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Long-term recovery of diaphragm strength in neuralgic amyotrophy

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Long-term recovery of diaphragm strength in neuralgic amyotrophy. P.D. Hughes, M.I. Polkey, J. Moxham, M. Green. ©ERS Journals Ltd 1999.

ABSTRACT: Diaphragm paralysis is a recognized complication of neuralgic amyotrophy that causes severe dyspnoea. Although recovery of strength in the arm muscles, when affected, is common, there are little data on recovery of diaphragm function. This study, therefore, re-assessed diaphragm strength in cases of bilateral diaphragm paralysis due to neuralgic amyotrophy that had previously been diagnosed at the authors institutions.

Fourteen patients were recalled between 2 and 11 yrs after the original diagnosis. Respiratory muscle and diaphragm strength were measured by volitional manoeuvres as maximal inspiratory pressure and sniff transdiaphragmatic pressure. Cervical magnetic phrenic nerve stimulation was used to give a nonvolitional measure of diaphragm strength: twitch transdiaphragmatic pressure.

Only two patients remained severely breathless. Ten of the 14 patients had evidence of some recovery of diaphragm strength, in seven cases to within 50% of the lower limit of normal. The rate of recovery was variable: one patient had some recovery after 2 yrs, and the rest took 3 yrs or more.

In conclusion, in most patients with diaphragm paralysis due to neuralgic amyotrophy, some recovery of the diaphragm strength occurs, but the rate of recovery may be slow.

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Neuralgic amyotrophy is an inflammatory condition of unknown aetiology affecting the brachial plexus that can lead to diaphragm paralysis. When both halves of the diaphragm are involved, dyspnoea can be severe, but the prognosis for improvement in such cases is not clear. When affected, weakness in the arm muscles usually improves [1], but few studies of return of diaphragm function have been conducted. There have been reports of resolution of dyspnoea and radiological improvement [2–5], but in an earlier study by the present authors no recovery of strength was found in patients with bilateral diaphragm paralysis [6]. However, patient recovery was not the main focus of that study, and the follow-up data were limited by the small patient numbers and short duration of follow-up. A larger series of patients with bilateral diaphragm paralysis is presented here, including some from the initial study, examined for long-term recovery of diaphragm strength in order to better define the prognosis of this condition.

Methods

Patients

After approval by an ethics committee, 19 patients with a clinical diagnosis of neuralgic amyotrophy affecting both halves of the diaphragm were identified from the authors clinical records. Fourteen patients could be traced, and all gave consent to further study.

Measurements and manoeuvres

Spirometry was obtained using a wedge bellows spirometer (Vitalograph, Buckinghamshire, UK), and the best of three efforts was used. Lung volumes were determined from whole-body plethysmography (Jaeger, Wurzburg, Germany), using the best of at least two reproducible measurements. Predicted values from the European Respiratory Society were used [7].

Global inspiratory muscle strength and diaphragm strength were assessed by measuring maximum static inspiratory mouth pressure (MIP) and transdiaphragmatic pressure (P_{di}) during maximal sniffs ($P_{di,sn}$) and magnetic phrenic nerve stimulation ($P_{di,tw}$).

MIP was measured from residual volume, while seated and wearing a nose-clip, using a flanged mouthpiece attached to a brass tube with a two-way valve and 2-mm leak to prevent glottic closure [8]. Maximal sniffs were performed from functional residual capacity (FRC) through unoccluded nostrils. For both manoeuvres, maximum effort was encouraged verbally with simultaneous visual feedback from a monitor [9] until no further increase in pressure could be obtained.

Phrenic nerve stimulation was performed using a Magstim 200 HP stimulator (Magstim Co., Whitland, UK) with a circular 90-mm coil (P/N 9784-00) positioned dorsally over the cervical spine [10]. Subjects rested for 20 min

before stimulation to minimize twitch potentiation [11]. After determining the optimum point, stimulations at 100% power output were delivered while the patient relaxed at FRC with the mouth closed. At least three satisfactory twitches were recorded for each subject.

P_{di} was measured using latex balloons passed pernasally and positioned in the oesophagus and stomach. Pressures were measured with Validyne MP-45 transducers (±200 cmH_2O), and Validyne amplifiers (Validyne Corp., Northridge, CA, USA). Signals were passed *via* a 12-bit NB-MIO-16 analogue–digital converter (National Instruments, Austin, TX, USA) to a Macintosh Centris computer (Apple Computers, Cupertino, CA, USA) running LabVIEW™ software (National Instruments) and sampling at 100 Hz. The P_{di} was obtained online by digital subtraction of oesophageal pressure (P_{oes}) from gastric pressure (P_{ga}) and was displayed on a monitor.

MIP was defined as the most negative pressure that could be sustained for 1 s; the best of at least three efforts was taken for analysis. Traces for $P_{di,sn}$ and $P_{di,tw}$ were accepted for analysis if the patient was relaxed at end-expiration at FRC, as determined by P_{oes} and P_{ga} traces and were defined as the height from baseline to peak pressure. The value taken for $P_{di,sn}$ was the greatest obtained after at least three attempts; for $P_{di,tw}$, the mean of at least three twitches was taken. Values recorded for $P_{di,sn}$ and $P_{di,tw}$ were compared with values that had been recorded at diagnosis using identical specification latex balloons, transducers and amplifiers with signal storage either on to computer as above, or on a paper-chart recorder, as was the practice at that time [6].

In the earliest cases $P_{di,tw}$ was elicited using bilateral percutaneous electrical phrenic nerve stimulation. This technique has now been superseded in the authors laboratory by magnetic phrenic nerve stimulation as it is more acceptable to clinical subjects and gives similar results for clinical purposes [12]. As the more recent cases were only familiar with magnetic stimulation, it was elected to study all the patients using this technique rather than revert to electric stimulation. The validity of this choice and its effect on the data will be discussed in more detail.

Analysis

Results of $P_{di,sn}$ and $P_{di,tw}$ were compared with the Wilcoxon matched pairs test (StatView 4.02, Abacus Concepts, CA, USA), accepting $p<0.05$ as statistically significant.

Results

Fourteen male patients with bilateral diaphragm paralysis at presentation were studied. Lung function data and age at the time of initial study are presented in table 1. The median time from onset of symptoms to establishing the diagnosis by respiratory muscle strength testing was 7.5 months (range 3–24 months). The median time from diagnosis to re-assessment was 55 months (range 25–132 months). At diagnosis, all the patients had a very severe diaphragm weakness, with preservation of expiratory muscle strength, as demonstrated by maximum expiratory mouth pressure (MEP) (table 2), except in one case where MEP at diagnosis was not recorded.

Baseline measurements of exercise tolerance were not available from the time of diagnosis, but 12 of the patients reported a subjective improvement in their exercise tolerance and reduction in dyspnoea. One patient had developed hypercapnic ventilatory failure in the intervening period and was found to have primary hypothyroidism in addition to diaphragm weakness. Appropriate thyroid medication and nocturnal nasal intermittent positive pressure ventilation (NIPPV) led to an improvement in blood gases that was maintained after subsequent withdrawal of nasal ventilation. In three subjects complaining of excessive somnolence during the period of review, sleep studies had been performed, leading to diagnoses of obstructive sleep apnoea; all three responded to nasal continuous positive airway pressure (CPAP). None of the remaining patients had any symptoms to suggest current nocturnal hypoventilation or sleep disordered breathing.

Two of the 14 patients had recovery of diaphragm strength to within the normal ranges for $P_{di,tw}$ (>19 cmH_2O) and $P_{di,sn}$ (>100 cmH_2O) [13, 14]. In these two patients,

Table 1. – Lung function data at first presentation

Patient No.	Age yrs	FEV1 % pred	FVC % pred	FEV1/FVC %	TLC % pred	RV % pred	Months to diagnosis
1	44	77	79	80	71	64	3
2	73	48	48	77	60	84	21
3	73	68	64	80	61	64	18
4	58	38	46	66	61	97	6
5	57	67	75	65	90	123	18
6	54	53	60	71	62	67	6
7	59	54	61	70	76	111	6
8	67	61	58	79	56	60	9
9	45	36	38	80	55	94	8
10	50	42	45	75	60	99	5
11	70	67	52	91	n/a	n/a	24
12	72	59	53	85	n/a	n/a	18
13	48	47	49	78	55	73	6
14	63	56	63	69	70	85	7
Mean	59.5	55.0	56.5	76.1	64.8	85.1	11.1
SD	10.4	12.0	11.6	7.3	10.4	8 20.3	7.0

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume.

Table 2. – Respiratory muscle strength at presentation and follow-up

Patient No.	MIP at diagnosis cmH_2O	MEP at diagnosis cmH_2O	MIP at follow-up cmH_2O	$P_{di,sn}$ at diagnosis cmH_2O	$P_{di,sn}$ at follow-up cmH_2O	$P_{di,tw}$ at diagnosis* cmH_2O	$P_{di,tw}$ at follow-up cmH_2O	Symptoms to follow-up months
1	58	210	96	10	111	0	22	75
2	45	150	53	10	57	0	15	86
3	46	105	37	7	8	6	3	76
4	10	115	44	2	32	0	6	54
5	42	222	56	20	40	4	7	150
6	50	238	103	20	107	0	19	58
7	30	117	63	8	89	0	16	64
8	30	n/a	37	33	42	0	5	85
9	27	135	68	10	73	2	17	42
10	19	91	20	6	32	1	14	37
11	23	129	8	16	28	2	3	52
12	18	92	35	3	20	0	3	48
13	41	158	50	13	20	0	3	31
14	20	100	34	0	61	0	9	91
Mean	32.8	143.2	50.3	11.3	51.4	1.1	10.1	67.8
SD	14.3	50.3	26.3	8.7	32.8	1.9	6.8	30.3

*: patients 1–8 and 14 were studied with bilteral electrical phrenic nerve stimulation at diagnosis. MIP: maximal inspiratory mouth pressure; MEP: maximal expiratory mouth pressure; $P_{di,sn}$: sniff transdiaphragmatic pressure; $P_{di,tw}$: transdiaphragmatic pressure.

MIP increased to over 70 cmH_2O, also within the normal range [8] (fig. 1). Another five patients showed recovery of either $P_{di,sn}$ to >50 cmH_2O or $P_{di,tw}$ to >10 cmH_2O. Of the remaining seven patients studied, only four had little or no improvement (patients 3, 11, 12 and 13). Overall, there were statistically significant improvements in diaphragm strength and MIP. The mean $P_{di,sn}$ increased from 11.3 to 51.4 cmH_2O (p=0.001), the mean $P_{di,tw}$ increased from 1.1 to 10.1 cmH_2O (p=0.002), and the mean MIP increased from 32.8 to 50.3 cmH_2O (p=0.012).

Table 3 shows the changes in spirometry and lung volumes. Five subjects showed no improvement in lung function (patients 5, 8, 10, 11, and 12), two of whom also had no recovery of diaphragm strength. The remaining nine subjects all had improvements in spirometry or lung volumes, but there was no clear relationship with the degree of recovery of diaphragm strength.

Figure 2a shows $P_{di,tw}$ plotted against time from onset of symptoms for the 10 subjects in whom recovery was detected. The four subjects with the greatest degree of recovery had similar rates of improvement, as judged from the slope of the line joining the data points, although it is unknown whether recovery follows a linear pattern. Additional data from intermediate assessments was available in four subjects and showed a lag period in recovery in three (fig. 2b), perhaps corresponding to re-innervation of the diaphragm.

Discussion

These data show that a significant recovery from diaphragmatic paralysis due to neuralgic amyotrophy may occur, although not in every case. Overall, the improvement is not as complete as neuralgic amyotrophy affecting the upper limb, where recovery of normal function is usual [1, 3].

An obvious difficulty for follow-up studies is patient selection and availability. An attempt to study as many patients as possible who had previously been diagnosed in the authors hospitals was made. In the last 12 yrs, the authors have diagnosed bilateral diaphragm paralysis due to neuralgic amyotrophy in 19 patients. As with any long-term study, some patients resided beyond reasonable travelling distance or could not be traced. The 14 patients presented in this study are likely to be representative of the authors clinic population. The patient group is the largest studied to date and for the longest follow-up and significantly adds to an earlier study by the authors [6].

Standardized methods and manoeuvres were used for assessing respiratory muscle strength, the only differences between the studies being the method of recording data and for some patients (numbers 1–8 and 14), the use of electrical phrenic nerve stimulation at diagnosis. There was no reason to believe that the data recording equipment would have affected these results as regular calibration and measurement of frequency response has always been performed. The authors elected to use the technique of magnetic phrenic nerve stimulation for follow-up measurements in this study as patients find it less uncomfortable, there is less difficulty in locating the phrenic nerves, and the results are more reproducible. Electrical phrenic nerve stimulation gives slightly lower values for $P_{di,tw}$ than magnetic stimulation because coactivation of upper thoracic muscles with the latter technique causes stiffening of the chest wall [12, 15, 16]. While this is insufficient to produce an inspiratory action in bilateral diaphragm paralysis [16], this effect may slightly overestimate the degree of recovery in those subjects originally studied with electrical stimulation. Conversely, diaphragm weakness at diagnosis may have been overestimated if phrenic nerve location was technically difficult with electrical stimulation. These factors may account for results obtained in patient 8, but the remaining patients had very low values for both $P_{di,tw}$ and $P_{di,sn}$ at diagnosis. By recording $P_{di,sn}$ as well as $P_{di,tw}$ an attempt was made to overcome these issues. Although most of this group of patients were able to perform the sniff manoeuvre without difficulty, measurement of $P_{di,tw}$ provides a nonvolitional assessment of

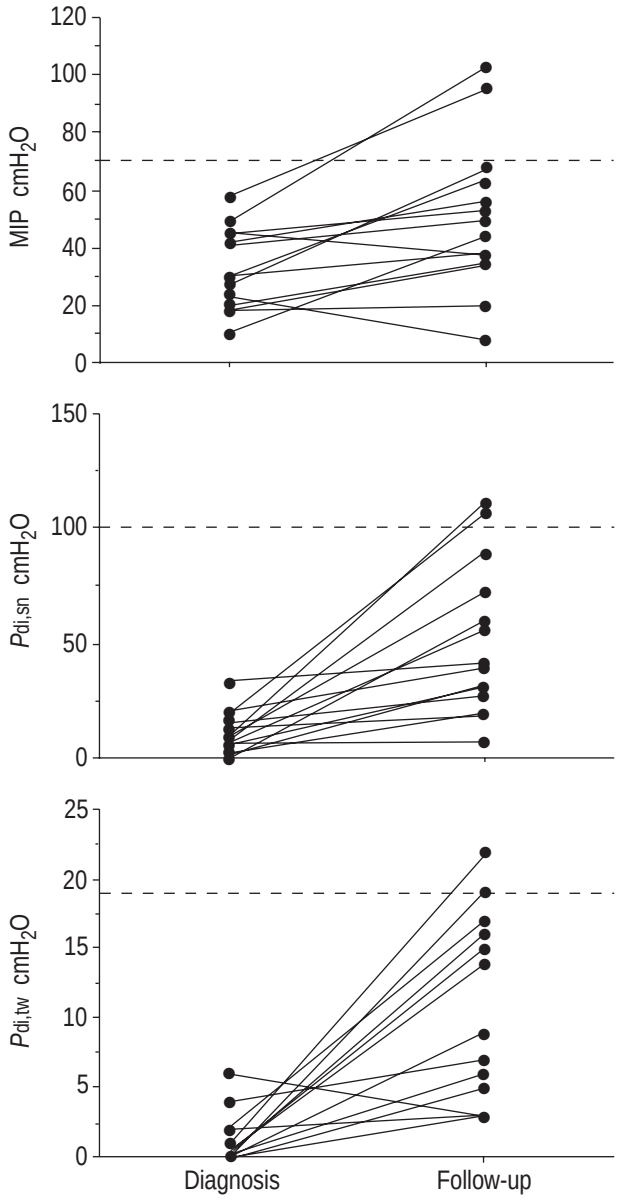

Fig. 1. – Progress of maximal inspiratory mouth pressure (MIP), sniff ($P_{di,sn}$) and twitch ($P_{di,tw}$) transdiaphragmatic pressure from diagnosis to follow-up. – – – –: lower limits of normal values.

diaphragm strength in subjects unable to produce a maximal sniff [14]. The benefit of this dual approach is demonstrated by patients 2 and 10 in whom considerable improvement in $P_{di,tw}$ occurred with a lesser degree of increase in $P_{di,sn}$.

At the time of diagnosis, these patients had a mildly reduced total lung capacity and reasonably preserved residual volume, in keeping with inspiratory muscle weakness [17]. Although the total lung capacity and forced vital capacity increased over the period of study for the group as a whole, there was no clear relationship between these improvements and recovery of diaphragm strength in individual patients. A reduced lung volume occurs in res-piratory muscle weakness due to changes in lung and chest wall elasticity as well as loss of pressure generation

Table 3. – Results of follow-up lung function tests

Patient No.	FEV1	FVC	TLC	RV
1	0.93	0.38	1.6	0.38
2	0.49	0.64	0.3	-0.45
3	-0.5	-0.61	1.03	0.77
4	0.4	0.33	0.98	0.24
5	0.43	-0.06	-0.02	-0.64
6	0.62	0.7	2.19	0.78
7	0.3	0.16	0.77	0.34
8	-0.26	-0.42	-0.27	0.56
9	1.41	1.52	0.91	-0.13
10	-0.03	-0.5	-0.22	0.36
11	-0.4	-0.1	n/a	n/a
12	0.1	0.13	n/a	n/a
13	0.25	0.7	1.11	0.11
14	0.71	1.05	0.45	0.19
Mean	0.3	0.3	0.7	0.2
SD	0.5	0.6	0.7	0.4

Numbers are absolute change from time of diagnosis. Data are presented in litres. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume.

[18]. Although recovery of inspiratory muscle strength might be expected to lead to an improvement in vital capacity, the other effects on respiratory mechanics may explain the lack of direct correlation between changes in diaphragm strength and lung volume. The effect of postural change on vital capacity can be used as an indicator of diaphragm weakness [19]. There was a trend towards a correlation between changes in $P_{di,tw}$ and percentage fall in vital capacity from erect to supine in a subgroup of nine subjects (r=0.62, p=0.07), suggesting that this may indeed be a useful means of follow-up in clinical practice.

Cases of neuralgic amyotrophy with diaphragm paralysis are often overlooked [20], and few are reported in the literature. Several series [3, 21] present data on idiopathic paralysis in which symptomatic improvement is common, although three out of four cases studied by TSAIRIS *et al.* [3] and six out of eight cases reported by RILEY [21] had no fluoroscopic evidence of recovery. Only MULVEY *et al.* [6] have previously reported any recovery of diaphragm strength in this condition [6]; none of the five patients with bilateral diaphragm paralysis studied 2–4 yrs after diagnosis had recovered, although recovery in three out of five cases of unilateral paralysis was observed. The present authors restudied three of their subjects with bilateral paralysis and found a significant recovery in one, but minimal recovery in the remaining two.

The time required for recovery is not clear; return of diaphragm movement, as judged by ultrasound or fluoroscopy, is reported in some cases in <1 yr, but no measurements of pressure generation are available [2, 4]. In the current patients in whom recovery was eventually observed, intermediate assessments after 1 yr showed no evidence of improvement. The shortest time for substantial recovery of strength in these subjects was 3 yrs and 1 month (patient 10), with some evidence of recovery in this patient at 2 yrs (fig. 2). It might be possible to detect early recovery by measurement of phrenic nerve latency, although this would need further study. Recovery by re-innervation of the phrenic nerve (approximate length 500 mm [22]), would be expected to be slow, and therefore some of the

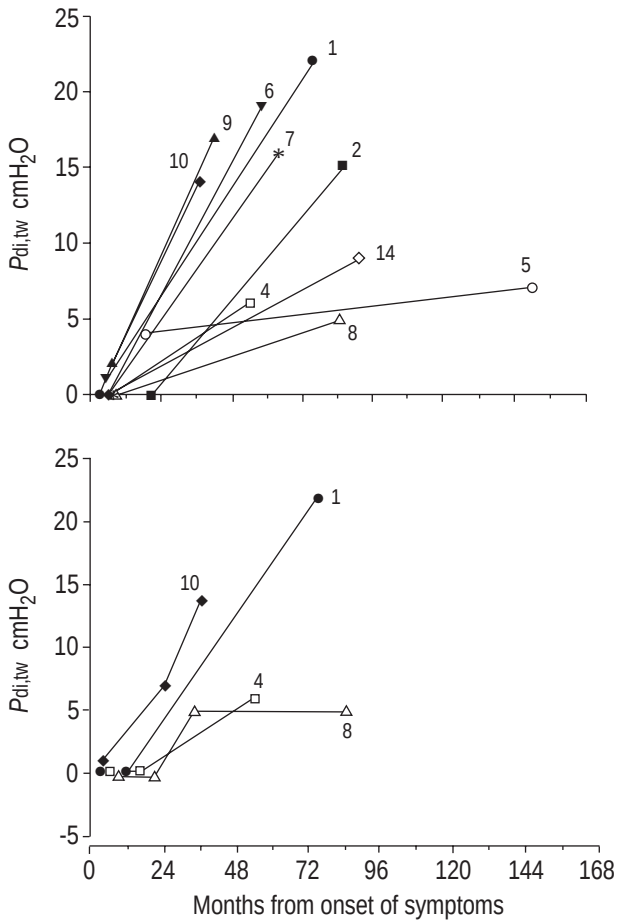

Fig. 2. – a) Recovery of twitch transdiaphragmatic pressure ($P_{di,tw}$) in 10 patients (indicated with numbers) in whom improvement was observed. b) Time course of recovery in patients with additional data from intermediate assessments.

patients may still not have reached a plateau. In upper-limb weakness, TSAIRIS *et al.* [3] noted continuing recovery up to 3 yrs from diagnosis, with a return to normal function in over 90% eventually. In general, the more elderly patients at diagnosis seemed to have the least recovery, but there was insufficient data to confidently support this assertion.

Despite the severe and persistent diaphragm dysfunction of some of these patients, only one subject developed symptoms suggesting nocturnal hypoventilation. A further investigation showed that this subject had developed primary hypothyroidism. The frequency of nocturnal hypoventilation in bilateral diaphragm paralysis remains undetermined. In the authors previous experience [6, 19], nocturnal oxygen desaturation occurred without any significant hypercapnoea. Patients with bilateral diaphragm paralysis in whom nocturnal hypoventilation occurs usually have weakness affecting other respiratory muscles or are overweight [23–25]. A recent study [26] of patients with isolated diaphragm paralysis showed no correlation between static respiratory or sniff P_{di} and nocturnal oxygenation, with varying patterns of central or obstructive hypopnoea among individual patients.

In conclusion, the prognosis for bilateral diaphragm paralysis due to neuralgic amyotrophy is for symptomatic improvement, with some recovery of diaphragm strength in the majority. These findings suggest that surgical plication, recommended by some authorities, should be withheld for at least 2 yrs if neuralgic amyotrophy is suspected as the cause of weakness. A conservative policy seems justified as only one patient, with another recognized cause of muscle weakness [27], developed ventilatory failure. These data suggest that patients with bilateral diaphragm paralysis due to neuralgic amyotrophy can be advised that recovery of diaphragm strength occurs in a significant proportion of patients, but may be delayed.

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