic lateral sclerosis patients, the cricopharyngeal sphincter had a tendency towards late opening and premature closing in relation to the upward and downward movements of the larynx, respectively.

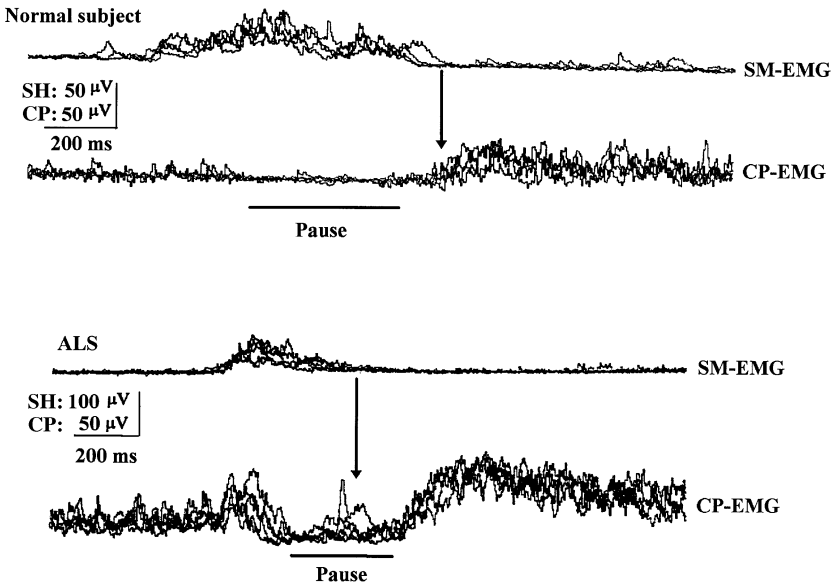

Fig. 8 Superimposed SM-EMG (top traces in each pair) and CP-EMG (lower traces in each pair) traces recorded from a normal subject and an amyotrophic lateral sclerosis patient with dysphagia (ALS) during water swallowing. The SM-EMG ended after the termination of the CP-EMG pause in the normal subject, whereas in the amyotrophic lateral sclerosis patient the activity of SM-EMG ceased before the cricopharyngeal sphincter had closed (vertical arrows).

the cricopharyngeal EMG: namely, the late opening and premature closure of the cricopharyngeal sphincter and unexpected bursts during the EMG pause. The duration of the CP-EMG pause was also shorter than in normal subjects, probably as a result of these abnormal changes. The cricopharyngeal sphincter, like other sphincter muscles, such as the external urethral sphincter muscle, has special functions and properties that are different from those of skeletal

Table 3 *The incidence of abnormalities related to swallowing parameters for dysphagic and non-dysphagic amylotrophic lateral sclerosis patients*

Parameters	With dysphagia		Without dysphagia
	Wet *n**/*n* (%)	Dry *n**/*n* (%)	Wet *n**/*n* (%)
(1) Prolongation of '0–2' interval of the sensor	9/32 (28)	5/15 (33)	2/8 (25)
(2) Prolongation of 'A–C' interval of the SM-EMG	17/32 (54)	8/15 (53)	2/8 (25)
(3) Prolongation of 'A–0' interval	14/32 (44)	9/15 (60)	2/8 (25)
(4) Increased swallowing jitter	0/32 (0)	0/15 (0)	0/8 (0)
(5) SM-EMG amplitude	0/32 (0)	0/15 (0)	0/8 (0)
(6) No. of cases with at least one of the abnormalities mentioned above (xx)	22/32 (69)		3/8 (38)
(7) Dsyphagia limit	35/35 (100)		0/8 (0)
CP-EMG parameters	With dysphagia *n**/*n* (%)		Without dysphagia *n**/*n* (%)
(1) Shortening of CP-EMG pause	6/25 (24)		2/4 (50)
(2) MUAP activity within pause	14/25 (56)		0/4 (0)
(3) Late opening	2/20 (10)		0/4 (0)
(4) Premature closure	8/20 (40)		1/4 (25)
(5) No. of cases with at least one of the abnormalities mentioned above	21/25 (70)		2/4 (50)

*n**= number of pathological cases; *n* = total cases. (xx) Three patients with severe dysphagia (grade 4 and dysphagia limit at 1 ml) were excluded. MUAP = motor unit action potential.

muscles. Although a striated muscle, it is innervated by the vagus nerve, and therefore it is not readily controlled by the voluntary motor system and is closed at rest (Miller, 1982; Goyal, 1984). During a swallow, the UES opens and the tonic activity of the cricopharyngeal muscle ceases simultaneously (Shipp *et al*., 1970; Asoh and Goyal, 1978; van Overbeek *et al*., 1985; Kahrilas *et al*., 1988; Cook *et al*., 1989; Elidan *et al*., 1990; Goyal *et al*., 1993; Ertekin *et al*., 1995). According to one view, the cessation of tonic activity of the cricopharyngeal sphincter muscle is believed to be due to central inhibition rather than to activity originating from the peripheral nervous system (Doty and Bosma, 1956; Miller, 1972, 1982; Jean and Car, 1979). However, no systematic study is available which shows this kind of inhibition in man. The contrary view is that the opening of the UES, together with the cessation of tonic activity in the cricopharyngeal muscle, is brought about by traction of the suprahyoid muscles which produce the anterior displacement of larynx (Asoh and Goyal, 1978; Goyal, 1984; Ekberg, 1986; Dodds *et al*., 1988; Cook *et al*., 1989; Jacob *et al*., 1989; Lang *et al*., 1991). Whatever the mechanism of opening of the upper oesophageal sphincter (i.e. central or peripheral), there is a time relationship between the activities of the suprahyoid-submental muscles of the laryngeal elevators and of the cricopharyngeal sphincter muscle during swallowing in normal subjects (Kahrilas *et al*., 1988; Lang *et al*., 1991; Ertekin *et al*., 1995, 1997). It is obvious that opening and closing mechanisms are remarkably disordered in amyotrophic lateral sclerosis patients with dysphagia, as detected by the CP-EMG and the laryngeal elevation parameters presented in this study. The shortening of the cricopharyngeal sphincter pause and late opening and premature closure with unexpected EMG bursts during the CP-EMG pause suggest that the cricopharyngeal sphincter muscle is hyper-reflexic/hypertonic, probably because of the central disinhibition of this muscle. On the other hand, the same abnormalities have been described by means of radiological and manometric studies in various non-neurological disorders which is known as 'cricopharyngeal achalasia' (Goyal, 1984; Dantas *et al*., 1990). Cricopharyngeal achalasia is basically described as incomplete relaxation of the cricopharyngeal muscle. Paradoxical contraction or fibrosis that shortens the cricopharyngeal muscle may prevent full dilatation of the UES during swallowing (Goyal, 1984). By means of the same radiological methods, achalasia-like phenomena have also been reported in certain neurological disorders (Donner and Silbiger, 1966; Jones *et al*., 1985; Dodds *et al*., 1990). The nature and cause of cricopharyngeal sphincter abnormalities cannot be determined easily by radiological observations alone, as it is necessary to apply neurophysiological techniques to determine the neurological or non-neurological origin of these conditions. The abnormalities in the cricopharyngeal sphincter EMG presented in this study have not been described previously, especially from the electrophysiological point of view, in particular for neurogenic dysphagia in amyotrophic lateral sclerosis patients. These abnormalities are probably not only related to simple spasms of the sphincter muscle but are also caused by lack of co-ordination and/or disinhibition caused by a central disorder linked to upper motor neuron disease.

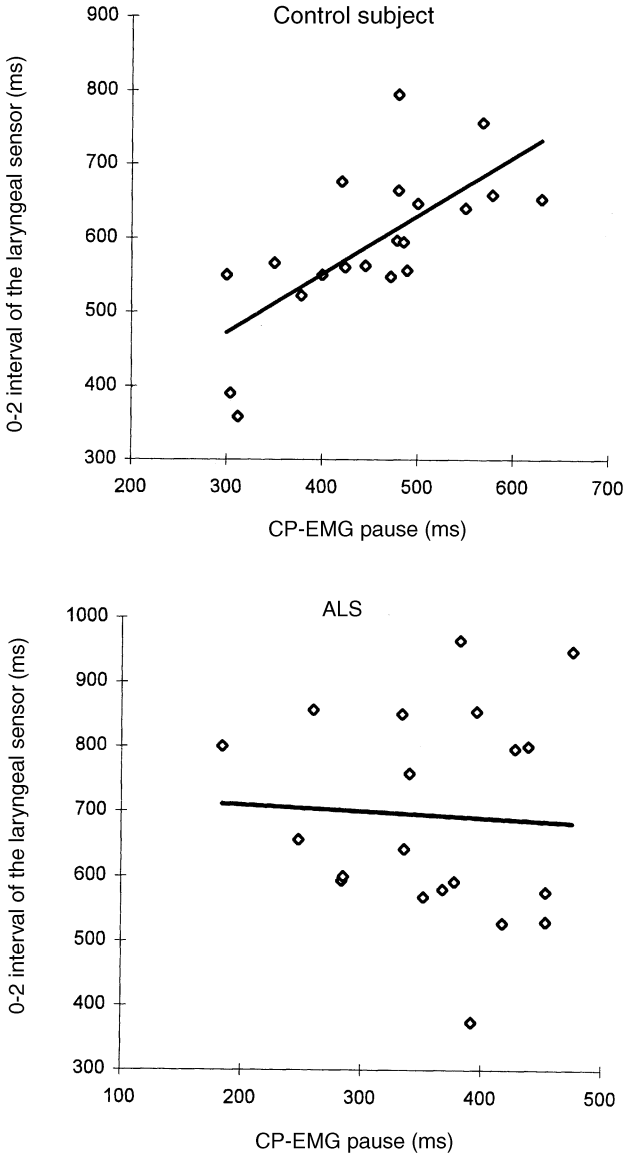

Fig. 9 Graphs of regression equations showing the correlation between the CP-EMG pause and the 0–2 interval of the laryngeal sensor obtained from normal subjects ($r = 0.71$, $P < 0.001$) and from amyotrophic lateral sclerosis patients with dysphagia (ALS) ($r = -0.10$, $P > 0.05$). In the amyotrophic lateral sclerosis group there was no correlation between these parameters.

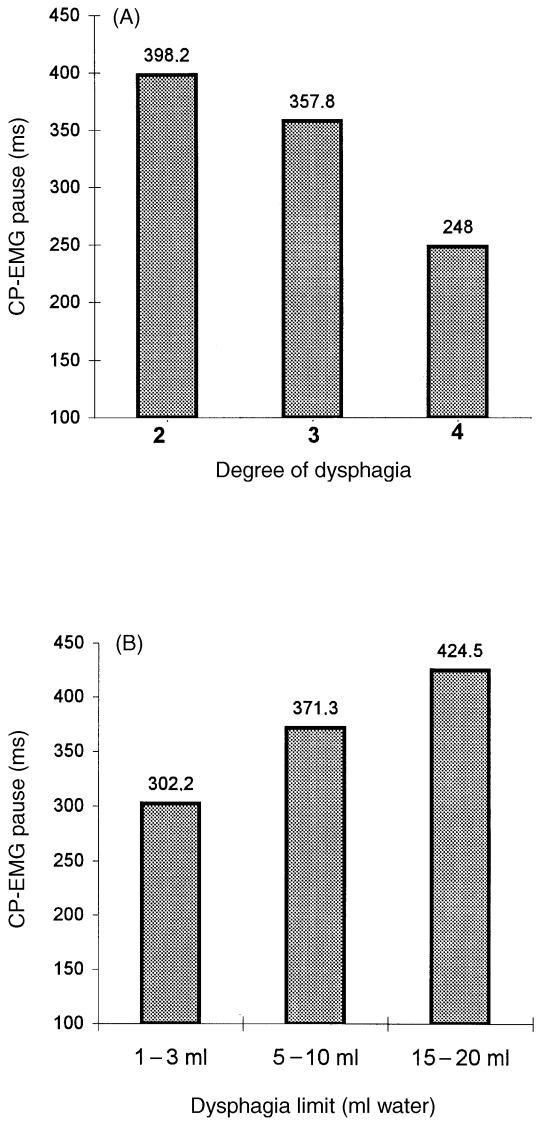

Fig. 10 Histograms showing the mean values of the CP-EMG pause in relation to the degree of dysphagia (**A**) and the dysphagia limit (**B**). Note that the severity of dysphagia increased and the amount of water swallowed in a single attempt decreased as the CP-EMG pause shortened. The numbers on the histograms represent the CP-EMG pause (ms) for each group of subjects.

Lack of co-ordination between laryngeal elevator muscles and the cricopharyngeal sphincter

Kristmundsdottir and colleagues have shown that the cricopharyngeal muscle in amyotrophic lateral sclerosis is not significantly different from that in normal subjects with respect to most histometric and histopathological parameters (Kristmundsdottir *et al.*, 1990). These authors thought that dysphagia was caused by interference from higher control centres leading to poorly co-ordinated relaxation of the pharyngo-oesophageal sphincter in amyotrophic lateral sclerosis. Therefore, it is possible that different kinds of involvement of the perioral, tongue and suprahyoid–submental muscle groups on the one hand and of the cricopharyngeal sphincter muscle of the UES on the other is one of the mechanisms of dysphagia in amyotrophic lateral sclerosis patients. The former group of bulbar muscles is involved in upper and/or lower motor dysfunction while the cricopharyngeal sphincter muscle is not affected by lower motor neuron involvement and is not paretic at all. But co-ordination between these two groups is disordered, probably because of upper motor neuron involvement, especially in the suprabulbar descending motor fibres. In this context, the first group of muscles is controlled densely by excitatory corticobulbar fibres and becomes weak in the course of

amyotrophic lateral sclerosis, while the cricopharyngeal sphincter of the UES is not under strong voluntary control in normal conditions (Kahrilas *et al*., 1991) and becomes hyper-reflexic and hypertonic without any weakness during the course of amyotrophic lateral sclerosis. The hyper-reflexic cricopharyngeal muscle of the UES is very important for dysphagia. It is probable that the inhibitory effects on cricopharyngeal motor neurons and/or interneurons are not in effect due to the central pathologies of the pseudobulbar syndrome of amyotrophic lateral sclerosis. The hyper-reflexic nature of the cricopharyngeal sphincter of the UES is not surprising, as it is well known that the mandibular reflex is often brisk in amyotrophic lateral sclerosis, and it has been reported that other brainstem reflexes, such as palatal and gag reflexes, are often initiated more easily in amyotrophic lateral sclerosis (Buchholz, 1994; Leighton *et al*., 1994; Hughes and Wiles, 1996*b*). Hughes and Wiles have stated that the loss of corticobulbar pyramidal fibres may lead to brisker palatopharyngeal reflex responses because of a reduction in descending inhibition, and therefore probably produces the swallowing disorders in amyotrophic lateral sclerosis (Hughes and Wiles, 1996*b*).

In patients with amyotrophic lateral sclerosis, UES abnormalities akin to those found in electrophysiological recordings have been described by others using video-fluoroscopic methods (Bosma and Brodie, 1969; Leighton *et al*., 1994; Briani *et al*., 1998). Indeed, for a long time cricopharyngeal myotomy has been used for relieving dysphagia in amyotrophic lateral sclerosis and in a number of other neurological disorders. The rationale behind this operation has been to alleviate upper oesophageal spasm and hypertonus, although the place of cricopharyngeal myotomy in the treatment of dysphagia in amyotrophic lateral sclerosis and in other disorders has long been debated and questioned (Lebo *et al*., 1976; Duranceau *et al*., 1987; Milford and Price, 1989; Elidan *et al*., 1990; MacDougall *et al*., 1995; Poirier *et al*., 1997; Briani *et al*., 1998).

The relationship between the laryngeal relocation time and the opening of the UES has been demonstrated clearly with different bolus volumes in normal subjects (Kahrilas *et al*., 1988; Cook *et al*., 1989; Jacob *et al*., 1989; Ertekin *et al*., 1997). The correlation of the laryngeal elevation and relocation time with the opening of the cricopharyngeal sphincter of the UES was found to disappear in the amyotrophic lateral sclerosis patients investigated in this study. This finding indicates that the biological adaptation and co-ordination between the submental muscles and the cricopharyngeal striated sphincter disappear during voluntarily triggered swallowing in amyotrophic lateral sclerosis. As a result of the shorter opening time and the premature closure of the cricopharyngeal sphincter that occur before the larynx descends from its upward position, the bolus will be retained in the pharyngeal spaces, and then, after the larynx has descended from its upper location, the bolus will escape into the airway and result in subglottal aspiration.

It is possible that the voluntarily triggered swallows are initiated by cortical descending inputs to the swallowing centres while the spontaneous and reflex swallows are initiated only by the bulbar swallowing centre (Jean and Car, 1979; Miller, 1982, 1993; Martin and Sessle, 1993). Therefore, in amyotrophic lateral sclerosis, voluntarily triggered swallows would become difficult as a result of progressive degeneration of the corticobulbar-pyramidal motor fibres. In the advanced stages of amyotrophic lateral sclerosis, voluntarily triggered swallows cannot be performed because of excessive loss of corticobulbar fibres. However, the purely reflex mechanism would still be in operation under the control of the bulbar swallowing centre. Therefore, the spontaneous and reflex swallows would be intact and the patients would be able to swallow their saliva, which was ~1 ml in volume (Logemann, 1996). Such spontaneous saliva swallowing was demonstrated by our electrophysiological method (Ertekin *et al*., 1998*b*).

It has been shown recently that the corticospinal and corticobulbar descending motor fibres are involved early and frequently in amyotrophic lateral sclerosis, as demonstrated by transcranial magnetic stimulation (Eisen *et al*., 1993; Prout and Eisen, 1994; Desiato and Caramia, 1997). As a result, striated spinal and bulbar muscles can become deficient both in their excitatory and in their inhibitory corticospinal/corticobulbar drives (Yokota *et al*., 1996; Desiato and Caramia, 1997; Enterzari-Taher *et al*., 1997; Ziemann *et al*., 1997). The motor neurons of the cricopharyngeal sphincter muscle must be released from this descending inhibitory control, and consequently they become hyper-reflexic, uncontrollable and unco-ordinated during swallowing in amyotrophic lateral sclerosis patients. This may lead to dysphagia, especially when accompanied by weakness in the striated muscles of the oropharynx and larynx. In other words, the central pacemaker or central swallowing programme at the bulbar centre becomes disturbed by the removal of inhibitory corticobulbar influences (Doty and Bosma, 1956; Doty *et al*., 1967; Miller, 1982; Zoungrana *et al*., 1997). Swallowing is finally restricted to the spontaneous-reflexive swallows; however, this kind of swallow can become risky for the patient because of lack of co-ordination in the cricopharyngeal sphincter during the advanced stages of the disease (Hillel and Miller, 1989; Strand *et al*., 1996).

In conclusion, two pathophysiological mechanisms operate in the dysphagia of amyotrophic lateral sclerosis patients: (i) the triggering of the swallowing reflex for the voluntarily initiated swallows is delayed, disordered and eventually absent while the spontaneous reflexive swallows are preserved until the preterminal stage of amyotrophic lateral sclerosis; and (ii) the cricopharyngeal sphincter muscle of the pharyngo-oesophageal segment becomes hyper-reflexic and hypertonic. As a result, the laryngeal protective system and the bolus transport system of deglutition lose their co-ordination during voluntarily initiated oropharyngeal swallowing. Thus, we propose that these pathophysiological changes in the dysphagia of amyotrophic lateral sclerosis patients are

primarily associated with the progressive degeneration of the excitatory and inhibitory corticobulbar pyramidal fibres.

Acknowledgements

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