

## Review article

# Respiratory complications related to bulbar dysfunction in motor neuron disease

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Bulbar dysfunction resulting from corticobulbar pathway or brainstem neuron degeneration is one of the most important clinical problems encountered in motor neuron disease (MND) and contributes to various respiratory complications which are major causes of morbidity and mortality. Chronic malnutrition as a consequence of bulbar muscle weakness may have a considerable bearing on respiratory muscle function and survival. Abnormalities of the control and strength of the laryngeal and pharyngeal muscles may cause upper airway obstruction increasing resistance to airflow. Bulbar muscle weakness prevents adequate peak cough flows to clear airway debris. Dysphagia can lead to aspiration of microorganisms, food and liquids and hence pneumonia. MND patients with bulbar involvement commonly display an abnormal respiratory pattern during swallow characterized by inspiration after swallow, prolonged swallow apnoea and multiple swallows per bolus. Volitional respiratory function tests such as forced vital capacity can be inaccurate in patients with bulbofacial weakness and/or impaired volitional respiratory control. Bulbar muscle weakness with abundant secretions may increase the risk of aspiration and make successful non-invasive assisted ventilation more difficult. We conclude that an evaluation of bulbar dysfunction is an essential element in the assessment of respiratory dysfunction in MND.

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Motor neuron disease (MND) is a progressive degenerative disorder characterized by loss of motor neurones in the cortex, brain stem, and spinal cord, which manifests as a variety of symptoms and signs due to combination of upper and lower motor neuron features affecting bulbar, limb, and respiratory musculature: death from respiratory failure occurs in the majority of patients. In man the pharynx serves as a common pathway for both swallowing and breathing and these activities share a common innervation and interacting control mechanisms so that, normally, swallowing causes minimal or no respiratory disturbances. This review

will describe how bulbar dysfunction can adversely affect respiratory function in MND (Table 1).

## Bulbar dysfunction in MND

Bulbar dysfunction is one of the most important clinical problems encountered in MND because it involves both communication and swallowing. In about 20% of MND patients overall, symptoms begin in bulbar muscles, but this percentage increases with age (1). Haverkamp and colleagues (2) noted bulbar presentation in only 15% of

Table 1. Respiratory complications related to bulbar dysfunction in MND

Bulbar dysfunction	Respiratory complication
Malnutrition Laryngeal/pharyngeal muscle weakness	Respiratory muscle weakness a) Upper airway obstruction b) Inadequate peak cough flows c) Aspiration/pneumonia
Multiple swallows/bolus and prolonged swallow apnoea Bulbofacial weakness Increased oropharyngeal secretions	Abnormal respiratory pattern during swallowing (inspiration after swallow) Inaccurate respiratory function tests Increased risk of aspiration during non-invasive positive pressure ventilation

patients younger than 30 years of age, but this increased to 43% of those older than 70 years. The presence of bulbar dysfunction can be diagnosed by videofluoroscopy/manometric methods even before the bulbar symptoms appear clinically (3, 4). Irrespective of the clinical syndrome which patients present, they almost all eventually develop bulbar symptoms (5–8); these may be predominantly due to lower motor neuron weakness (bulbar palsy), upper motor neuron weakness (pseudobulbar palsy) or a mixture. Table 2 summarizes some common bulbar physical signs and symptoms in MND.

A bulbar onset (dysarthria and/or dysphagia) is a poor prognostic factor confirmed in various epidemiological studies (9–15). Bulbar dysfunction and related respiratory complications are often a major handicap and impediment to quality of life in MND (16, 17). Recent electrophysiological studies (18) have confirmed two principal pathophysiological mechanisms that operate to cause dysphagia in MND. Firstly, 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 MND. Secondly, the cricopharyngeal sphincter muscle of the upper oesophageal sphincter becomes hyper-reflexive and hypertonic. As a result, co-ordination between the laryngeal protective system and the bolus transport system of deglutition is lost during voluntarily initiated swallowing. These pathophysiological changes were proposed to be related to progressive degeneration of

excitatory and inhibitory corticobulbar fibres. Other evidence for such underlying mechanisms comes from a comparison of palatal and pharyngeal motor responses in healthy adults and MND patients: pharyngeal motor responses were brisker in patients with MND than in matched normal subjects: a brisk pharyngeal response was associated with symptoms of a swallowing problem and reduced swallowing capacity (19). Loss of corticobulbar fibres may lead to brisker palatal and pharyngeal responses due to a reduction in descending inhibition by analogy with a brisk jaw jerk and brisk tendon reflexes; if such loss also impairs behavioural modulation and control of swallowing it may explain the association found between a brisker pharyngeal response and impaired swallowing (20).

**Respiratory complications related to bulbar dysfunction in MND**

Malnutrition and respiratory muscle weakness

Chronic malnutrition is common in MND patients with bulbar muscle weakness and may have a considerable bearing on respiratory function and survival. The degree of malnutrition (as defined by body mass index (BMI <18.5 kg/m<sup>2</sup>)) has a significant independent prognostic value (21). Improvement in the nutritional status of MND patients (quantified by an improvement in BMI) via enteral feeding by gastrostomy resulted in improved survival by 6 months follow-up in one study (22).

Table 2. Bulbar involvement in MND

Anatomic site	Innervation	UMN signs	LMN signs	Symptoms
Masseter/temporalis	V	Brisk jaw jerk or jaw clonus	Jaw weakness	Chewing fatigue
Facial muscles	VII	Weakness, emotional activation	Weakness	Drooling, inability to use a straw
Palate/pharynx/larynx	IX, X	Brisk gag reflex, hyperactive laryngeal reflexes	Absent/diminished palate and pharyngeal movements, uvula deviation	Dysphagia, nasopharyngeal reflux on swallowing, coughing and choking
Tongue	XII	Slow spastic movements	Atrophy, fasciculations, deviation, weakness	Inability to clear buccal sulcus of food, impaired bolus formation and oral transport difficulties

UMN = upper motor neuron, LMN = lower motor neuron.

Food deprivation results in reduction in the diameter of type II muscle fibres of the diaphragm (23, 24). Despite relative conservation of type I fibres, diaphragm and body mass appear to decrease in equal proportions (23, 25), and changes in inspiratory muscle strength correlate closely with changes in body cell mass (26). Maximum diaphragm isometric strength, endurance, maximum static inspiratory and expiratory pressures (23, 27), and maximum voluntary ventilation decrease during fasting (27). In addition, semistarvation blunts hypoxic (28, 29) and hypercapnic (30) ventilatory drive. Prolonged food deprivation also impairs respiratory muscle function by reducing available energy substrates (31). In chronic starvation, branched-chain amino acids, a component of muscle tissues, become an important energy substrate for diaphragm activity (31). Malnutrition also impairs cell-mediated and humoral immunity (32, 33), and alveolar macrophage phagocytic activity decreases (34, 35), resulting in a diminished response to chest infection.

#### Upper airway obstruction

Neuromuscular diseases associated with bulbar manifestations can give rise to upper airway obstruction due to abnormalities of the control and strength of the laryngeal and pharyngeal muscles (36). Malfunction of the upper airway muscles increases resistance to airflow, producing characteristic changes in the contour of the flow-volume loop. There are two different patterns of abnormality suggesting upper airway obstruction in neuromuscular disease: firstly, with vocal cord weakness or paralysis, inspiration causes a fall in airway pressure, narrowing the segment further, producing a loop in which inspiratory flow is far lower than flow in the expiratory phase when airway pressure increases. Secondly, the loop may reveal "sawtooth" (acceleration and deceleration) flow oscillations on both inspiration and expiration; these fluctuations, are due to tremulous movements of weakened upper airway muscles and in particular the vocal cords and soft palate. It has been shown that upper airway obstruction is a frequent finding in MND patients with bulbar manifestations although, per se, unrelated to prognosis (37). Upper airway obstruction may present with sleep-disordered breathing notably accompanied by stridor. Ambulatory multi-parameter monitoring during sleep has shown that some MND patients with predominantly bulbar features, even at an early clinical stage when they do not present with daytime respiratory failure, may show sleep-disordered breathing of the apnoea/hypoapnoea pat-

tern (38). Fig. 1 illustrates some characteristic flow volume loops in MND patients.

The presence of upper motor neuron bulbar signs appears to be associated with the severity and duration of choking attacks in patients with MND (39). If spastic dysarthria and brisk palatal/pharyngeal reflexes are associated with the presence of excessively brisk laryngeal closure reflexes then the reflexes may be triggered at a lower threshold than usual, and enhance the risk of upper airway obstruction leading to feeling of choking. It might be expected that insufficient pharyngeal clearance with pooling of saliva or detritus in the valleculae or pyriform fossae, and premature oral loss of food material could act as provocative factors in triggering such episodes.

#### Peak cough flows

A normal cough involves taking a deep breath to about 2–3 l (40), closing the glottis, and using expiratory muscles to create sufficient thoracoabdominal pressures to generate 6 to 16 l/s of peak cough expiratory flows (PCEF), depending on sex, height, and age (40, 41), on glottic opening. The effectiveness of airway mucus clearance is largely dependent on the magnitude of the PCEF (42). Bulbar muscle function is vital both for closing the glottis to permit adequate generation of precough pressures and for optimizing airway patency by vocal cord abduction during the explosive decompression that actually generates the flows. Thus several factors may combine in MND to reduce that cough flow (38). It has been demonstrated that MND patients with sufficient bulbar muscular function to permit assisted peak flows of greater than 3 l/s can benefit from continuous long-term non-invasive ventilatory support (43). Once PCEF decreases below this level, however, flows are inadequate to clear airway debris, and it is just a matter of time until airway encumbrance results in acute respiratory failure and tracheostomy or death.

#### Aspiration

The diagnosis and management of oropharyngeal dysphagia is often centred on the detection and treatment of prandial aspiration in an attempt to prevent or minimize laryngeal penetration and aspiration. Laryngeal penetration is the entry of oropharyngeal contents into the larynx proximal to the true vocal folds, whereas aspiration is the passage of material into the lungs (44). Aspiration of large solids can lead to upper airway obstruction, which if complete can lead to death within minutes owing to immediate asphyxiation. Smaller volumes of aspirated solids may pass through the larynx and

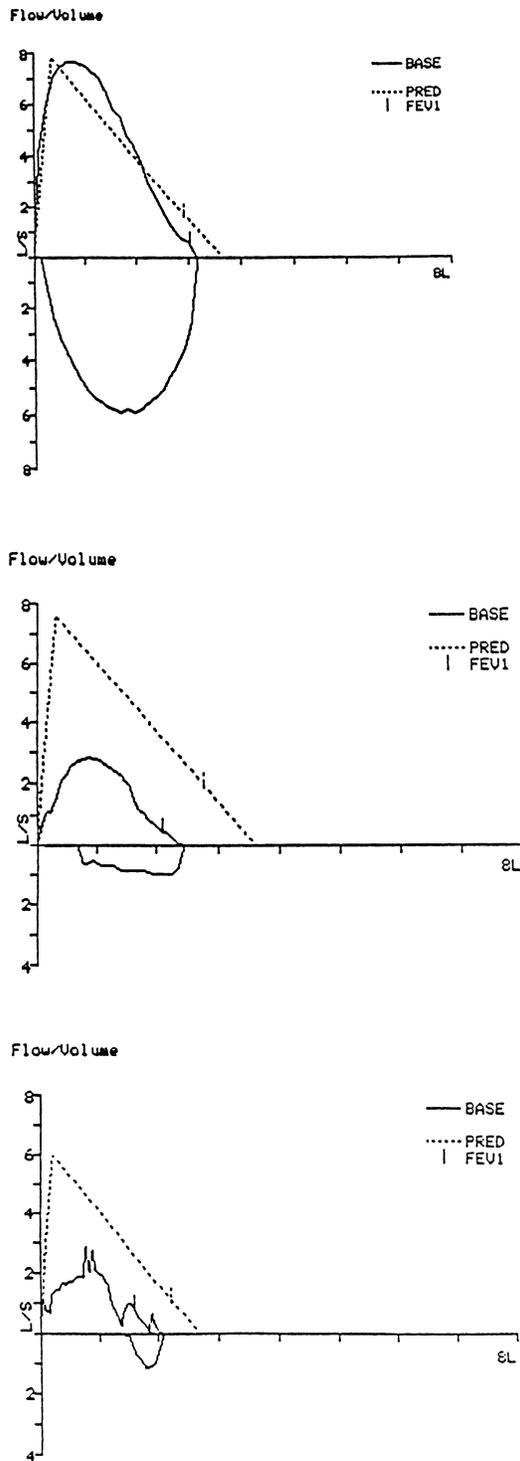


Fig. 1. An example of a normal flow volume loop (top), a loop with plateauing of the inspiratory flow (middle), and a loop with sawtooth flow oscillations (bottom). Y-axis represents the flow rate (litres/s), and the X-axis volume of expired air (litres). The inspiratory phase is below and the expiratory phase above the horizontal line. Pred FEV1 = predicted forced expiratory volume in 1 s, base = actual forced expiratory volume in 1 s.

lodge in the bronchi, usually at the branch points of the lower lobes with unremoved material leading to pneumonia, abscess formation, empyema or localized bronchiectasis (45). Although dysphagia in MND or other neurological disease is believed to cause aspiration of food and liquids and hence pneumonia, the evidence in the literature for linking these events is not uniformly strong: some studies have found that patients who aspirated food or liquid were significantly more likely to develop pneumonia (46, 47) but other studies have failed to find such an association (48). Once aspiration has occurred, cough and mucociliary clearance act to mechanically drive the material out of the lungs, and lymphatics and alveolar macrophages represent the cellular level of host response. Factors that can affect those defence mechanisms, such as weak cough, immunocompromized health status, smoking (impaired pulmonary clearance), may increase the risk of aspiration pneumonia.

The nature of the aspirate and its content of microbiological organisms may be of importance in determining the outcome of an aspiration event. It was shown that the number of decayed teeth, the frequency of brushing teeth and being dependent for oral care were significantly associated with aspiration pneumonia (49). Oral/dental disease may be a contributory factor to pneumonia by increasing the levels of oral bacteria in the saliva and aspirated oropharyngeal secretions. The likelihood that pneumonia will result from a given episode in which oral secretions are aspirated reflects a balance between the size and virulence of the bacterial inoculum on the one hand and the integrity of the patients mechanical and immune defences of the lungs on the other.

A significant number of MND patients display oropharyngeal colonization by potential respiratory pathogens (PRPs) which seems to increase the risk of developing chest infection in patients with bulbar dysfunction (50). Potential factors in MND which may promote abnormal oropharyngeal bacterial flora growth include: poor oral hygiene due to difficulty cleaning teeth, food residues due to reduced mechanical effect of tongue, reduced oral food and fluid intake, pooling of saliva in valleculae and pyriform fossae, increased tendency for post deglutition inspiration (see later) and reduced saliva production due to anticholinergic drugs. If PRPs colonization is considered to be associated with chest infection, measures to improve oral hygiene may be of value in management.

Co-ordination of respiration and swallowing

Swallowing must interact with breathing so that swallow causes minimal or no disturbance of

continual breathing. In awake human adults, swallow events are accompanied by an apnoeic period (the swallow apnoea) lasting between 0.6 and 2.0 seconds (51, 52), and this swallow apnoea is followed by expiration in 95% of swallows (53). This sequence of a swallow followed by expiration may be a useful mechanism for clearing the pharyngeal recesses of foreign residues before subsequent inspiration and is regarded as one of several mechanisms by which the airway is protected from aspiration during swallowing.

MND patients commonly display an abnormal respiratory pattern during swallowing characterized by: inspiration after the swallow, prolonged swallow apnoea and multiple swallows per bolus (54, 55). Patients with an abnormal respiratory pattern were more likely to have a lower swallowing capacity (volume/swallow) than those without. It seems possible that the automatic respiratory control system prevails over the swallowing reflexes when the maintenance of ventilation is particularly important in conditions of loaded breathing because the time available for breathing could be significantly reduced during repeated swallows each accompanied by apnoea. Patients with upper motor neuron bulbar signs had significantly more swallow apnoeas followed by inspiration than those without (54). Loss of corticobulbar fibres might weaken descending inhibition of inspiration triggered by the automatic respiratory system so increasing the likelihood of an inspiration event following a swallow. However, an abnormal breathing pattern during swallowing was unrelated to chest infections, episodes of coughing and choking during meals and prognosis and it may be that post swallow apnoea inspiration is more important as an indicator of disordered swallowing rather than as an important mechanism of aspiration per se or of symptom production (55).

### Respiratory function tests

Volitional respiratory tests such as forced vital capacity (FVC), and maximum mouth pressures, are often used to monitor respiratory function in MND and are, in part, predictive of survival time (56). However, these measurements can be inaccurate in patients with bulbar dysfunction. Firstly, patients with bulbofacial weakness can not hold the mouthpiece of the spirometer firmly between their lips. The resultant escape of air around the mouthpiece yields values for the FVC and mouth pressures that are spuriously low. This can be at least partially avoided either by using a rubber mouthpiece with a flange that fits firmly between the lips and gums or a well-fitting face mask that covers the mouth and nose. Secondly, the accuracy of these volitional

respiratory tests depends on the effort by the patient. This effort is dependent on activation of the descending corticobulbar and corticospinal pathways (57), which are themselves frequently affected by the disease. Some MND patients with predominant upper motor neuron involvement may have clinically overt impairment of the ability to modulate or suspend inspiration and expiration whilst spontaneous breathing or reflexly induced (e.g. by cough) breaths may be less affected if the lower motor neurones are intact. Therefore, volitional respiratory function tests should be interpreted cautiously in MND patients with bulbar dysfunction. Non-volitional tests such as measurement of transdiaphragmatic pressures using oesophageal and gastric catheters (58), and electrical (59) and magnetic phrenic nerve stimulation (60) may overcome these difficulties by clarifying the lower motor neuron component of the problem. However, these procedures are invasive, require highly specialized equipment and are only available in a few centres. Venous serum chloride and bicarbonate, as metabolic indicators of the degree of respiratory acidosis and cautiously interpreted, may potentially provide useful information concerning prognosis and respiratory function in MND based on a blood sample taken at home. A chloride level below the lower limit of normal and a bicarbonate level above the upper limit of normal seem to be sensitive indicators of impending respiratory decompensation (61, 62). Such a measurement represents, of course, the net endpoint of multiple factors influencing breathing efficiency.

### Assisted mechanical ventilation

Usually the primary aim of the treatment of respiratory failure in MND is to alleviate distressing symptoms. Non-invasive intermittent positive pressure ventilation by nasal mask (NIPPV) has been used increasingly frequently in recent years. The aim of NIPPV should be to provide symptomatic relief; enhancing quality of life rather than prolonging it. NIPPV avoids tracheostomy and has shown to improve respiratory symptoms (63). Bulbar dysfunction with abundant secretions may increase the risk of aspiration and make successful NIPPV more difficult. However, since the aim of treatment is palliative; contraindications are relative if NIPPV results in symptomatic improvement. It has been shown that obstructive sleep apnoea (due to bulbar dysfunction) can be a contributory factor to the respiratory complications of some MND patients, and therapy with nocturnal continuous positive airway pressure may provide symptomatic benefit in those patients (64). Polysomnographic studies are

occasionally useful in recognizing obstructive sleep apnoea in this context (65).

**Conclusion**

Bulbar dysfunction is one of the most common clinical problems encountered in MND. Swallowing and breathing share neuroanatomical pathways, muscles, and physical structures and therefore it is not surprising that bulbar dysfunction can result in various respiratory complications. A careful consideration of bulbar dysfunction should always form a part of the respiratory assessment of such patients.

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