Ventilatory failure in myasthenia gravis

IT FERGUSON, RP MURPHY, RG LASCELLES

From the Department of Neurology, Manchester Royal Infirmary, Manchester, UK

SUMMARY This retrospective study over the decade 1969-1978 examines the precipitating factors and outcome in thirty-one patients with myasthenia gravis who developed ventilatory failure. An unusual example of chronic alveolar hypoventilation is discussed in detail. The most favourable outcome occurred in younger patients with a hyperplastic thymus, in contrast to a poorer outlook for older patients with an atrophic gland. Eleven patients died during the period of follow up: three deaths were unrelated to myasthenia but the remaining eight were attributed directly or indirectly to it. The mortality of 36% represents a marked improvement on a 70% mortality in a similar group of patients, reported from this hospital for the years 1960-1968.

"A stout girl, looking well, came to the hospital on account of general weakness; she could scarcely walk or move about, she spoke slowly and had slight strabismus. The house physician was inclined to regard the case as one of hysteria . . . every movement of her limbs and speech was performed so slowly and deliberately that the case seemed rather one of lethargy from want of will than an actual paralysis. She spoke most indistinctly, swallowed with great difficulty, and was quite unable to cough. The limbs were, however, not paralysed, as she was able to get out of her bed. It was shortly afterwards seen that her respiration was becoming affected, the difficulty of which rapidly increased, and in a few hours she died. The medulla oblongata was very carefully examined, and no disease found."¹

This account by Samuel Wilks in 1877 of a 22-year-old girl with bulbar paralysis, who died of ventilatory failure, is widely regarded as one of the earliest case reports of the disease later known as myasthenia gravis. We use the term ventilatory failure as defined by Sykes, McNicholl and Campbell.² This state is characterised by a raised arterial carbon dioxide (pCO_2) and results either from a reduction in total ventilation, or from a failure to compensate for impaired carbon dioxide elimination by increasing ventilation. This most feared of all complications of myasthenia gravis may occur suddenly or insidiously and is often difficult to detect particularly during the early stages of the

disease. The 8% mortality rate during the first year of severe myasthenia prior to the institution of the anticholinesterase drugs in 1934 was due mainly to this occurrence.³ Improved respiratory care has been a major factor in the steady reduction in mortality.

Ashworth and Hunter⁴ when reporting their findings in ten myasthenic patients with ventilatory failure who were admitted to the Respiratory Care Unit at Manchester Royal Infirmary during the period 1960-1968 found a 70% mortality rate.

The purpose of the present study is to examine the precipitating factors and outcome of ventilatory failure in a further thirty-one myasthenic patients admitted to the same hospital during the following decade. An unusual case of chronic alveolar hypoventilation is discussed in detail.

Patients and results

Between 1969 and 1978, 31 out of 154 patients attending the Neurological Service with myasthenia gravis developed ventilatory failure. In all of these, voluntary respiratory effort either ceased or was so ineffective as to require assisted ventilation. The majority of our patients experienced sudden ventilatory failure and therefore required immediate resuscitation. Blood gas values (all abnormal) were obtained in only ten of the 31 cases and only four had vital capacity measurements prior to assisted ventilation.

The group consisted of 17 men whose mean age at onset of myasthenia was 54 years (range 27 to 76 years) and 14 women with a mean age of 38 years (range 12 to 64 years). The interval between the onset of myasthenic symptoms and ventilatory failure varies from 5 days to 27 years. The length of this interval bore no relationship to the age of the patient. We have divided the patients into four categories depending on the presumed precipitating cause of their breathing difficulty:

Address for reprint requests: Dr RG Lascelles, Department of Neurology, The Royal Infirmary, Manchester M13 9WL, UK.

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myasthenic crisis, cholinergic crisis, steroid induced crisis, and brittle crisis (see fig 1).

Fig 1 Distribution of patients and number of episodes of assisted ventilation related to the precipitating cause of ventilatory failure. NB Two patients in the myasthenic crisis group died before artificial ventilation could be started.

During the decade under study 11 of the 31 patients died (four patients were not available for follow up). Death occurred on average 9.8 months (range 2 days to 9 years) after the onset of ventilatory failure and in those cases, the average total duration of myasthenic symptoms prior to the onset of failure was 4 years (range 3 months to 15 years). The causes of death are outlined in table 1. Seven patients died from disease

Table 1 Cause of death

Cause of death	No of cases
Unknown (sudden)	4
Myocardial infarction	1
Carcinoma of lung	1
Carcinoma of breast	1
Pneumonia	3
Acute renal failure—	
Systemic lupus erythematosus	1
Total	11

not directly related to myasthenia, and four patients died suddenly, probably from ventilatory failure. Seventeen of the 20 patients who survived were available for follow up at the end of 1978. Fourteen were symptom free although on drugs and able to lead a normal life. Three were moderately well—two with proximal limb weakness and one with ophthalmoplegia. The average age at the onset of myasthenia in those who survived was 44 years and 54 years in those who died (average age at the time of death was 57.5 years).

Thymectomy was performed in twenty-one of the thirty-one cases and histological information is available in nineteen. The results of thymic histology are shown in table 2. The thymus in 50% of the survivors showed

Table 2 Thymus histology

Histology	Patients who died	Patients who survived
Hyperplasia	0	7
Thymoma	1	4
Atrophy	5	2
Histology not available	1	1
Total	7	14

germinal centre hyperplasia, a feature not present in any of the patients who died, whereas 71% of the group who died has an atrophic or involuted gland as opposed to 14% of the survivors. Four of the five patients who had a thymoma survived—two had thymectomy performed prior to their respiratory arrest and three subsequently.

MYASTHENIC CRISIS

The myasthenic group consisted of 12 patients who developed ventilatory failure associated with a rapidly progressive weakness. Six had associated respiratory infection. Ten of the 12 patients required artificial ventilation and six died. Two deaths were sudden before ventilation could be started and four followed respiratory aid. One patient died of a myocardial infarction, two of bronchopneumonia and the remaining three from ventilatory failure. Of six survivors, two require alternate day prednisolone and the remainder are maintained on anticholinesterase alone.

CHOLINERGIC CRISIS

Patients were allocated to this group if they developed increasing weakness with a concomitant increase in anticholinesterase intake. The commonest muscarinic side effects included colic, diarrhoea, lacrimation and excessive oropharyngeal secretions. These features were present in all cases. Meiosis and bradycardia were noted in only one patient. Nicotinic signs, characterised by fasciculations and cramps were not observed in any case. Although the important precipitating factor was an increase in oral anticholinesterase dose in the days preceding the onset of the crisis, the total daily dose of anticholinesterase did not exceed 360 mg of neostigmine and 840 mg of pyridostigmine. In four cases, respiratory arrest immediately followed a test injection of either edrophonium chloride or neostigmine. There were eight patients in the cholinergic group who accounted for ten admissions to the Respiratory Care Unit. Three of these patients subsequently died. One patient died one year after the episode of ventilatory failure from carcinoma of the breast. Another died 9 years later from renal failure secondary to systemic lupus erythematosus. The third patient died one year later from mediastinal infection following a tracheostomy. Of the four survivors, two required alternate day prednisolone and two are maintained on a small dose of pyridostigmine. One patient was not available for follow up.

STEROID INDUCED CRISIS

Eleven patients developed breathing difficulty requiring ventilatory assistance after being given corticotrophin

Ventilatory failure in myasthenia gravis

injections, either Synacthen 1.5 mg daily or ACTH gel 80 IU daily. One patient was taking alternate day prednisolone 25 mg. Four of the eight survivors are now taking alternate day prednisolone. Ventilatory failure occurred on average 5.8 days after starting steroids. Three of the patients in this group exhibited features suggestive of cholinergic excess as evidenced by excessive secretions and abdominal colic without any increase in anticholinesterase. These patients also appear in the cholinergic crisis group. Three patients died at varying intervals following the episode of ventilatory failure. One died 9 years later of renal failure secondary to systemic lupus erythematosus. Another died during the night, six months later, and a further patient also died suddenly during sleep 2 months later. We presume both these patients died of ventilatory failure.

BRITTLE CRISIS

We found the three patients in this group very difficult to assess because they appeared to show many of the features of alternating myasthenic and cholinergic crises, often compounded by a chest infection. The term "brittle crisis" has been suggested by Osserman and Genkins⁵ for this category of case. All the patients in this group are alive and moderately well on alternate day prednisolone. One patient benefited from plasmapheresis. Two patients were of exceptional interest because they developed chronic alveolar hypoventilation and we report one case in detail.

Case report In 1967 this 26-year-old woman presented with diplopia and neck weakness following the birth of her first child. Her symptoms improved gradually until, when three months into her second pregnancy, she developed similar symptoms but with additional bulbar weakness. An edrophonium chloride test confirmed the diagnosis of myasthenia gravis and she was treated with pyridostigmine and ephedrine. Apart from a mild relapse during her third pregnancy, she remained well from 1963 to 1972. Treatment of her myasthenia was discontinued in 1972. Following a minor road traffic accident in 1974, she complained of persistent fatigue, somnolence, morning headaches, breathlessness and ankle oedema, which were all attributed to mild hypertension (140/105 mmHg). This was treated with methyl dopa and a diuretic. In 1977 propranolol was added and she developed mild congestive cardiac failure which settled with diuretics. It had been noted between 1974 and 1977 that she had a persistently high serum bicarbonate—46 mmol/l. She was admitted to Manchester Royal Infirmary on 24 November 1978. On examination she was tachypnoeic with mild central cyanosis, pitting leg and sacral oedema despite large doses of diuretics and digoxin. Her jugular venous pressure was elevated, 4 cm above the sternal angle and her blood pressure was 140/90 mmHg. There was no clinical evidence of cardiomegaly but chest examination revealed limited expansion and decreased air entry with mild bilateral basal crepitations. There was mild bilateral ptosis, a transverse smile with weak orbiculares oculi et oris. She spoke with a nasal voice and exhibited proximal limb weakness and fatigability.

A chest radiograph showed a mild bilateral basal inflammatory change but no evidence of cardiomegaly. An electrocardiogram showed no evidence of cardiomegaly or strain. Repetitive nerve stimulation studies revealed a decremental response at a stimulation rate of 20 Hz characteristic of myasthenia gravis. On the day following admission, without warning, she collapsed, was apnoeic and deeply cyanosed. Her breathing recovered spontaneously but was rapid and shallow, 25-30 breaths per minute. Measurements of arterial gases at that time revealed PO_2 5.71 and pCO_2 20.48 kPa (on oxygen with an Ambu bag). Tensilon 20 mg was given intravenously over a period of two minutes and although there was some improvement in breathing, she was intubated and ventilated for three days after which a tracheostomy was performed. During the following sixteen days, she attempted to breathe spontaneously but on three occasions her pCO_2 rapidly rose (fig 2). She

Fig 2 Brittle crisis—case report: chronic alveolar hypoventilation. Apnoeic episodes occurred during periods of ineffective respiratory effort.

stopped breathing and once again required assisted ventilation. Increasing doses of anticholinesterases and a prolonged course of alternate day prednisolone had little effect on a profound respiratory acidosis. Arterial acid base values then were pH 7.28, pCO_2 11.49, PO_2 13.30 (on O_2) kPa, base excess +22, standard bicarbonate 42 mmol/l. Pulmonary function tests (table 3) excluded any intrinsic lung disease but did confirm marked weakness of respiratory muscles both inspiratory and to a greater extent expiratory groups. The findings suggested that the ventilatory failure was secondary to muscular weakness. There appeared to be an element of alveolar hypoventilation or insensitivity of the afferent chemoreceptive drive, because she tolerated high levels of CO_2 with remarkably little distress. A thymectomy was performed on 17 January 1979 revealing on histology small islands of lymphocytes, thymic epithelial cells and cystic Hassall's corpuscles. On the second day after operation

Table 3 Case report (brittle crisis)—pulmonary function tested with tracheostomy tube removed and the opening sealed

	Pre-thymectomy 12 January 1979	Post-thymectomy 15 February 1979	16 April 1980
Minute ventilation volume	8.9 l/min	7.1	—
Maximum voluntary ventilation	14.0 l/min	22.4	18.0
	Predicted value		
Forced expiratory volume (1 second)	1.15 (2.5) l	1.78	1.46
Vital capacity	1.32 (3.2) l	1.95	1.63
Arterial blood sample from indwelling cannula:			
pH	7.35		7.37
pCO ₂	9.68 kPa		9.31
After 2½ minutes maximum voluntary ventilation			
pH	7.38		7.44
pCO ₂	8.91 kPa		7.32
Maximum inspiratory pressure at the mouth:	-80 cm of H ₂ O (normal)		
Maximum expiratory pressure:	+27 cm of H ₂ O (low)		

she was taken off the ventilator and has not required further help with breathing. Her general state and hypercapnia gradually improved for six months but one year later she once again complained of fatigue, morning headaches and a feeling of panic which she felt was due to shortness of breath when lying flat. Diaphragmatic screening showed no abnormality but the vital capacity erect/supine was 1.1/0.75 l. She preferred to sleep propped up with three pillows. When lying supine she exhibited inward movement of her abdominal wall during inspiration. The arterial pCO₂ began to rise again and this did not change with any alteration in posture or whilst she was asleep. She is now moderately handicapped by a low respiratory reserve and gross leg oedema.

Comment Persistent fatigue, somnolence, and early morning headaches are symptoms suggestive of long-standing hypercapnia and hypoxaemia due to alveolar hypoventilation. This was reflected in the compensatory metabolic alkalosis which had been noted four years prior to her original episode of ventilatory failure. Both intolerance of the supine posture and paradoxical inward movement of the abdominal wall during inspiration suggested diaphragmatic paralysis despite normal fluoroscopic screening (now considered an unreliable indicator of diaphragmatic weakness). A more sensitive index is the vital capacity measurement supine/erect⁶ and in this patient it was abnormal. We think it unlikely that the gross oedema and the elevated jugular venous pressure were due to right heart failure as there was no electrocardiographic evidence to suggest right ventricular hypertrophy or strain and suggest rather that they were due to an overall increase in extra cellular volume. This can result from hypercapnia and respiratory acidosis diminishing the renal blood flow leading to an excessive fluid and electrolyte retention.⁷

Discussion

Ventilatory insufficiency may occur in any patient with myasthenia gravis. In the early stages, recognition of this state may be delayed because selective affection of the diaphragm and intercostal muscles

can occur even with a normal resting breathing pattern. Arterial blood gases may be normal at rest and mild respiratory distress only occur during exertion.⁶ Before ventilatory failure becomes established, it is important to detect any early decrease in ventilatory reserve. When the vital capacity has fallen to 25% of the predicted value (approx 1.2 to 1.0 l), this suggests that ventilatory failure is imminent. However, even this stage may go unnoticed and the patient suddenly become apnoeic or exhibit such poor voluntary breathing effort as to require respiratory assistance.

Many factors contribute to the development of ventilatory failure—infection, retention of excessive secretions (as a result of inhaled saliva or during a cholinergic crisis) due to an ineffective cough, lung collapse with ventilation/perfusion inequality and alveolar hypoventilation due to respiratory muscle weakness. Plum and Wolff⁸ have emphasised that patients with mild respiratory muscle weakness tend to have a low tidal volume and breathe faster than healthy subjects. This altered pattern of breathing need not be associated with abnormal blood gases and is consistent with a reflex tachypnoea.⁹ Microatelectasis and alteration in alveolar elastic properties are considered to be the main factors determining the increase in breathing rate.¹⁰ This inefficient mode of breathing results in an increase in dead space and a fall in effective ventilation.

The earliest change in blood gases in a patient with incipient ventilatory failure is a fall in arterial PO₂. The arterial PCO₂ may initially be low due to the reflex tachypnoea.⁶ Lung collapse may occur as a result of large and small airway obstruction due to infection and tenacious secretions. This results in the perfusion of underventilated areas of lung. The hypoxaemia then increases and now combined with hypercapnia, they form the hall-

Ventilatory failure in myasthenia gravis

marks of ventilatory failure associated with neuromuscular disease.¹¹ These features are seen particularly in patients with diaphragmatic paralysis.

The importance of the diaphragm as the principal muscle of inspiration is illustrated by patients with bilateral diaphragmatic paralysis whose vital capacity can be reduced to 65% of normal.⁹ Such patients may develop the syndrome of chronic alveolar hypoventilation which proved to be an important factor in two cases. Newsom-Davis and his colleagues¹² have reported a group of patients, including a myasthenic, with diaphragmatic paralysis, several of whom showed alveolar hypoventilation. Hypercapnia and hypoxaemia occurred particularly when the patients were asleep or lying supine. They suggest that this may be due to the gravitational displacement of abdominal contents and the diaphragm into the thoracic cavity. It is of interest that one of the patients in our series who had chronic alveolar hypoventilation felt very breathless when lying supine and preferred to lie propped up with pillows or on her side. Her abnormal vital capacity erect/supine ratio reflected this symptom.

Six of our patients died unexpectedly at night, during sleep, but in two of these patients additional factors may have contributed to ventilatory failure. One patient had chronic bronchitis and the other had a severe myasthenic myopathy with profound bulbar weakness and wasting. In the remaining four cases who died during sleep, the likely cause of death would appear to be ventilatory failure. Fishman, Goldring and Turino¹³ have emphasised that patients with alveolar hypoventilation are particularly dependent on the central neural drive associated with a state of wakefulness. Such patients may benefit from nocturnal assisted ventilation and their daytime arterial gas values may even return to normal, which implies that the pattern of breathing during sleep can influence the level of ventilation during the wakeful state.¹⁴

The classical myasthenic crisis may result from spontaneous acceleration of the disease or the use of drugs causing neuromuscular blockade.¹⁵ Infection, emotional or physical trauma and even excessive rise in body temperature as occurred in one of our patients have all been cited as precipitating causes.

The cholinergic crisis with respiratory muscle weakness due to depolarisation block is usually accompanied by gastrointestinal symptoms and an excess of oropharyngeal secretions. The most valuable clinical muscarinic feature is said to be the size of the pupil which should not be allowed to contract to less than 2 mm.¹⁵ In this series only one case had meiosis at the time of ventilatory failure. We found, as did Voisin,¹⁶ that the peripheral

nicotinic signs of fasciculation and muscular cramps were a rare feature during the state of crisis. Osserman and Genkins⁵ stress that edrophonium should be avoided wherever the possibility of a cholinergic crisis is suspected. A test dose of edrophonium or neostigmine may actually precipitate apnoea as occurred with four patients in our series.

The dramatic decrease in muscle strength with corticotrophin as a result of increase in neuromuscular blockade is a feature unique to myasthenia gravis.¹⁷ It has been suggested that this unwanted action of corticotrophin is due to the acceleration of hydrolysis of acetylcholine by an increase in cholinesterase activity at the neuromuscular junction.¹⁸ However, recent experimental evidence in rabbits with experimental autoimmune myasthenia gravis given corticotrophin suggests the mechanism may be due to enhancement of the immunological response.¹⁹

In humans this decrease in strength usually occurs within the first five days of steroid treatment.¹⁷ Ventilatory failure in our corticotrophin-treated group took place on average at 5.8 days (range 3-10 days).

In our series the best outcome was seen in the younger patients with a hyperplastic thymus where the precipitating cause for ventilatory failure was a cholinergic crisis. The worst result occurred in the older patients with a short history of myasthenia and an atrophic gland. The cause of ventilatory failure in the latter group was usually a myasthenic crisis and the clinical picture was frequently compounded by unrelated pathology.

Voisin and his colleagues¹⁶ have reported a 30% mortality in a study of nine myasthenics with respiratory failure. Figures from this hospital during 1960-1968 show a 70% mortality rate⁵ but the mortality over the following decade as reported in the present series was 36%. If one excludes the two patients with carcinomatosis and the case of systemic lupus erythematosus, then the mortality falls to 26%. This is almost certainly due to an improvement in ventilatory care.

We appreciate that the earlier detection of impending ventilatory failure in our patients could have been aided by the serial monitoring of vital capacity.

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References

- 1 Wilks S. Cases of bulbar paralysis. *Guy's Hosp Rep* 1877;37:(third series) pt. 22, 54.

- ² Sykes MK, McNicholl MW, Campbell EJH. *Respiratory Failure*. 2nd ed. Oxford: Blackwell, 1976:96.
- ³ Osserman KE, Kornfield P, Cohen E, *et al*. Studies in myasthenia gravis: Review of 282 cases at The Mount Sinai Hospital, New York City. *Arch Int Med* 1958;**102**:72.
- ⁴ Ashworth B, Hunter AR. Respiratory failure in myasthenia gravis. *Proc Roy Soc Med* 1971;**64**:489.
- ⁵ Osserman KE, Jenkins G. Critical reappraisal of the use of edrophonium chloride (Tensilon) test in myasthenia gravis and the significance of clinical classification. *Ann NY Acad Sci* 1966;**135**:312.
- ⁶ Newsom-Davis J. The respiratory system in muscular dystrophy. *Br Med J* 1980;**36**:135.
- ⁷ Harris P, Heath D. *The Human Pulmonary Circulation*. 2nd ed. Edinburgh: Churchill Livingstone, 1977:328.
- ⁸ Plum F, Wolff HG. Observations on acute poliomyelitis with respiratory insufficiency. *JAMA* 1951;**146**:442.
- ⁹ Newsom-Davis J, Loh L, Casson M. *Respiratory Centres and afferent systems*. Congress series 1976; **59**:199. Paris: Duron B. ed INSERM.
- ¹⁰ Gibson GJ, Pride NB, Newsom-Davis J, Loh L. Pulmonary mechanics in patients with respiratory muscle weakness. *Am Rev Resp Dis* 1977;**115**:389.
- ¹¹ Crofton J, Douglas A. *Respiratory Diseases*. Oxford: Blackwell, 1969:339.
- ¹² Newsom-Davis J, Goldman M, Loh L, Casson M. Diaphragm function and alveolar hypoventilation. *Q J Med* 1976;**45**:87.
- ¹³ Fishman AP, Goldring RM, Turino GM. General alveolar hypoventilation: a syndrome of respiratory and cardiac failure in patients with normal lungs. *QJ Med* 1966;**35**:261.
- ¹⁴ Loh L, Hughes JMB, Newsom-Davis J. Gas exchange problems in bilateral diaphragm paralysis. *Bull Eur Physiopathol Respir* 1979;**15** (Supp):137.
- ¹⁵ Simpson JA. In: Walton JN, ed. *Disorders of Voluntary Muscle*. 2nd ed. Edinburgh: Churchill Livingstone, 1974:541.
- ¹⁶ Voisin C, Wattel F, Scherpereel PL *et al*. Les accidents respiratoires aigues au cours de la myasthénie et leur traitement. *Lille Méd* 1972;**17**(6):54.
- ¹⁷ Grob D, Namba T. Corticotrophin in generalised myasthenia gravis: effect of short intensive courses. *JAMA* 1966;**198**:703.
- ¹⁸ Namba T, Brunner NG, Shapiro MS, Grob D. Corticotrophin therapy in myasthenia gravis: effects, indications and limitations. *Neurol (Minneapolis)* 1971;**21**:1008.
- ¹⁹ Fuchs S, Bartfield D, Eschav I *et al*. Immune regulation of experimental myasthenia. *J Neurol Neurosurg Psychiatry* 1980;**43**:261.