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Screening for sleep-disordered breathing in neuromuscular disease using a questionnaire for symptoms associated with diaphragm paralysis

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ABSTRACT: 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.

We developed a self-administered multiple choice questionnaire containing five questions (Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (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.

NMD patients with involvement of the respiratory muscles scored mean±SD 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.

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.

KEYWORDS: Diaphragm, myopathy, respiratory muscles

Sleep-disordered breathing (SDB) has substantial impact on public health [1–4]. Whilst the majority of patients have obstructive sleep apnoea (OSA) [4, 5], other causes of SDB may similarly cause health problems [6–12]. In the present study, we considered the group of patients with neuromuscular disease (NMD) who are affected by SDB 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 (ESS) [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 ESS has been validated in patients with 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 SDB could be identified using a symptom-based questionnaire.

For editorial comments see page 231.

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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 NMD patients with diaphragm involvement; in particular, it should include items that capture the impact of gravity on the diaphragm and abdominal contents. Secondly, it should be applicable to as many adults with NMD 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 SDB and, finally, 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 NMD from peer-reviewed articles and international guidelines [9, 10, 23–26], reviewing evidence-based literature and guidelines to develop clinical questionnaires [27, 28], 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. In total, 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 NMD 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 and the Royal Brompton Hospital (both London, UK) have experience with NMD patients over more than three decades with full evaluation of several hundreds of patients [9, 25, 29, 30].

The resulting self-administered questionnaire (table 1) was focused on symptoms associated with breathlessness that are 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 to yield 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 (18:00–20:00 h). Age, height, weight and sex were recorded. The SDB in NMD Questionnaire (SiNQ)-5 (table 1) was completed by the patient, without assistance, in a quiet room.

In addition, the ESS was measured [20].

The patients were grouped into the following subgroups: 1) patients with respiratory muscle weakness; 2) patients with obstructive sleep apnoea; and 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 American Thoracic Society (ATS)/European Respiratory Society (ERS) joint statement on respiratory muscle testing [29]. This included volitional (sniff manoeuvres) and nonvolitional (phrenic nerve stimulation) tests of inspiratory muscle strength, as well as expiratory muscle strength (maximal expiratory pressure). For this purpose, the patients had an oesophageal balloon catheter, filled with 0.5 mL of air, and a gastric balloon catheter (Coopersurgical, Trumbull, CT, USA), filled with 2.0 mL of air, inserted *via* one nostril. Correct positioning was confirmed as described by BAYDUR *et al*. [31] Twitch transdiaphragmatic pressure (P_{di}) was measured seated, at functional residual capacity, wearing a nose clip, after uni- and bilateral anterolateral magnetic phrenic nerve stimulation [32, 33], using 48-mm figure-of-eight coils connected to a magnetic stimulator (Magstim 200; Magstim Co., Whitland, UK).

TABLE 1 The SiNQ-5, a self-administered questionnaire to screen for sleep-disordered breathing in neuromuscular disease

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.

Do you feel breathless, if			
you lie down? (*e.g.* on your bed)	Yes (2)	Sometimes (1)	No (0)
you bend forward? (*e.g.* to tie your shoelaces)	Yes (2)	Sometimes (1)	No (0)
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)	

Numbers in parentheses represent scores.

TABLE 2 Characteristics of the tested subjects

Characteristic	Group 1	Group 2	Group 3
Subjects n	32	35	58
Age yrs	56±12	43±16*	60±13
Males/females n	21/11	19/16	43/15
BMI kg·m^{-2}	31.0±7.5	30.5±9.9	33.1±7.9
ESS#	10.0±5.6	4.4±3.1***	8.7±5.4
SiNQ-5¶	6.8±2.3	1.0±2.0***	2.5±2.3***

Data are presented as mean±SD unless otherwise stated. Healthy subjects (group 2) were slightly younger than neuromuscular (group 1) and obstructive sleep apnoea patients (group 3), but matched for body mass index (BMI). There was no difference in the Sleep-Disordered Breathing in Neuromuscular Disease (SiNQ)-5 score between group 1 and group 3. ESS: Epworth Sleepiness scale. #: out of 24; ¶: out of 10. *: p<0.05; ***: p<0.001.

All of the patients in this group had inspiratory muscle weakness. Diaphragm weakness was defined as a sniff P_{di} of <100 cmH_2O for males and <70 cmH_2O for females and, additionally, a twitch P_{di} for both sexes <18 cmH_2O, as previously described [30]. 29 patients of this group also had significant SDB with a respiratory disturbance index (RDI) >5 events·h^{-1}.

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 SDB, 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 [30].

Group 3

Patients with 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, Andover, MA, USA). Polysomnography was scored according to international guidelines [22]. Apnoea was defined as zero flow for >10 s; hypopnoea was scored as decrease from baseline of >50% for >10 s. 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 unpaired t-test between groups. In addition, a linear regression analysis was performed, entering variables into a forward model to establish independent predictors of NMD combined with SDB. 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 <0.05 was considered significant [34].

TABLE 3 Diagnosis of the patients with neuromuscular diseases

Diagnosis	Subjects n
Neuralgic amyotrophy	22
Facial scapular humeral muscular dystrophy	3
Myasthenia gravis	2
Mitochondrial myopathy	2
Myotonic dystrophy	2
Charcot–Marie–Tooth syndrome type Ia	1

RESULTS

There were three groups in this study: 1) patients who were identified by comprehensive respiratory muscle tests as having respiratory muscle weakness; 2) healthy subjects with normal respiratory muscle strength; and 3) patients with OSA (tables 2 and 3).

The NMD patients (group 1) had diminished strength, as measured by volitional sniff tests, and marked weakness in nonvolitional twitch tests of respiratory muscle strength. 11 of the NMD patients had unilateral diaphragm weakness or paralysis, six had bilateral diaphragm paralysis and the others had global nonlateralised diaphragmatic weakness. A mean±SD pressure of 3.4±1.9 cmH_2O in the unilateral twitch P_{di} reveals the severity of the overall weakness in this population. The healthy subjects (group 2) and patients with OSA (group 3) had normal inspiratory muscle strength [30] (table 4).

Compared to NMD patients (group 1), healthy subjects (group 2) and patients with OSA (group 3) slept longer, including longer rapid eye movement (REM) sleep, all groups had similar sleep efficiency. Normal subjects (group 2) had an RDI <5 events·h^{-1}; NMD patients (group 1) had moderately elevated RDI, with a wide standard deviation, and OSA patients (group 3) had the highest RDI (table 5).

TABLE 4 Respiratory muscle test results

Test	Group 1	Group 2	Group 3#
Sniff P_{di} cmH_2O	54.1±28.9	129.1±34.7***	115.0±33.4***
Bilateral twitch P_{di} cmH_2O	12.0±6.7	27.2±4.3***	NA
Unilateral twitch P_{di} cmH_2O			
Weaker side	3.4±1.9	10.6±2.0***	NA
Stronger side	7.8±4.3	13.7±2.9***	NA
$P_{E,max}$ cmH_2O	91.0±17.2	106.5±24.6**	99.6±22.0

Data are presented as mean±SD. P_{di}: transdiaphragmatic pressure; $P_{E,max}$: maximal expiratory pressure; NA: not assessed. #: 33 patients with obstructive sleep apnoea performed respiratory muscle tests with normal test results, none of them had nonvolitional tests. ** p<0.01; *** p<0.001.

TABLE 5 Polysomnography test results

Test	Group 1	Group 2	Group 3#
TST min	276.4±109.6	342.8±111.4*	333.0±106.7*
REM min	40.0±27.6	79.5±18.0***	62.5±45.7*
Sleep efficiency %	72.1±21.9	75.8±15.4	77.8±18.2
RDI events·h^{-1}			
Total	15.9±16.7	0.2±0.6***	38.7±32.6**
REM	18.2±18.0	0.3±1.3***	36.3±28.2*

Data are presented as mean±SD. Neuromuscular disease patients (group 1) slept slightly shorter and had reduced rapid eye movement (REM) sleep time. The respiratory disturbance index (RDI) was lowest in normal subjects (group 2), elevated in group 1 and highest in obstructive sleep apnoea patients (group 3). Most respiratory events in group 1 were centrally related apnoeas and hypopnoeas. TST: total sleep time. *: p<0.5; **: p<0.01; ***: p<0.001.

With a cut-off of five or more points in the SiNQ-5 score, there was a sensitivity of 86.2% a specificity of 88.5% to identify SDB in NMD patients (group 1). From cross-tabulation, we calculated a positive predictive value of 69.4.% and a negative predictive value of 95.5% (tables 6 and 7).

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

A linear regression analysis revealed that a SiNQ-5 score of five or more points was the only significant independent predictor to determine SDB in NMD 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 *P*di, bilateral; p=0.523) did not reach significance. The resulting model accounted for ~60% of the cases of NMD and SDB (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 NMD patients on two occasions ⩾4 weeks apart. Their first scores differed from the second score by one point in three cases; all other subjects reached the same score on both occasions. We also measured 15 normal subjects twice. All normal subjects scored the same on both occasions.

TABLE 6 Cross-tabulation of Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ-5) scores and patients with neuromuscular disease (NMD) and sleep-disordered breathing (SDB)

NMD and SDB	SiNQ-5		
	0–4 points	5–10 points	Total
No	85	11	96
Yes	4	25	29
Total	89	36	125

Data are presented as n. Cross-tabulation of those who had 0–4 or 5–10 points in the SiNQ-5, and those who had SDB caused by NMD. 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 Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ-5) to assess respiratory muscle weakness associated with sleep-disordered breathing for different questionnaire's scores

SinQ-5 score	Sensitivity	Specificity	PPV	NPV
⩾4 points	0.931	0.781	0.563	0.974
⩾5 points	0.862	0.885	0.694	0.955
⩾6 points	0.828	0.906	0.727	0.946

PPV: positive predictive value; NPV: negative predictive value.

DISCUSSION

In this study, we have shown that the SiNQ-5 could be used as a clinical tool to prioritise subsequent investigations for SDB 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 SDB. 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 pre-test probability to the clinician, at least amongst patients referred to a regional centre. A screening tool is helpful and important when sleep

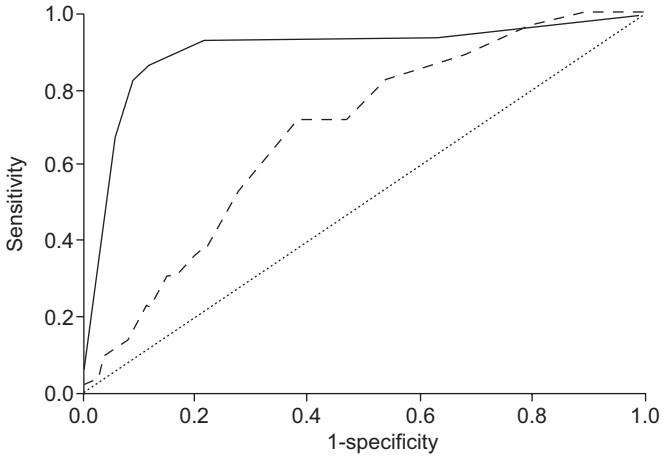

FIGURE 1. Receiver operating characteristic curve for the Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ-5; ——) and Epworth Sleepiness scale (ESS; ------) scores identifying sleep-disordered breathing in neuromuscular disease patients. Area under the curve for the SiNQ-5 was larger than for the ESS. ·····: reference line.

laboratories have waiting lists and patients affected could be offered treatment.

The overall time spent on this questionnaire, including explanation, completion, scoring and interpretation should be, on average, 2–5 min. Administering the questionnaire is independent of the investigator and should not be influenced by the patient's 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 of the 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 NMD, such as muscular dystrophy or motor neurone disease. One approach to this problem would be to consider that, since paralysis with truncal rigidity and inability to bend forward increases the clinical pre-test probability of SDB, 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 comphrensive 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-reviewed, and is thus limited to the purely 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 pre-test 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 [35, 36]. In this study, we have included patients with predominantly inspiratory, and particularly diaphragm, muscle weakness, because patients at risk to develop SDB 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 relatively strong diaphragm are unlikely to develop SDB or REM sleep hypoventilation [1, 3]. Such patients, despite their serious underlying conditon, could safely be stratified to a less urgent sleep study. Patients with pain may have fragmented sleep, but do not develop SDB *per se*. We therefore think that the questionnaire can be an option to screen for SDB in such patients, although it is probably most useful in ambulatory patients with mild-to-moderate NMD.

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: first, they are straightforward and easy to answer without explanation; secondly, 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 NMD who are at risk of developing SDB. Further studies are required to assess its robustness in more generally selected populations and in children.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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