Phrenic neuropathy and diaphragm dysfunction in neuralgic amyotrophy

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Neurology® 2018;91:e843-e849. doi:10.1212/WNL.0000000000006076

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Abstract

Objective
To describe the clinical phenotype and recovery of diaphragm dysfunction caused by neuralgic amyotrophy in a large cohort of patients, to improve accurate awareness of this entity, and to encourage adoption of a standardized approach for diagnosis and treatment.

Methods
This observational cohort study recruited adult patients with neuralgic amyotrophy and symptoms of idiopathic phrenic neuropathy from the database of the Dutch expert center for neuralgic amyotrophy and the Dutch centers for home mechanical ventilation. Demographic and clinical information on diagnosis, symptoms, and recovery was obtained from chart review. We attempted to contact all patients for a follow-up interview.

Results
Phrenic neuropathy occurs in 7.6% of patients with neuralgic amyotrophy. Unilateral diaphragmatic dysfunction and bilateral diaphragmatic dysfunction are frequently symptomatic, causing exertional dyspnea, orthopnea, disturbed sleep, and excessive fatigue. Diagnostic practices varied widely and were often not optimally targeted. The majority of patients experienced at least moderate recovery within 2 years.

Conclusion
We recommend screening every patient with neuralgic amyotrophy for diaphragm dysfunction by asking about orthopnea and by performing upright and supine vital capacity screening and diaphragm ultrasound in cases of suspected phrenic neuropathy to optimize diagnosis and care.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Diaphragm dysfunction can arise from a various etiologies. When no underlying cause is found, phrenic neuropathy can be classified as idiopathic or as a subform of neuralgic amyotrophy. Two large case series reported unilateral or bilateral phrenic neuropathy in ≈7% of patients with neuralgic amyotrophy.

The most prominent symptoms of diaphragm dysfunction are orthopnea, exertional dyspnea, and dyspnea during water immersion. Diaphragm dysfunction can be confirmed by pulmonary function tests, diaphragm EMG, and trans-diaphragmatic pressure measurements. Imaging modalities for diaphragm dysfunction include chest x-ray, fluoroscopy, and diaphragm ultrasound. Treatment consists of supportive measures (sleeping in a semirecumbent position), nocturnal noninvasive positive pressure ventilation (NIV), or surgical plication of the diaphragm.

Patients with neuralgic amyotrophy with phrenic neuropathy are considered to be rare. Recently, however, the incidence of neuralgic amyotrophy was found to be 1 per 1,000 per year. With ≈7% of patients with neuralgic amyotrophy having phrenic neuropathy, this entity is probably also not as uncommon. However, our clinical experience is that the diagnosis of diaphragm dysfunction in neuralgic amyotrophy is not often considered by physicians, and many patients go undiagnosed for long periods of time. Diagnostic approaches also seem to vary widely, as does treatment.

The aim of this observational study was to report the clinical phenotype, recovery tendency, and diagnostic practice variations in a large cohort of patients with neuralgic amyotrophy with diaphragm dysfunction. Our goal is to improve awareness of this entity and to encourage adoption of a standardized approach for diagnosis and treatment to optimally serve patients’ needs.

Methods

Study design

This was an observational cohort study from June 1, 2012, to December 1, 2016. Patients were recruited either directly from a multidisciplinary tertiary referral outpatient clinic (Radboud University Medical Center of expertise for neuralgic amyotrophy) or via referral from 1 of the 4 home mechanical ventilation centers in the Netherlands. In addition, all patients with neuralgic amyotrophy already registered before 2012 in the local neuromuscular database (1,347 patients as of December 1, 2016) were included if they met the inclusion criteria outlined below.

Standard protocol approvals, registrations, and patient consents

The institutional ethics committee approved the study design, and informed consent was waived because the chart review method was used for data collection. For the follow-up part of the study, patients were contacted by their own caregiver by telephone and were required to provide their oral consent before further data were collected.

Study population

Eligible patients had to be ≥18 years of age and diagnosed with neuralgic amyotrophy, with clinical evidence of diaphragm dysfunction based on symptoms of orthopnea at any time during the course of their neuralgic amyotrophy attack. Neuralgic amyotrophy was diagnosed in patients who fit the clinical presentation of the disorder as described previously. The diagnosis of diaphragm dysfunction was supported by additional symptoms of exertional dyspnea, a paradoxical breathing pattern on clinical examination, and laboratory tests such as vital capacity (VC) decrease of >500 mL or 10% of the predicted value upright or supine; a 10% (for unilateral paresis) to 30% (for bilateral paresis) decrease in VC from upright to supine; a >30% reduction in maximum static inspiratory pressure (MIP); an elevated hemidiaphragm on chest x-ray or CT; paradoxical movement or paralysis on fluoroscopy; or abnormal diaphragm diameter or thickening ratio on ultrasound when available. Patients were excluded if another cause for the phrenic neuropathy was identified, if they were known to have clinically significant respiratory symptoms before their neuralgic amyotrophy attack (e.g., because of severe chronic obstructive pulmonary disorder [COPD] or other pulmonary pathology), or if they had a severe (life-threatening) comorbidity such as cardiac failure or end-stage malignancy.

Data collection

Demographic information collected included age at onset, sex, type of neuralgic amyotrophy (idiopathic or hereditary), history of smoking, COPD or other pulmonary disorder, and general medical history. The side of the affected phrenic nerve(s), concomitant brachial or lumbosacral plexus palsy, and typical symptoms such as orthopnea, exertional dyspnea, sleep disturbances, and paradoxical breathing were noted when available. Time from symptom onset to diagnosis of diaphragm dysfunction due to phrenic neuropathy was calculated. Results of available pulmonary function tests, imaging (x-ray, CT, MRI, ultrasound), phrenic nerve conduction studies, and needle EMG were collected. Pulmonary function tests were not included if an appropriate reference value was not provided or could not be calculated from available anthropometric parameters. The proportion of patients referred

Glossary

COPD = chronic obstructive pulmonary disorder; MIP = maximum static inspiratory pressure; NIV = noninvasive positive pressure ventilation; VC = vital capacity.
to a center for home mechanical ventilation, started on NIV, or referred for diaphragmatic surgery was also recorded.

Additional outcome data were collected via a structured telephone interview reporting current respiratory symptoms, degree of spontaneous improvement, and functional limitations in daily activity. Attempts were made to contact all study patients. Recovery was defined as good when all symptoms of diaphragm dysfunction had disappeared, and some recovery meant an improvement without complete symptom resolution.

Statistical analysis
Data were analyzed and descriptive statistics were performed with IBM SPSS statistics (IBM SPSS Statistics for Windows, version 22.0, 2013; Armonk, NY). Values are presented as percentage of the group and median (range). We used the independent t test (numeric data) and $\chi^2$ test (nominal and ordinal data) to assess differences between bilateral and unilateral affected patients with neuralgic amyotrophy. Statistical significance was defined as $p < 0.05$.

Data availability
The anonymized data of this study will be available for sharing from the first author on request for purposes of replicating procedures and results.

Results
Clinical phenotype
One hundred two patients with neuralgic amyotrophy (24% female) with diaphragm dysfunction were identified; 61 (60%) were in the local neuromuscular database at the start of the study, and 41 (40%) were prospectively included during the 4-year study period. The calculated frequency of phrenic neuropathy in our neuralgic amyotrophy population was 7.6% (102 of 1,347 known patients with neuralgic amyotrophy). We also identified a further 12 patients with idiopathic phrenic neuropathy (11 male, median age 56 [29–83] years) without evidence of neuralgic amyotrophy, i.e., without brachial or lumbosacral plexus involvement. Although these patients may represent an isolated subform of neuralgic amyotrophy with only phrenic nerve involvement, they were not included in this study.

The median age at onset was 50 years; the male-to-female ratio was 3:1. Fifty-six percent had unilateral phrenic nerve involvement; 28% had bilateral involvement; in 16%, the site of phrenic nerve involvement was not determined initially and could not be determined afterward. All patients had brachial plexus involvement, and 23% also had lumbosacral plexus involvement. Thirteen percent of the patients had a positive family history of neuralgic amyotrophy (i.e., hereditary neuralgic amyotrophy). There was no difference in onset age or sex distribution between patients with unilateral and those with bilateral diaphragm dysfunction, but patients with hereditary neuralgic amyotrophy had bilateral involvement significantly more often ($p = 0.010$). Right-sided phrenic neuropathy occurred more frequently ipsilateral to right-sided brachial plexus involvement (75%) compared to left-sided phrenic neuropathy and ipsilateral plexopathy (52%). Bilateral phrenic neuropathy occurred most often with bilateral (52%) brachial plexus involvement. The median time needed to diagnose diaphragm dysfunction was 20 weeks for the whole cohort, with a large range from 0 to 114 weeks. Patients with bilateral dysfunction had a tendency to be diagnosed earlier than those with unilateral dysfunction (median delay, 8 [range 0–60] vs 13 [range 0–114] weeks, respectively, $p = 0.064$); the delay to diagnosis for patients in whom the side was unknown was also long (median 28 [range 0–73] weeks).

The most frequently reported symptoms that were still present at the time of presentation to our clinic were persisting exertional dyspnea (91%), sleep disturbance (89%), orthopnea (88%), and excessive daytime fatigue (85%). Paradoxic breathing on physical examination was found in 22%. Only 2 patients, both with unilateral phrenic neuropathy, reported no ongoing complaints during their first visit to our center. All symptoms were reported with similar frequency in both unilateral and bilateral phrenic nerve involvement except for orthopnea, which was more frequent in bilateral (97%) than in unilateral (72%) phrenic neuropathy ($p = 0.006$).

Diagnostic testing
A variety of ancillary investigations had been used to augment the clinical assessments (table 1). The number of patients fulfilling the different criteria for abnormal pulmonary function tests indicating diaphragm dysfunction is shown in table 2. The frequency of an abnormal VC tended to be higher in the supine than in the upright position for both volume criteria and percentage drop: 93% vs 78%, respectively ($p = 0.085$), for >500-mL volume decrease and 98% vs 79%, respectively ($p = 0.084$), for a >10% drop. The calculation of the percentage difference between upright and supine VC measurements did not increase diagnostic sensitivity for diaphragm dysfunction overall. However, a difference of >30% between upright and supine VC was found more frequently in patients with bilateral phrenic neuropathy, although the numbers were small. The MIP was abnormal all but 1 patient tested but did not differ between bilateral or unilateral involvement.

A large proportion of the patients, 33 of 46 (72%), fulfilled the criteria for an abnormal upright-supine VC difference of 10% to 30%, indicative of unilateral diaphragm weakness; of this group, 8 patients (24%) actually had bilateral phrenic
neuropathy. Only 7 of 46 patients (15%) met the criteria for an abnormal upright-supine VC difference of >30% indicative of bilateral diaphragm weakness, of whom 2 patients (13%) actually had only unilateral phrenic neuropathy.

**Treatment**

Fifty-six of 94 (60%) patients were referred to a center for home mechanical ventilation, and 35 of them (63% of those referred) actually started with NIV. Patients with bilateral phrenic neuropathy tended to be more often referred to a center for home mechanical ventilation (79% vs 53% with unilateral involvement, \( p = 0.006 \)), and NIV was started significantly more often in that setting (78% vs 53%, respectively, \( p = 0.004 \)). Thirteen of 35 patients (37%) reported mask-fitting problems, resulting in 3 patients being unable to comply with the NIV. A positive effect of NIV was reported in 69% of patients, with no clear differences in effect between unilateral and bilateral phrenic neuropathy (\( p = 0.941 \)). Plication surgery of the diaphragm was considered in 19 patients in total but was performed in only 7 patients; the reported results were variable, ranging from no effect at all to fewer respiratory complaints but still needing NIV to no respiratory complaints anymore.

**Recovery**

Information on overall recovery as estimated by the patient or caregiver was available from a review of the medical records for 79 patients (77%) with an average follow-up duration of 1.6 years (median 1.2 years, range 6 weeks–13.3 years) and 2 outliers with a follow-up of 20.5 and 21 years. We were able to contact 80 of 102 patients, 36 of whom were willing to participate in a more extensive structured follow-up telephone interview (45% response rate). We were unable to trace the other 22 patients because of a lack of available accurate contact

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**Table 1** Ancillary investigations of diaphragm function

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage of total</th>
<th>Abnormal result, % patients tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function test</td>
<td>89 (83/93)</td>
<td>87</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>79 (65/82)</td>
<td>89</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>53 (36/68)</td>
<td>81</td>
</tr>
<tr>
<td>Chest CT</td>
<td>66 (21/32)</td>
<td>52</td>
</tr>
<tr>
<td>Phrenic nerve NCS</td>
<td>22 (15/69)</td>
<td>33</td>
</tr>
<tr>
<td>Diaphragm ultrasound</td>
<td>29 (19/65)</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviation: NCS = bilateral phrenic nerve conduction studies.

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**Table 2** Pulmonary function test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage of total</th>
<th>Phrenic neuropathy</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC upright done</td>
<td>75 (70/93)</td>
<td>Unilateral</td>
<td></td>
</tr>
<tr>
<td>( &gt;500 \text{-mL decrease} )</td>
<td>78 (49/63)</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>( &gt;10% \text{ decrease} )</td>
<td>79 (55/70)</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>VC supine done</td>
<td>53 (49/93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &gt;500 \text{-mL decrease} )</td>
<td>93 (40/43)</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>( &gt;10% \text{ decrease} )</td>
<td>98 (48/49)</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>VC upright-supine done</td>
<td>49 (46/93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%–30% difference</td>
<td>72 (33/46)</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>&gt;30% difference</td>
<td>15 (7/46)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>MIP done</td>
<td>15 (14/93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP &gt;30% decrease</td>
<td>93 (13/14)</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: MIP = maximal inspiratory pressure of the norm; VC = vital capacity of the predicted value.

Percentage of total (number of patients/number of patients with available data). Values for VC and MIP represent median (range). The \( p \) values indicate the statistical difference between unilateral and bilateral phrenic neuropathy.

\( ^* \) Compared to the predicted value.
information. The average follow-up for these 36 patients was 5.2 years (median 4.0, range 1.1–17.6 years). Details of the estimated recovery percentage and residual complaints can be found in table 3. The overall self-rated recovery proportions were comparable to the data available from medical chart review. Persistent complaints were frequent. More than half of the patients were still under supervision of a center for home mechanical ventilation, and 10 patients still used NIV, more often in bilateral than unilateral phrenic neuropathy (p = 0.040).

## Discussion

This observational cohort study reports findings from 102 patients with neuralgic amyotrophy and concomitant diaphragm dysfunction, which makes it the largest cohort in the literature to date and provides much-needed information on symptoms, diagnostic testing, and prognosis. Our most important findings are that (1) 7.6% of the patients with neuralgic amyotrophy in our population have phrenic nerve involvement, (2) both unilateral diaphragm dysfunction and bilateral diaphragm dysfunction cause symptoms, (3) the diagnostic approach is not uniform and generally takes a long time, and (4) a large proportion of the patients show at least a moderate recovery.

Similar to neuralgic amyotrophy itself, we believe that diaphragm dysfunction in the context of neuralgic amyotrophy is underrecognized by physicians. For instance, Tsao et al. identified 33 patients with phrenic neuropathy and after further neurologic examination found that 40% also met criteria for neuralgic amyotrophy of the brachial plexus. It is therefore recommended that clinicians screen patients with idiopathic phrenic neuropathy for additional neurologic symptoms (specifically scapular weakness or dyskinesia), and vice versa, because those conditions need specific guidance and treatment.

Compared to other large cohort studies of patients with neuralgic amyotrophy in general, the current cohort had a higher male-to-female ratio of 4:1 (vs 3:2 reported previously), and patients were on average 10 years older at onset (50 vs 41 years for neuralgic amyotrophy in general), which is similar to previous smaller case series on phrenic neuropathy in neuralgic amyotrophy. A relatively large proportion of the current patients also had lumbosacral plexus involvement during the neuralgic amyotrophy episode with phrenic neuropathy, which might be due to an increase in hepatitis E virus–related cases of neuralgic amyotrophy in Europe, who often show a more extensive clinical phenotype.

The proportion of patients with unilateral diaphragm dysfunction was much higher in the current cohort (56%) than in previous studies that reported bilateral phrenic neuropathy much more frequently. In addition, the median time to diagnose phrenic nerve involvement in our cohort was 20 weeks, with a tendency for patients with bilateral diaphragm dysfunction to be diagnosed earlier than patients

## Table 3 Recovery and persistent symptoms on final follow-up

<table>
<thead>
<tr>
<th>Patients with known outcome</th>
<th>Percentage of total</th>
<th>Phrenic neuropathy, n</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Unknown</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery (self-rated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24 (19/79)</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some</td>
<td>44 (35/79)</td>
<td>22</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>32 (25/79)</td>
<td>11</td>
<td>4</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional telephone follow-up available</td>
<td>35 (36/102)</td>
<td>21</td>
<td>11</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage recovery (self-rated), %</td>
<td>30 (0–100)</td>
<td>20 (0–95)</td>
<td>30 (0–100)</td>
<td>87 (50–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopnea</td>
<td>69 (25/36)</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td></td>
<td>0.115</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exertional</td>
<td>83 (30/36)</td>
<td>17</td>
<td>9</td>
<td>4</td>
<td></td>
<td>0.952</td>
</tr>
<tr>
<td>On stooping</td>
<td>61 (22/36)</td>
<td>16</td>
<td>6</td>
<td></td>
<td></td>
<td>0.210</td>
</tr>
<tr>
<td>Water immersion</td>
<td>39 (14/36)</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td></td>
<td>0.722</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>31 (11/36)</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td></td>
<td>0.725</td>
</tr>
<tr>
<td>CHMV referral</td>
<td>56 (20/36)</td>
<td>11</td>
<td>8</td>
<td>1</td>
<td></td>
<td>0.266</td>
</tr>
<tr>
<td>Nighttime NIV</td>
<td>28 (10/36)</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
<td>0.040</td>
</tr>
</tbody>
</table>

Abbreviations: CMHV = center for home mechanical ventilation; NIV = nocturnal non-invasive positive pressure ventilation. Percentage of total (number of patients/number of patients with available data). Values for percentage recovery (self-rated) represent median (range).
unilateral weakness. Both findings might be due to the severity of the initial symptoms in patients with bilateral affection, but our cross-sectional study did not provide specific information about this initial phase. It did show that at the time of presentation to our tertiary referral clinic, both patients with unilateral and patients with bilateral phrenic neuropathy report a significant, and similar, proportion of symptoms such as exertional dyspnea, sleep disturbance, and excessive daytime fatigue. Only orthopnea was found to be statistically more frequent in patients with bilateral phrenic neuropathy (97%) than in patients with unilateral neuropathy (72%). These results are comparable to other, smaller, case series of phrenic neuropathy in neuralgic amyotrophy but contrast strongly with previous literature on diaphragm dysfunction in general that suggests that the majority of patients with unilateral involvement are asymptomatic or only experience dyspnea on exertion, while patients with bilateral phrenic neuropathy have severe respiratory impairment. Because no studies have prospectively looked at signs of diaphragm dysfunction in all patients with neuralgic amyotrophy, either with or without symptoms, we currently do not know how often phrenic neuropathy occurs in neuralgic amyotrophy without clinical diaphragm dysfunction.

This study confirms the impression that there currently is no uniform way of diagnosing phrenic neuropathy in neuralgic amyotrophy, and the clinical evaluation and ancillary laboratory investigations used varied widely. A >10% or >500-mL VC decrease from upright to supine and a >30% reduction in the MIP value from the reference are the tests most often found to be abnormal in this group, suggesting they may be the most sensitive for the diagnosis. In contrast, conventional chest x-ray and upright pulmonary function testing were used most frequently in this group, even though these tests have a known suboptimal sensitivity and specificity for detecting diaphragm dysfunction. Currently, the most sensitive ancillary test for phrenic neuropathy besides pulmonary function testing is probably quantified diaphragm ultrasound, but this was performed in only a minority of cases (30%, all at our referral center), suggesting that the technique is not yet widely implemented in practice.

Treatment of diaphragm dysfunction due to phrenic neuropathy primarily consists of supportive measures, but NIV is indicated when the patient shows signs of nighttime hyperventilation, orthopnea, or severe sleep deprivation because of REM sleep-related awakenings. About half of the patients in this cohort were referred to 1 of the 4 centers for home mechanical ventilation in the Netherlands, and the majority experienced a positive effect of this treatment. Fortunately, the majority of our patients showed at least some spontaneous recovery within 2 years, but the rate of persistent complaints was high. Overall, recovery in our group seems comparable to or possibly slightly better than previously reported outcomes. In cases with little to no recovery, surgical plication of the diaphragm may improve dyspnea by reducing dysfunctional hemidiaphragm excursion during inspiration.

However, in patients with different neuromuscular disorders causing diaphragm weakness, the benefits of plication are modest at best, and the outcomes in our cohort were in line with that finding. From our study results we recommend screening every patient with neuralgic amyotrophy for diaphragm dysfunction by asking specifically about orthopnea, assessing phrenic nerve function by both upright and supine VC measurements, and including diagnostic diaphragm ultrasound to confirm or exclude phrenic neuropathy. Conversely, we recommend screening all patients diagnosed with phrenic neuropathy of unknown cause for signs and symptoms of brachial plexopathy to optimize treatment and care in both groups.

Author contributions
Nens van Alfen designed the study; collected, analyzed, and interpreted the data; and drafted the paper. Jonne Doorzuin co-designed the study, analyzed the data, and critically revised the draft for intellectual content. Marieke van RosmaLEN collected data and critically revised the draft for intellectual content. Jeroen van Eijk and Yvonne Heijdra contributed data and critically revised the draft for intellectual content. Andrea Boon critically revised the draft for intellectual content and language. Michael GaytAnt, Ries van den Biggelaar, and Roy Sprooten contributed data and critically revised the draft for intellectual content. Peter Wijkstra codesigned the study, interpreted the data, and critically revised the draft for intellectual content. Jan Groothuis designed the study; collected, analyzed, and interpreted the data; and drafted the paper. All authors agree to be accountable for all aspects of the work, and all approved the final version of the manuscript.

Study funding
No targeted funding reported.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received November 27, 2017. Accepted in final form May 25, 2018.

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Phrenic neuropathy and diaphragm dysfunction in neuralgic amyotrophy
Nens van Alfen, Jonne Doorduin, Marieke H.J. van Rosmalen, et al.
Neurology 2018;91:e843-e849 Published Online before print July 27, 2018
DOI 10.1212/WNL.0000000000006076

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