Respiratory insufficiency in neuronopathic and neuropathic disorders

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Summary

Twenty-nine patients with a neuronopathic or neuropathic disorder were referred for assessment of respiratory insufficiency between 1978 and 1994. Diagnoses included spinal muscular atrophy (6), chronic idiopathic demyelinating neuropathy (4), Vialetto-van Laere syndrome (3), hereditary motor and sensory neuropathy (3) and a miscellaneous group (5). We also describe seven patients with Guillain-Barre syndrome (GBS) who required long-term ventilatory support for over 6 months to 7 years after the initial illness. Respiratory insufficiency occurred as a consequence of respiratory muscle weakness, impaired bulbar function and restrictive lung defects. In some groups presentation was with progressive nocturnal hypoventilation culminating in acute respiratory failure. Five patients with GBS or chronic idiopathic demyelinating neuropathy were weaned from ventilatory support up to 18 months after the initial illness. The remaining 24 patients required continuous or nocturnal ventilatory support using intermittent positive-pressure ventilation (13), negative pressure ventilation (4), nasal-mask-delivered intermittent positive-pressure ventilation (4), nasal-mask-delivered continuous positive-pressure ventilation (3), mouthpiece-assisted ventilation by day (2) and rocking bed (1). None have been weaned from support after a period of ventilation ranging from one month to 10 years. Eight patients have subsequently died.

Introduction

Respiratory insufficiency is a well-recognized complication of acute idiopathic demyelinating polyneuropathy (Guillain-Barré syndrome),¹,² motor neuron disease,³ and poliomyelitis⁴ but it is less frequently described in other neuronopathic and neuropathic disorders. In many cases diaphragmatic weakness is a major component,⁵ but other mechanisms that contribute to such hypoventilation include weakness of other respiratory muscles, impaired bulbar function, upper airway obstruction, restrictive lung defects due to scoliosis or repeated respiratory tract infections and, in some diseases, an additional central component.⁶ We have previously described the use of assisted ventilation in patients with motor neuron disease³ and poliomyelitis.⁴ In this study, we review the management of patients with respiratory failure and respiratory insufficiency due to other neuronopathic and neuropathic disorders.

Methods

Twenty-nine patients with a neuronopathic or neuropathic disorder were referred to The Lane Fox (formerly Phipps) Unit (St Thomas’ Hospital) and The Batten/Harris Unit (The National Hospital) for assessment of respiratory insufficiency between 1978 and 1994. Patients with Guillain-Barré syndrome (GBS) who required ventilatory support for <6 months, and those with motor neuron disease or poliomyelitis...
were excluded from this study. Clinical details were obtained by direct observation or retrospectively from the casenotes. We reviewed the neurological presentation, the development of respiratory symptoms and signs, and the duration and nature of respiratory support. Eight patients have subsequently died. Two patients with Vialetto-van Laere syndrome have been reported previously, without specific reference to respiratory complications, and another, with Krabbe's leucodystrophy, was described before the development of respiratory symptoms. The diagnosis was made or confirmed by a neurologist, and was supported by standard haematological and biochemical investigations, electromyography studies (EMG) and nerve biopsy where appropriate.

Patients were considered for ventilatory support after the development of respiratory failure or respiratory insufficiency. Respiratory failure was defined as $P_aO_2 < 8$ kPa (60 mmHg) alone or with $P_aCO_2 > 6.7$ kPa (50 mmHg). Respiratory insufficiency was considered to be present if there was evidence of a progressive decline in forced vital capacity (FVC) together with nocturnal hypoventilation or daytime hypercapnia. Nocturnal hypoventilation was identified by clinical history and, in most cases, confirmed with an indwelling arterial line or digital pulse oximeter showing episodes of respiratory failure during sleep. Diaphragmatic weakness was identified by orthopnoea and paradoxical abdominal movements on inspiration or sniff. Further evidence was provided by a reduction in forced vital capacity (FVC) of one-third between the erect and supine positions, and the presence of reduced or paradoxical diaphragmatic movement during screening in the supine position. Generalized respiratory muscle weakness was suggested by the development of respiratory insufficiency in the absence of primary lung disease.

**Results**

Tables 1 and 2 summarize the presentation and respiratory features of patient groups and Table 3 the duration and modes of ventilation used. The indications for and role of the different forms of ventilatory support used have been described elsewhere. Some patients received more than one mode of ventilation. Diagnoses include GBS (8), spinal muscular atrophy (SMA) (6 patients), chronic idiopathic demyelinating polyneuropathy (CIDP) (4), Vialetto-van Laere syndrome (3), hereditary motor and sensory neuropathy (HMSN) (3) and a miscellaneous group (5).

**Guillain-Barré syndrome**

There were eight patients with GBS (all male), with a mean age of 52.7 years (range 37–68). Of these, seven presented with flaccid quadriplegia and developed respiratory failure at a mean age of 45.9 years (range 30–68). In three patients, the neurological illness was preceded by symptoms of gastroenteritis and in one of this group *Campylobacter jejuni* was isolated from blood cultures. The time between onset of neurological symptoms and the need for ventilatory support ranged between 1 and 8 days (mean 4 days). All had respiratory muscle weakness with FVC between 0.1 and 0.9 l and five had severe bulbar weakness. All patients initially required intermittent positive-pressure ventilation (IPPV) via a tracheostomy and this was continued in four patients who could not be weaned and remained ventilator-dependent 11 months, 12 months, 3 years and 7 years after the initial illness. These patients remained quadriplegic with vital capacity less than 1 l and two have died. Three patients were weaned after ventilation for 6, 10 and 18 months; in all three vital capacity increased to greater than 1 l before weaning was possible. Weaning was achieved either by the use of intermittent mandatory ventilation or placing the patient on a T-piece circuit for increasing periods. All three had profound residual weakness at the time of successful weaning. Whilst all three showed some improvement in their motor deficit, two remained wheelchair-bound, one and four years after ceasing ventilatory support; the third patient

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Relationship between neurological and respiratory presentation</th>
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<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>8</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>6</td>
</tr>
<tr>
<td>CIDP</td>
<td>4</td>
</tr>
<tr>
<td>Vialetto-van Laere</td>
<td>3</td>
</tr>
<tr>
<td>HMSN</td>
<td>3</td>
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</table>
Respiratory insufficiency began to develop improved peripheral power a year after weaning and was wheelchair-bound for a further year. None died and they remained without respiratory support 5, 6 and 2 years after weaning; one had a tracheostomy to aid suctioning because of bronchiectasis.

The remaining patient, a 57-year-old, had made a full neurological recovery following an episode of GBS at the age of 14 which was characterized by peripheral weakness but did not necessitate ventilatory support. He presented again at the age of 53 with symptoms of obstructive sleep apnoea (OSA) without evidence of diaphragmatic or bulbar weakness. His symptoms resolved with CPAP by nasal mask.

**Spinal muscular atrophy**

There were six patients with a spinal muscular atrophy (one male, five female) with a mean age of 43.1 years (range 24–59). Three had onset of neurological symptoms at less than two years, one at 13 years, and two between 35 and 45 years. The four patients with onset at <15 years were wheelchair-bound at the time of respiratory presentation. Respiratory presentation was at a mean of 21.2 years (range 9–37) after the first neurological symptom.

The characteristics of respiratory insufficiency are summarized in Table 2. Three patients were in respiratory failure at the time of respiratory presentation. Four patients had diaphragmatic weakness and three nocturnal hypoventilation. The mean FVC in the supine position was 0.6 I (range 0.2–1.0). Bulbar weakness and recurrent respiratory tract infections were common, with marked scoliosis found in three patients with neurological onset at less than 5 years.

Table 3 documents the ventilatory support that this group required for a mean period of 7.2 years (range 2–10 years). No patient was weaned from respiratory support. Patients in respiratory failure required continuous IPPV (two) or iron-lung ventilation (one) but were subsequently weaned to nocturnal IPPV via a tracheostomy (two) or nasal-mask-delivered IPPV (one). One of the remaining patients used nocturnal nasal-mask-delivered IPPV (having initially been managed using nasal CPAP), one negative pressure ventilation (using a Pneumobelt), and one mouthpiece-assisted ventilation by day. All reported symptomatic relief with concurrent improvement in daytime arterial blood gas analyses.

**Chronic idiopathic demyelinating neuropathy**

There were four patients with CIDP (three male, one female) with a mean age of 72 years (range 67–75). One patient had motor neuropathy with multifocal...
conduction block. All presented in respiratory failure a mean of 5.5 years (range 0.33–20) after neurological presentation. Three had marked diaphragmatic weakness and the mean FVC was 0.7 l (range 0.3–1.5). Two patients remained on respiratory support: one used a rocking bed at night and an iron lung during intercurrent infections, and the other used nasal-mask-delivered IPPV. Two patients with short periods between neurological and respiratory presentations (4 and 5 months) were weaned from support. One required only supplemental oxygen during intercurrent respiratory tract infections whilst the other required IPPV for a month via a tracheostomy but was successfully weaned from respiratory support.

Vialetto-van Laere syndrome

There were three patients with Vialetto-van Laere syndrome (one male, two female) with mean age of onset of neurological symptoms at 15.7 years (range 12–18). All had a previous history of sensorineural deafness and presented with marked bulbar and facial weakness with a progressive, predominantly motor, neuropathy; two had clinical evidence of diaphragmatic weakness. Respiratory presentation was between 0.5 and 1.5 years later and two were in respiratory failure. The mean FVC was 1.2 l (range 0.9–1.4). Both patients with respiratory failure required IPPV via a tracheostomy and neither could be weaned from this mode of support. The third patient used a Tunnicliffe jacket, initially at night only, but subsequently for increasing periods during the daytime. Two patients have died, both within 1.5 years of the commencement of assisted ventilation.

Hereditary motor and sensory neuropathy

There were three patients with HMSN (all female) with a mean age of 33.7 years (range 15–56). Two patients had the demyelinating form (type I) and a family history consistent with autosomal dominant inheritance. The other patient was thought to have a recessively inherited axonal degeneration (type II). All had significant peripheral weakness and two were wheelchair-bound. Two had marked diaphragmatic weakness and two scoliosis; the mean FVC was 0.9 l (range 0.5–1.2). One patient had evidence of nocturnal hypoventilation and is being considered for nocturnal respiratory support. Two were in respiratory failure at the time of respiratory presentation (6 and 11 years after neurological presentation). Both required IPPV via tracheostomy initially. One was weaned to nocturnal IPPV via tracheostomy, whilst the other required trials of nocturnal iron-lung and nasal-mask-delivered IPPV as domiciliary support.

Other patients

Patient 1

A 72-year-old female presented with pain and weakness in both arms and 4 months later became progressively short of breath on exertion. Two months later she suffered a respiratory arrest, requiring IPPV and attempts to wean were unsuccessful. EMG was consistent with anterior horn cell degeneration. She died 8 days later and post-mortem examination showed carcinoma of the bronchus and anterior horn cell degeneration.

Patient 2

A 63-year-old female presented with right wrist drop and impaired fine finger movements; examination revealed distal wasting and weakness in the upper limbs. EMG showed a demyelinating neuropathy and an IgM κ paraprotein was found on serum electrophoresis. There was little progression until 3 years later when she developed acute respiratory failure during a respiratory tract infection. FVC was 1.2 l. She initially used a rocking bed at night but increasing respiratory difficulties necessitated the use of IPPV via a tracheostomy at night. She died 8 months later.

Table 3: Duration and nature of respiratory support

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>n</th>
<th>Mean duration of ventilation (years (range))</th>
<th>Nasal CPAP</th>
<th>IPPB</th>
<th>RB</th>
<th>NPV</th>
<th>Nasal IPPV</th>
<th>IPPV</th>
<th>Weaned from support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain-Barré syndrome</td>
<td>8</td>
<td>2.0 (0.5–7)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>6</td>
<td>7.2 (2–10)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CIDP</td>
<td>4</td>
<td>0.73 (0.1–2)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vialetto-van Laere</td>
<td>3</td>
<td>0.93 (0.3–1.5)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HMSN</td>
<td>3</td>
<td>2.2 (0.5–5)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

IPPV, intermittent positive-pressure ventilation; NPV, negative-pressure ventilation; IPPB, mouthpiece-assisted ventilation by day; RB, rocking bed; nasal IPPV, nasal-mask-delivered intermittent positive-pressure ventilation; nasal CPAP, nasal-mask-delivered continuous positive-airway-pressure ventilation.
Patient 3
A 42-year-old female with Krabbe’s leucodystrophy presented with orthopnoea and symptoms of obstructive sleep apnoea. She had bulbar and diaphragmatic weakness, with FVC 0.5 l and nocturnal hypventilation. Treatment with nasal CPAP improved her symptoms and nocturnal hypventilation.

Patient 4
A 32-year-old female with spinocerebellar degeneration and anterior horn cell degeneration of undetermined aetiology presented with orthopnoea and shortness of breath on exertion. She had diaphragmatic weakness, with FVC 0.3 l. She was in respiratory failure but it was thought inappropriate to add respiratory support, and she died a year later. Postmortem examination showed degeneration of spinocerebellar tracts, cerebellar cortical atrophy and marked anterior horn cell degeneration.

Patient 5
A 44-year-old male had a 26-year history of a relapsing axonal polyneuropathy of undetermined aetiology. During this period he had six relapses mainly associated with infections, with predominant motor involvement and some residual impairment. He was treated with steroids and azathioprine with some improvement. He presented during a further relapse with bulbar, intercostal and diaphragmatic weakness resulting in respiratory arrest. FVC was 1.0 l. He received IPPV via a tracheostomy at our hospital before transfer to the referring centre.

Discussion
Guillain-Barré syndrome
It is estimated that 14% of patients with Guillain-Barré syndrome require assisted ventilation.11 The need for ventilatory support is normally precipitated by one of two mechanisms. First, bulbar weakness may impair airway protection leading to aspiration of secretions,12 clearance of which is impeded by respiratory muscle weakness and poor cough. Second, weakness of the respiratory muscles can cause respiratory failure per se. In GBS, respiratory weakness is caused by global inspiratory and expiratory muscle weakness in association with evidence of abnormalities of phrenic nerve function.13

The requirement for long-term respiratory support is unusual: in one prospective series of 100 cases of GBS, no patient was ventilated for more than 6 months.14 There have been a number of case reports of patients receiving ventilation for more than 6 months15-20 but none have been ventilated for more than one year. Our series confirms that a small group of patients with GBS require long-term ventilatory support which can extend to 7 years after initial presentation. We show that IPPV via a tracheostomy is an appropriate mode of support in those with combined bulbar and respiratory muscle weakness. It further demonstrates that weaning of such patients is possible, even up to 18 months after the initiation of ventilatory support. In our patients weaning became possible after the FVC had increased above 1 l; other measures of diaphragmatic function, including maximum transdiaphragmatic pressure, may better correlate with recovery of spontaneous ventilation.21

In our severely affected patients the onset of GBS was rapid, with a mean time to requirement for ventilation of 4 days. Further, a high proportion gave a history of preceeding gastroenteritis, with C. jejuni isolated in one case. Both these features have previously been shown to be associated with a poor outcome in GBS.14,22 Long-term neurological disability can occur in GBS.23-26 It is not clear whether, in our case of a man developing OSA 39 years after recovery from GBS, the respiratory presentation is related to such residual impairment.

Spinal muscular atrophy
The classification of the spinal muscular atrophies is complicated because they are both clinically and genetically heterogeneous. Harding27 divides the autosomal recessive forms of proximal SMA as follows: type I (acute infantile or Werdnig-Hoffman disease) has onset before 6 months and is fatal by the age of 7-18 months; type II (chronic childhood or Kugelberg-Welander) in which weakness is noted between the ages of 3 months and 15 years with a life expectancy of 18 months to 40 years; and type III (adult onset or Kugelberg-Welander) which develops between 15 and 60 years of age, with normal life expectancy. Under this classification, four of our patients were of type II and two of type III SMA. Bulbar weakness, where present, was mild and occurred in female patients, excluding the alternative diagnosis of X-linked bulbospinal neuropathy (Kennedy’s syndrome).

Ventilatory failure has been described in all three types of proximal SMA and occurs as a consequence of weakness of respiratory28 and bulbar29 muscles. Patients with early onset have marked scoliosis in addition.30 Some have suggested a possible central component to hypoventilation.31

Recently, a variety of forms of long-term respiratory support have been employed in all forms of proximal SMA. These have included IPPV via a tracheostomy29,32,33 or via the mouth34 and negative pressure ventilation (NPV).28,35,36 We describe further
patients maintained on IPPV and NPV with symptomatic relief and correction of blood gas abnormalities. In addition we describe two patients maintained for 3 and 4 years respectively using nasal-mask-delivered IPPV. This has the advantage of correcting upper airways obstruction in patients with bulbar weakness which can be exacerbated by NPV.36

Chronic idiopathic demyelinating polyneuropathy
CIDP may follow a slow monophasic or a relapsing course. By definition, the maximal neurological deficit is not reached until at least 8 weeks from the first symptoms.37 Onset is usually gradual but can be rapid in a proportion of cases.38 Motor neuropathy with multifocal conduction block probably represents a predominantly motor variant of CIDP.39 Ventilatory support has been required in some patients15,38,46 but is less commonly necessary than in GBS.2,19 long-term assisted ventilation is rarely reported.15 We describe two patients who have required nocturnal ventilation for up to 2 years using a rocking bed and nasal-mask-delivered IPPV, respectively.

Vialetto-van Laere
Vialetto-van Laere syndrome (a form of hereditary bulbar motor neuronopathy27) is a disorder characterized by bilateral nerve deafness, accompanied by involvement of other cranial nerves, including the motor components of the seventh and ninth to twelfth nerves. The onset is usually in childhood and most cases are sporadic.7 Bulbar and respiratory muscle weakness precipitate respiratory failure. We describe three patients with the typical phenotype of this condition who developed respiratory symptoms within 1.5 years of neurological presentation. All received symptomatic relief from respiratory support, but two died within 1.5 years of commencing assisted ventilation.

Hereditary motor and sensory neuropathy
Diaphragmatic involvement in HMSN type I and II has been previously documented41-43 and this is mirrored by abnormalities of phrenic nerve function in HMSN I13,44 Two pedigrees have been reported with dominantly inherited axonal neuropathy in whom respiratory failure was a prominent feature: this has been termed HMSN IIC.45 However, few patients with classical HMSN have required ventilatory support;41,43,46 one of these patients was also diabetic.43 We describe two patients with HMSN and marked diaphragmatic weakness and scoliosis who have required IPPV to correct symptomatic hypoventilation and respiratory arrest.

Other patients
We describe ventilatory failure in five other patients, in three of whom an underlying aetiology was determined. Paraneoplastic neuropathies can present with respiratory muscle weakness and bulbar symptoms similar to those seen in GBS.47-49 The neuropathy of the syndrome of monoclonal gammopathy of undetermined significance (MGUS) is typically a slowly progressive sensorimotor neuropathy and in two large series ventilatory insufficiency has not been recorded.50,51 Bulbar weakness has been documented in late onset Krabbe’s leukoencephalopathy52 and was a prominent feature in our case with OSA. Chronic relapsing axonal neuropathy is rare53 and respiratory failure has not been described.

Conclusions
The development of respiratory insufficiency is well-recognized in patients with poliomyelitis and motor neuron disease3-4 but can develop in patients with other neuropathic or neuronopathic disorders. The mode of ventilatory support used must be tailored to the patient’s specific needs, considering the level of disability and pattern of weakness.3-6 There are at least ten different artificial methods of supporting respiration and each has several minor variants. The choice of respiratory support is partly determined by the degree of respiratory dependence,5 thus with FVC < 300 ml a patient is likely to require continuous support via an iron lung or IPPV via a tracheostomy; FVC 300–700 ml indicates nocturnal ventilation with some daytime support (e.g. nasal-mask-delivered IPPV, IPPV via a tracheostomy or iron lung); with FVC 700–1000 ml nocturnal respiratory assistance alone is likely to be needed (e.g. nasal-mask-delivered IPPV, negative pressure ventilation54 or rocking bed55).

We demonstrate that respiratory insufficiency and respiratory failure can occur in a range of neuronopathic and neuropathic disorders, due to weakness of respiratory muscles, abnormal bulbar function or restrictive lung defects. Appropriate management can provide symptomatic relief and, as with other neuromuscular disease,56,57 reduce morbidity and mortality.

References
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476  R.M. Chalmers et al.


