Sleep-Disordered Breathing in Neuromuscular Disease with Diaphragm Paralysis Questionnaire

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Abstract

Background Patients with neuromuscular disease (NMD) are at risk of developing sleep-disordered breathing (SDB) following respiratory muscle involvement. We hypothesised that a questionnaire based on clinical symptoms and signs of diaphragm weakness can be used to screen for SDB in such patients.

Patients&Methods We developed a self-administered multiple choice questionnaire containing five questions (SiNQ-5), scoring 0-10 points. 125 patients were enrolled, 32 with respiratory muscle weakness, 35 subjects with normal respiratory muscle strength, and 58 patients with obstructive sleep apnoea (OSA). All subjects underwent full polysomnography.

Results NMD patients with involvement of the respiratory muscles scored 6.8(2.3) out of 10 points, significantly higher than both OSA patients (2.5(2.3)) and normal subjects (1.0(2.0), p<0.001). A score of five or more points in the SiNQ-5 had a sensitivity of 86.2%, specificity of 88.5%, positive predictive value of 69.4%, and a negative predictive value of 95.5% to identify NMD with combined SDB.

Conclusion A short self-administered questionnaire, the SiNQ-5, based on clinical symptoms can reliably screen for SDB in patients with diaphragm weakness. However, comorbidities, such as heart failure, that have symptoms influenced by posture could alter diagnostic accuracy.
Introduction

Sleep-disordered breathing (SDB) has substantial impact on public health. [1-4] Whilst the majority of patients have obstructive sleep apnoea, [4, 5] other causes of SDB may similarly cause health problems. [6-12] Of relevance for this study is the group of patients with neuromuscular disease (NMD) who are affected by sleep-disordered breathing because of weakness of the respiratory muscles [9, 13-18] influenced by posture and sleep stage [9, 19] and who do not necessarily present with symptoms, such as daytime fatigue, that are measured by the Epworth Sleepiness scale. [20]

The ‘Gold standard’ for the detection of ventilatory sleep-disorders is polysomnography. [21, 22] However, it is costly and not always immediately available. Therefore, less expensive techniques for domiciliary diagnosis, based predominantly on the registration of flow and detection of respiratory effort, have already been developed to screen for SDB.

The question arises as to whether nocturnal ventilatory problems could be identified by screening questionnaires. The Epworth Sleepiness Scale (ESS) has been validated in patients with obstructive sleep apnoea (OSA) [20] and is widely used in sleep laboratories. A comparable tool is not available specifically for patients with NMD. Polysomnography could be selectively offered to those more at risk and treatment, including nocturnal non-invasive ventilation in patients with NMD could be made available more quickly.
Therefore, we hypothesised that NMD patients with sleep-disordered breathing could be identified using a symptom based questionnaire.

**Methods**

*Development of the questionnaire*

The concept of this questionnaire was derived from physiological observations in patients with respiratory muscle weakness. Diaphragm weakness is associated with unfavourable mechanical changes [23] associated with posture. [9, 24, 25] Patients with diaphragm paralysis develop breathlessness with immersion in water. [26] The greater the fall in vital capacity when supine the more likely it is that patients develop SDB. [25]

A useful questionnaire should fulfill several requirements. First it should include symptoms that respiratory clinicians consider to be important for assessing neuromuscular patients with diaphragm involvement in particular it should include items which capture the impact of gravity on the diaphragm and abdominal contents. Second it should be applicable to as many adults with neuromuscular disease as possible. Thirdly it should be reliable and reproducible in a stable state of the disease, and discriminate between patients with different levels of diaphragm weakness. Fourthly it should be valid to actually measure sleep-disordered breathing and lastly it should be short and easy both to complete and analyse.

*Item generation phase*

Our research group created a list of symptoms asked for by clinicians to assess patients in clinics with neuromuscular disease, from peer-reviewed articles and
international guidelines, [9,10,23-26] reviewing evidence-based literature and guidelines to develop clinical questionnaires, [35,36] and talking to respiratory consultants, specialist nurses and physiotherapists active in teaching hospitals with large respiratory centres. Respiratory physicians, physiologists and specialist physiotherapists from the participating centres were then involved in selecting appropriate and most commonly used questions to assess symptoms. Altogether, 34 respiratory physicians and specialists were involved in the item reduction phase. All of the hospitals involved are amongst the largest tertiary referral centres for neuromuscular patients in their regions and have established respiratory muscle, physiology and sleep laboratories attached to their facilities. The respiratory muscle laboratory at King’s College Hospital London and the Royal Brompton Hospital have experience with neuromuscular patients over more than three decades with full evaluation of several hundreds of patients. [9,25,27,31]

The resulting self-administered questionnaire (Table 1) is focused on symptoms associated with breathlessness likely to be caused by inspiratory, and particularly diaphragmatic muscle weakness. Subjects were asked to circle the answer to each question, which will be rated as 0 (« no »), 1 (« sometimes ») or 2 (« yes ») points. The answers from each question were converted into numbers yielded a final score between 0 and 10 points for the questionnaire.

_Evaluation_

The study was approved by King’s College Hospital local research ethics committee and informed consent was obtained by each participant. Patients came to the hospital in the early evening (18.00-20.00h). Age, height, weight and gender were recorded.
The SiNQ-5 (Table 1), was filled in by the patient, without assistance, in a quiet room.

In addition, the Epworth Sleepiness Scale (ESS) was measured. [20]

The patients were grouped into the following subgroups:

1) Patients with respiratory muscle weakness.
2) Patients with obstructive sleep apnoea.
3) Healthy control subjects.

**Group 1** These patients were recruited from the respiratory muscle laboratory at King’s College Hospital. They underwent respiratory muscle testing according to the ATS/ERS joint statement on respiratory muscle testing. [27] This included volitional (sniff manoeuvres) and non-volitional (phrenic nerve stimulation) tests of inspiratory muscle strength, as well as expiratory muscle strength (PEmax). For this purpose, the patients had an oesophageal, filled with 0.5ml of air, and a gastric balloon catheter (Coopersurgical, Trumbull, CT, USA), filled with 2.0ml of air, inserted via one nostril. Correct positioning was confirmed as described by Baydur et al. [28] Twitch transdiaphragmatic pressure was measured seated, at functional residual capacity, wearing a nose clip, after unilateral (UAMPS) and bilateral anterolateral magnetic phrenic nerve stimulation (BAMPS), [29, 30] using 48mm figure-of-eight coils connected to a magnetic stimulator (Magstim 200, Magstim Co, Wales, UK).

All of the patients in this group had inspiratory muscle weakness. Diaphragm weakness was defined as a sniff Pdi of less than 100cmH₂O for males and less than 70cmH₂O for females and, additionally, a twitch Pdi for both genders below
18cmH₂O, as previously described. [31] 29 patients of this group also had significant sleep-disordered breathing with a respiratory disturbance index (RDI) >5h.

**Group 2)** Healthy control subjects were recruited from hospital staff, their family members and friends and those patients investigated in the sleep laboratory who did not have sleep-disordered breathing and were otherwise well. None of the subjects had a history of NMD or lung disease, all subjects had normal pulmonary function and respiratory muscle test results that excluded respiratory muscle weakness. [31]

**Group 3)** Patients with obstructive sleep apnoea (OSA) were recruited after the diagnosis had been confirmed by polysomnography in symptomatic patients, or typical pulse oximetry traces. Diagnosis of OSA was then confirmed with a polysomnography. Of this group, 33 individuals had volitional respiratory muscle tests.

**Polysomnography**

All patients underwent full polysomnography using either Alice 3 or Alice 5 equipment (Respironics, USA). Polysomnography was scored according to international guidelines. [22] Apnoea was defined as zero flow for >10s, hypopnoea was scored as decrease from baseline of more than 50% for over 10s. An event was scored as central if no inspiratory effort was detected using thoracic or abdominal plethysmography, otherwise it was scored as obstructive.

**Statistics**
Following testing for normality the scores of the questionnaire were analysed using independent t-test between groups. In addition, a linear regression analysis was performed entering variables into a forward model to establish independent predictors of neuromuscular disease combined with sleep-disordered breathing. Cross tabulation of SiNQ-5 test results was used to calculate sensitivity, specificity, positive and negative predictive value as well as the odds ratio. A receiver-operating-characteristics (ROC) curve was created and the area under the curve (AUC) calculated. A p-value of less than 0.05 was considered significant. [32]

**Results**

There were three groups in this study, I) patients who were identified by comprehensive respiratory muscle tests as having respiratory muscle weakness, II) healthy subjects with normal respiratory muscle strength, and III) patients with obstructive sleep apnoea. (Table 2+3)

The group of neuromuscular patients had diminished strength, as measured by volitional sniff tests, and marked weakness in nonvolitional twitch tests of respiratory muscle strength. Eleven of the NMD patients had unilateral diaphragm weakness or paralysis, six had bilateral diaphragm paralysis and the remaining had global non-lateralised diaphragmatic weakness. An average pressure of 3.4 (1.9) cmH\textsubscript{2}O in the unilateral transdiaphragmatic twitch pressure reveals the severity of the overall weakness in this population. The healthy subjects and patients with obstructive sleep apnoea had normal strength of the inspiratory muscles. [31] (Table 4)
Compared to neuromuscular patients, healthy subjects and patients with OSA slept longer, including longer REM-sleep. All groups had similar sleep efficiency. Normal subjects had an RDI below 5/h, neuromuscular patients had moderately elevated RDI, with a wide standard deviation, and OSA patients had the highest RDI. (Table 5)

With a cutoff of five or more points in the SiNQ-5 score there was a sensitivity of 86.2%, a specificity of 88.5% to identify sleep-disordered breathing in neuromuscular patients. Calculated from the cross tabulation below we calculated a positive predictive value of 69.4.0% and a negative predictive value of 95.5%. (Table 6+7)

The ROC-curve identified a larger AUC of 0.901 (SE 0.040, 95% CI 0.822-0.979) for the SiNQ-5 than for the ESS (AUC 0.684, SE 0.052, 95% CI 0.582-0.787) to detect SDB in patients with NMD. (Figure 1)

A linear regression analysis revealed that a SiNQ-5 score of five or more points was the only significant independent predictor to determine sleep-disordered breathing in neuromuscular patients (p=0.001), whilst entering age (p=0.709), sex (p=0.298), BMI (p=0.703), ESS score (p=0.468) and diaphragmatic strength (Twitch PDI, bilateral; p=0.523) did not reach significance. The resulting model accounted for approximately 60% of the cases of neuromuscular disease and sleep-disordered breathing ($R^2=0.638$, adjusted $R^2=0.581$, SE of the estimate=0.343, p<0.001)

We had the chance to evaluate 11 stable neuromuscular patients on two occasions at least 4 weeks apart, their 1st scores differed from the 2nd score in 3 cases by one point,
all other subjects reached the same score on both occasions. We also measured fifteen normal subjects twice. All normal subjects scored the same points on both occasions.

Discussion

In this study, we have shown that the SiNQ-5 could be used as a clinical tool to prioritise subsequent investigations for sleep-disordered breathing in patients with inspiratory muscle weakness. The questionnaire is based on common clinical observations associated with respiratory muscle weakness and its impact due to posture. The SiNQ-5 has a good accuracy to identify those at risk. A score of five or more points was the only independent predictor of respiratory muscle weakness with combined sleep-disordered breathing. The results of a SiNQ-5 may assist in the decision to admit a patient with suspected respiratory muscle weakness to a sleep laboratory for polysomnographical investigation. A high odds ratio for patients with a score of five or more points in the SiNQ-5 indicate a high pretest probability to the clinician, at least amongst patients referred to a regional centre. A screening tool is helpful and important when sleep laboratories have waiting lists and patients affected could be offered treatment.

The overall time spent on this questionnaire, including explanation, filling it in, scoring and interpretation should be, on average, between 2-5 minutes. Administering the questionnaire is independent of the investigator and should not be influenced by the family or friends. In the subset of patients and normal subjects, in whom we studied the questionnaire on different occasions, it was highly reproducible.

Limitations to this study
We acknowledge that there may be circumstances under which several tasks mentioned in the questionnaire cannot be performed, usually in the context of known neuromuscular disease such as muscular dystrophy or motor neurone disease. One approach to this would be to consider that, since paralysis with truncal rigidity and inability to bend forward increases the clinical pretest probability of sleep-disordered breathing, one should score “2” points (“Yes”) in the SiNQ-5 for each item that patients cannot answer or tasks that cannot be performed due to their neuromuscular problems. However an alternative caveat would be that since such patients require a more comprehensive specialist evaluation which would also encompass bulbar function, aspiration risk and the ability to clear sputum, the SiNQ-5 is likely to prove most useful when assessing patients with clinically isolated diaphragm paralysis.

Item generation was partly based on peer-reviewed publications describing symptoms of patients with diaphragm weakness and the impact of gravity and posture. The final version of this questionnaire has not been sent out to patients or peer-review and is thus limited to the pure observational approach of clinicians and peer-reviewed literature. A potential limitation is that other diseases, such as heart failure, might be associated with breathlessness and posture as well. Therefore, we recommend that the medical history should be screened for severe cardiac or airway diseases explaining potential symptoms to increase chances of pretest probability and guarantee diagnostic accuracy. In the case that severe disease other than NMD is present, elevated scores of the SiNQ-5 would need careful interpretation.

Immersion in water aggravates patients with diaphragmatic weakness but can improve
patients with abdominal paralysis. [33,34] In this study, we have included patients with predominantly inspiratory, and particularly diaphragm muscle weakness, because patients at risk to develop sleep-disordered breathing are those with reduced inspiratory muscle strength. The use of the SiNQ-5 in patients with predominantly expiratory muscle weakness may therefore be limited.

We accept that due to a wide spectrum of neuromuscular problems in such patients a screening tool may not identify the entire range of symptomatic presentations. However, in patients with respiratory muscle weakness but selective relative sparing of the diaphragm, e.g. early spinal muscular atrophy, the SiNQ-5 would score low. However patients with a relative strong diaphragm are unlikely to develop sleep-disordered breathing or REM-sleep hypoventilation.1 3 Such patients, despite their serious underlying condition, could safely be stratified to a less urgent sleep study. Patients with pain may have fragmented sleep, but do not develop sleep-disordered breathing per se. We therefore think that the questionnaire can be an option to screen for sleep-disordered breathing in such patients, although it is probably most useful in ambulatory patients with mild to moderate neuromuscular disease.

The SiNQ-5 was tested for reproducibility in both patients and normal subjects and proved satisfactory. Conceptually, answers using a continuous scale could identify smaller changes over time. However, whilst creating the questionnaire we agreed to select “Yes-No“ answers for several reasons: Firstly, they are straightforward and easy to answer without explanation, second they are quick to analyse and, thirdly, the threshold effect from the patients’ point of view is clearer. Lastly, using this questionnaire with a potential range from 0-10 points allows to monitor and follow
the progress of the disease with a semiquantitative approach.

Conclusion

This study reports the accuracy of a self-administered and symptom-based screening questionnaire to identify patients with respiratory muscle weakness following neuromuscular disease who are at risk of developing sleep-disordered breathing. Further studies are required to assess its robustness in more generally selected populations and in children.
Conflict of interest: the authors have no conflict of interest with regard to the content of this manuscript.
References


Table Legends

Table 1: The SiNQ-5, a self-administered questionnaire to screen for sleep-disordered breathing in neuromuscular disease. Scores are printed in brackets.

Table 2: Characteristics of the tested subjects. Differences are marked comparing group I to II and group I to III, * p<0.05, *** p<0.001. Healthy subjects were slightly younger than neuromuscular and OSA patients, but matched for BMI. There was no difference in the SiNQ-5 score between normal subjects and OSA patients.

Table 3: Diagnosis of the patients with neuromuscular diseases, numbers (n) are stated on the right.

Table 4: Respiratory muscle test results. All test results in cmH<sub>2</sub>O. Differences are marked comparing the group of healthy subjects and OSA patients to NMD patients; *** p<0.001, ** p<0.01; # 33 patients with OSA performed respiratory muscle tests with normal test results, none of them had nonvolitional tests.

Table 5: Polysomnography test results compared to neuromuscular patients, *** p<0.001, ** p<0.01, * p<0.5. NMD patients slept slightly shorter and had reduced REM-sleep time. The RDI was lowest in normal subjects, elevated in NMD patients, and highest in OSA patients. Most respiratory events in the NMD patients were centrally related apnoeas and hypopnoeas.

Table 6: Cross tabulation of SiNQ-5 scores and patients with NMD and SDB. NMD = neuromuscular disease, SDB = sleep-disordered breathing, SiNQ-5 = sleep-disordered breathing in neuromuscular disease questionnaire. Cross tabulation of those who had 0-4 points or 5-10 points in the SiNQ-5, and those who had sleep-disordered breathing caused by neuromuscular disease. Based on this cross tabulation there is an odds ratio of 48.3 for someone who scores five or more points to have NMD with combined SDB.
**Table 7:** Accuracy of the SinQ-5 to assess respiratory muscle weakness associated with sleep-disordered breathing for different questionnaire’s scores.
Figure Legends

Figure 1: ROC-curve for the SiNQ-5 and ESS scores identifying SDB in NMD patients, respectively. Area under the curve (AUC) for the SiNQ-5 was larger than for the ESS.
Table 1

Dear Patient,

The following questions may help us to decide whether you may have disordered breathing during sleep related to muscle weakness. Please circle the most appropriate answer to each question.

Thank you for your cooperation.

<table>
<thead>
<tr>
<th>Do you feel breathless, if … you lie down? (e.g. on your bed)</th>
<th>Yes (2)</th>
<th>Sometimes (1)</th>
<th>No (0)</th>
</tr>
</thead>
</table>

… you bend forward? (e.g. to tie your shoelaces)  

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (2)</th>
<th>Sometimes (1)</th>
<th>No (0)</th>
</tr>
</thead>
</table>
… you swim in water or lay in a bath?       | Yes (2) | Sometimes (1) | No (0) |
Have you changed your position when in bed?   | Yes (2) |               | No (0) |
Have you noticed a change in your sleep (waking more, getting up, poor quality sleep)? | Yes (2) |               | No (0) |

Table 2

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Neuromuscular (n=32)</td>
<td>Healthy (n=35)</td>
<td>OSA (n=58)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>56 (12)</td>
<td>43 (16)*</td>
<td>60 (13)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>21 / 11</td>
<td>19 / 16</td>
<td>43 / 15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.0 (7.5)</td>
<td>30.5 (9.9)</td>
<td>33.1 (7.9)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (x/24 points)</td>
<td>10.0 (5.6)</td>
<td>4.4 (3.1)***</td>
<td>8.7 (5.4)</td>
</tr>
<tr>
<td>SiNQ-5 (x/10 points)</td>
<td>6.8 (2.3)</td>
<td>1.0 (2.0)***</td>
<td>2.5 (2.3)***</td>
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**Table 3**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuralgic Amyotrophy</td>
<td>22</td>
</tr>
<tr>
<td>Facial scapular humeral muscular dystrophy</td>
<td>3</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>2</td>
</tr>
<tr>
<td>Mitochondrial myopathy</td>
<td>2</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>2</td>
</tr>
<tr>
<td>Charcot Marie Tooth Syndrome Type 1a</td>
<td>1</td>
</tr>
<tr>
<td>Group</td>
<td>I</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular</td>
</tr>
<tr>
<td><strong>Sniff Pdi</strong></td>
<td>54.1 (28.9)</td>
</tr>
<tr>
<td><strong>Twitch Pdi, bilateral</strong></td>
<td>12.0 (6.7)</td>
</tr>
<tr>
<td><strong>Twitch Pdi, unilateral</strong> (weaker side)</td>
<td>3.4 (1.9)</td>
</tr>
<tr>
<td><strong>Twitch Pdi, unilateral</strong> (stronger side)</td>
<td>7.8 (4.3)</td>
</tr>
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<td></td>
<td>I</td>
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<tr>
<td>----------------</td>
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<tr>
<td><strong>PEmax</strong></td>
<td>91.0 (17.2)</td>
</tr>
</tbody>
</table>

**Table 5**

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>Neuromuscular</td>
<td>Healthy</td>
<td>OSA</td>
</tr>
<tr>
<td><strong>TST (min)</strong></td>
<td>276.4 (109.6)</td>
<td>342.8 (111.4)*</td>
<td>333.0 (106.7)*</td>
</tr>
<tr>
<td><strong>REM (min)</strong></td>
<td>40.0 (27.6)</td>
<td>79.5 (18.0)***</td>
<td>62.5 (45.7)*</td>
</tr>
<tr>
<td><strong>Sleep Efficiency (%)</strong></td>
<td>72.1 (21.9)</td>
<td>75.8 (15.4)</td>
<td>77.8 (18.2)</td>
</tr>
<tr>
<td><strong>RDI, total (h⁻¹)</strong></td>
<td>15.9 (16.7)</td>
<td>0.2 (0.6)***</td>
<td>38.7 (32.6)**</td>
</tr>
<tr>
<td><strong>RDI, REM (h⁻¹)</strong></td>
<td>18.2 (18.0)</td>
<td>0.3 (1.3)***</td>
<td>36.3 (28.2)*</td>
</tr>
</tbody>
</table>
Table 6

<table>
<thead>
<tr>
<th>NMD+SDB</th>
<th>SiNQ-5</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4 points</td>
<td>5–10 points</td>
<td>Total</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>11</td>
<td>96</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>36</td>
<td>125</td>
</tr>
<tr>
<td>SinQ-5 Score</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>≥4 points</td>
<td>0.931</td>
<td>0.781</td>
<td>0.563</td>
</tr>
<tr>
<td>≥5 points</td>
<td>0.862</td>
<td>0.885</td>
<td>0.694</td>
</tr>
<tr>
<td>≥6 points</td>
<td>0.828</td>
<td>0.906</td>
<td>0.727</td>
</tr>
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</table>