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Laryngeal involvement in mitochondrial myopathy

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Abstract
A patient with a slowly progressive mitochondrial myopathy is presented. Mitochondrial myopathies are a diverse group of disorders both clinically and at the cellular level. In common with other neuromuscular disorders, bulbar symptoms may occur. However, though pharyngeal symptoms have been documented in all forms of the disorder, no previous account has described problems at the laryngeal level. We discuss the clinical findings and comment on the therapeutic options.

Key words: Myopathy, mitochondrial; Larynx

Introduction

A wide variety of neuromuscular disorders may cause ventilatory insufficiency due to respiratory muscle weakness (Hanson, 1991). However, a number of recent reports highlight the fact that respiratory failure in such disorders may in some cases be due to upper airway involvement, as in myasthenia gravis, where rarely, stridor may be the presenting feature (Friedmann and Goffin, 1966; Schmidt-Nowara *et al.*, 1984; Winter and Koopmann, 1990). Laryngeal symptoms in mitochondrial myopathy have not previously been recognized, though pharyngeal problems are well described (Peyronnard *et al.*, 1980; Manni *et al.*, 1991; Fernandez-Sola *et al.*, 1992). We describe a patient with mitochondrial myopathy whose laryngeal symptoms are a prominent part of the symptomatology.

Case report

A 36-year-old lady presented to the Royal Eye Hospital, Manchester, with a 15-year history of a progressive bilateral ptosis. It was noted that she had slight limitation of external ocular muscle function in all directions and that she had recently become myopic. Also of note was a family history of bilateral ptosis affecting the patient's brother and cousin, and possibly one of the patient's four children. A provisional diagnosis of a familial progressive external ophthalmoplegia was made. Upon review by a neurologist, the additional features of proximal myopathy, mild dysphagia, periodic aspiration of liquids, a non-explosive cough and weak voice were noted, and a number of investigations performed. ECG, nerve conduction studies and repetitive stimulation test were normal, suggesting normal peripheral nerve and muscle end-plate function. A Tensilon test was negative, but electromyography (EMG) demonstrated some myopathic features. Analysis of a quadriceps muscle biopsy using NADH tetrazolium reductase, revealed subsarcolemmal accumulations of mitochondria. In view of the absence of ragged red fibres on modified Gomori trichrome stain, further testing with cytochrome oxidase and succinate dehydrogenase (SDH) was carried out, and confirmed the diagnosis of a mitochondrial myopathy.

In view of the bulbar symptoms, ENT and speech therapy opinions were requested. Examination revealed bowing and incomplete adduction of both vocal folds (Figure 1). Speech therapy assessment revealed the following characteristics. Tongue, lip and jaw movements were all reduced and articulation was slightly lax. There was overall marked nasality which increased with volume but with no audible nasal escape. The pitch was within normal limits for the female voice but was reduced in range giving a moderate level of monotony. There was reduction in both the mean and range of volume, while attempts to increase the volume were associated with vocal fatigue within a few minutes. Breath control was reduced due to glottic air escape giving a whisper quality to the voice. The poor laryngeal closure was demonstrated using an electrolaryngograph (Figure 2). Electrolaryngograph waveforms were consistent and had a small amplitude indicative of incomplete mucosal contact and a sloping rising phase demonstrating a slow closing phase. Increasing the volume eradicated the whisper quality and gave rise to dramatically increased amplitude shown on the electrolaryngograph. This indicated greater mucosal contact consistent with more complete glottic closure and is a typical finding when a normal voice becomes louder. The rising phase of the wave was also much steeper showing a more rapid closure (Fourcin and Abberton, 1971).

These findings indicated that improved glottic closure would be achievable with speech therapy. The extent of any improvement would however depend upon the rate of progression of the underlying condition. An expectant policy was therefore pursued.

One year after the initial otolaryngological review, the patient's symptoms had not significantly changed. Given the progressive nature of the disorder, at some point, medialization of one vocal fold may have to be performed, but at present, a policy of periodic review is being followed.

Discussion

Mitochondrial myopathies are a group of clinically heterogenous disorders which have in common a number of pathological changes in muscle mitochondria. The characteristic features on light microscopy include the demonstration of a significant percentage of ragged red fibres as shown by the modified trichrome Gomori stain and stains for oxidative enzymes such as succinate dehydrogenase and NADH tetrazolium reductase. On electron microscopy, large aggregates of subsarcolemmal mitochondria may be found, though the size and structure of such mitochon-

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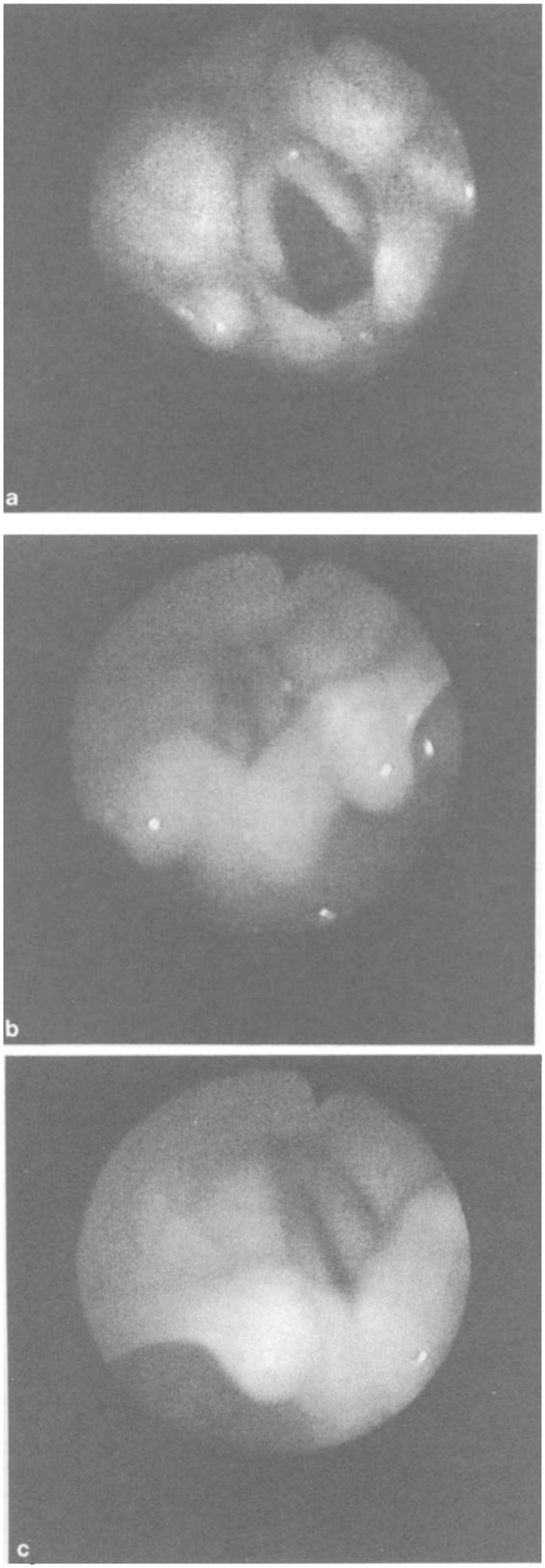

FIG. 1

(a) Maximum abduction; (b) maximum adduction at initial phonation; (c) maximum adduction when fatigued.

dria may vary considerably (DiMauro *et al.*, 1985). The morphological findings are however, not specific for the particular type of mitochondrial myopathy and indeed some morphological changes within these organelles may be found in other types of muscular disease including myotonic dystrophy, polymyositis and polymyalgia rheumatica (DiMauro *et al.*, 1985; Pauzner *et al.*, 1991; Harle *et al.*, 1992).

Mitochondrial myopathies may also be classified by biochemical means into those due to defects of substrate utilization, of oxidation phosphorylation coupling, and of the respiratory chain (DiMauro *et al.*, 1985). It is unfortunate from a clinical point of view that an individual biochemical defect may produce a number of quite different symptoms, while similar patterns of disease may arise from different biochemical abnormalities.

Because of such difficulties, reports of patients with mitochondrial myopathies have tended to group patients into clinical syndromes and a number of these are recognized. At one end of the disease spectrum are individuals with a slowly progressive proximal myopathy alone. At the other extreme, there may be in addition multisystem involvement with cerebral, cardiac, and renal disease (DiMauro *et al.*, 1985). The first description of a syndrome in which the defect was shown to be within the mitochondria was by Luft and his co-workers in 1962 who described a patient with hypermetabolism due to defective coupling of oxidative phosphorylation in muscle mitochondria (Luft *et al.*, 1962). Four years earlier, Kearns and Sayre (1958) had described patients with retinitis pigmentosa, external ophthalmoplegia, ptosis, and complete heart block. The syndrome has alternatively been termed oculocraniosomatic neuromuscular disease and may have additional features in some individuals including short stature, proximal myopathy, ataxia and sensorineural hearing loss. The syndrome is usually sporadic, in contrast to two other disorders in which a positive family history is often found. The first of these is myoclonic epilepsy with ragged red fibres (MERRF); and the second mitochondrial myopathy encephalopathy lactic acidosis and stroke-like episodes, (MELAS) syndrome. All three syndromes tend to present in childhood or adolescence and have a poor long-term outlook. Mitochondrial myopathies may however, present as an adult form in which ptosis and external ophthalmoplegia are early findings with a slowly progressive and variable involvement of craniosomatic muscles (DiMauro *et al.*, 1985; Cros *et al.*, 1992).

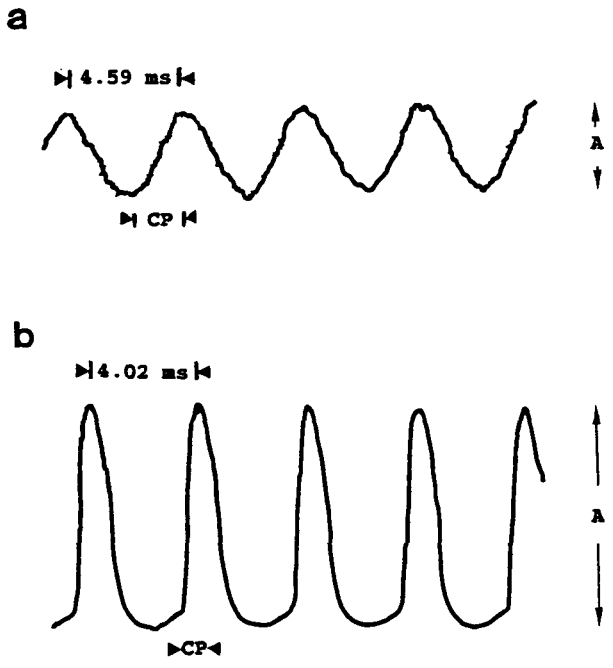

FIG. 2

Electrolaryngography showing: (a) habitual phonation; (b) loud phonation. A = amplitude; CP = closing phase.

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Dysphagia has been described in all the above types of mitochondrial myopathy in the absence of cranial nerve palsies (Peyronnard *et al.*, 1980; Manni *et al.*, 1991; Fernandez-Sola *et al.*, 1992), as have respiratory abnormalities due to either weakness and fatigue of the inspiratory muscles or disordered central regulation (Manni *et al.*, 1991; Cros *et al.*, 1992). Laryngeal involvement has however not been documented but may exist more commonly than is recognized. Our patient presented a history similar to myasthenia gravis, with ptosis, external ophthalmoplegia and dysphonia, all of which worsened with fatigue. Though neuropathies have been recognized in mitochondrial myopathies (Peyronnard *et al.*, 1980), this fatiguability and the bilateral adductor weakness suggest that the abnormality of laryngeal function was due to weakness of the muscles themselves, rather than of a neuropathic nature.

In our patient there were no systemic features such as renal, cardiac or cerebral abnormalities, thus the patient may expect to have a long-term survival unless symptom progression becomes more rapid. As in all patients with bulbar neuromuscular dysfunction, the treatment options are constrained by a desire to improve voice and swallowing, whilst at the same time providing an adequate airway. At present, a conservative approach is being adopted, though a (reversible) medialization procedure to one vocal fold is an option should the voice quality become unacceptable or aspiration clinically significant. As it is likely that the abductors of the larynx will also become weaker in time, a tracheostomy may be required in the longer term.

Conclusion

The case presented here is of a patient with a slowly progressive mitochondrial myopathy. To our knowledge, this is the first report of a case in which laryngeal symptoms form a significant part in such a disorder.

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