Lung function tests in patients with neuromuscular disorders: how, when and why?

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Summary

Neuromuscular disorders (NMD) may soon or later affect the lung function according to the clinical progression of any NMD leading often to chronic ventilatory failure. Either the respiratory muscles and the central drive of breathing may be differently involved during the natural history of any different NMD.
The evaluation of lung function test should be routinely performed in every NMD patients at least at diagnosis and during follow-up. Also respiratory sleep disturbances and cough efficiency must be carefully checked in every patient with NMD.
The present review describes the most useful test to routinely assess lung function in NMD, with particular emphasis on respiratory muscles evaluation. An early assessment of lung function together with use of non invasive home mechanical ventilation may help improved quality of life and prolonged life expectancy.

KEY WORDS: neuromuscular disorders, myopathies, lung function tests, spirometry, maximal inspiratory pressure, maximal expiratory pressure, respiratory sleep disturbances, cough effectiveness.

Introduction

Neuromuscular disorders (NMD) are a wide spectrum of different diseases affecting the muscles, and/or the nerves and/or the neuromuscular junction. Respiratory muscles are often involved at various level and at different stages of these condition. In some cases the deterioration of the respiratory muscles evolve in parallel with the skeletal muscles. In other cases involvement of the diaphragm and the accessory respiratory muscles overtake the other muscles, in some other cases there is no evidence of any respiratory symptom in the course of the disease (1). A good number of neuromuscular disease starts at younger or later childhood and last over lifetime in adulthood. Therefore it is advisable to set up discussion and/or a working group between paediatricians and adult respiratory specialists.

It is important in terms of quality of life and mortality to assess the muscle weakness and also to define the rate of the progression.

In childhood the most common neuromuscular disorders are Duchenne's muscular dystrophy (DMD) and spinal muscular atrophy. Both conditions start early during childhood, but nowadays last up to the third or even the forth decade of life (1-3).
In adulthood heterogeneous forms of NMD can occur with different progression rate. There are conditions with fast deterioration such as motoneuron diseases (1) and diseases with temporary critical conditions such as in the critical state of *myasthenia gravis* (2). It is important in terms of quality of life and mortality to assess the muscle weakness and also to define the rate of the progression. The clinicians must be alert with regard the possible existence respiratory muscle weakness which can start with an acute or returning respiratory infection or can show symptoms of unexplained dyspnoea, orthopnoea or cough during swallow, weak cough, daytime somnolence, deterioration in concentration ability or fatigue. The present mini-review provides a short overview of the respiratory evaluation and respiratory follow up of patients with NMD.

Mechanism of chronic ventilatory insufficiency in neuromuscular disease

Probably it is worth to describe the different forms of respiratory symptoms. Some of them arise from the reduced strength of the muscles: ineffective cough or dyspnoea on exertion or in supine position (orthopnoea) while others are due to reduced endurance of the muscle: nightime and later hypercapnia or even hypoxaemia both durig sleep and awake. Both the reduction in strength and endurance of the respiratory muscles are causing alteration of the sleep structure, primarily reducing quantity of rapid eye

The ability to keep ventilation at an adequate level can be seen on the balance between the strength and endurance of the inspiratory and expiratory muscles on one hand and respiratory load on the other.

Dysnutrition is a common problem in neuromuscular disease as low protein intake further reduces muscle including respiratory muscle quantity.

movement (REM) sleep hypersomnia. On the other hand over time the respiratory musculature structural change causes rib cage deformity. Inability to cough can lead to pulmonary atelectasis on the long run.

As there is a rather big reserve of ventilator capacity, there is usually no sign of respiratory problem under 50% reduction in vital capacity or the maximal inspiratory pressure reduces below 30% (3). This observation supports the fact that this large reserve capacity is masking the respiratory muscle involvement for a long time.

We have to make a clear distinction between muscle fatigue and muscle weakness. While fatigue is changing over rest, weakness is not. In healthy subjects, when the diaphragm in the risk of fatigue the pressure-time index (inspiratory time/total respiratory cycle time) and mean transdiaphragmatic pressure/maximum trasdiaphragamatic pressure exceeds the "fatigue threshold" value of 0,15 (3). Patients will adopt a breathing pattern to minimise their inspiratory time and transdiaphragmatic pressure which is ending up in a lower tidal volume. As a result of this process, patients avoid the feeling respiratory fatigue but finally higher arterial carbondioxide level will appear. Meanwhile there are evidences that the fatigue threshold is lower in subjects with neuromuscular diseases (3, 4). Compared to inspiratory muscles, less data are available on the role of expiratory muscles, concerning the development of the ventilatory dysfunction. It was found that decreased maximum expiratory pressure (MEP) in not an independent risk factor of hypercapnia (3). On the other hand patients with reduced ability of cough are also at risk of developing pulmonary atelectasis and recidive pulmonary infection. Effective cough can only be produced with a MEP higher than 50-60 cm H_20 (4).

Another important factor for ventilatory dysfunction in NMD is the involvement of the central control of breathing. This is partly because the central drive of breathing is very much individualized. On the other hand due to the not rare case of sleep disorders in neuromuscular disease leading to bicarbonate retention which resets the carbondioxide setpoint (4). The ability to keep ventilation at an adequate level can be seen on the balance between the strength and endurance of the inspiratory and expiratory muscles on one hand and respiratory load on the other (Figure 1). The respiratory load consists of the lung, the ribcage and the airway mechanics. This is controlled by the central respiratory drive. Reduction in the respiratory muscle function raises the respiratory load which eventually results is alveolar hypoventilation.

In adult patients with NMD the respiratory function may be affected also by other co-morbidities worsening and anticipating the occurrence of chronic respira-

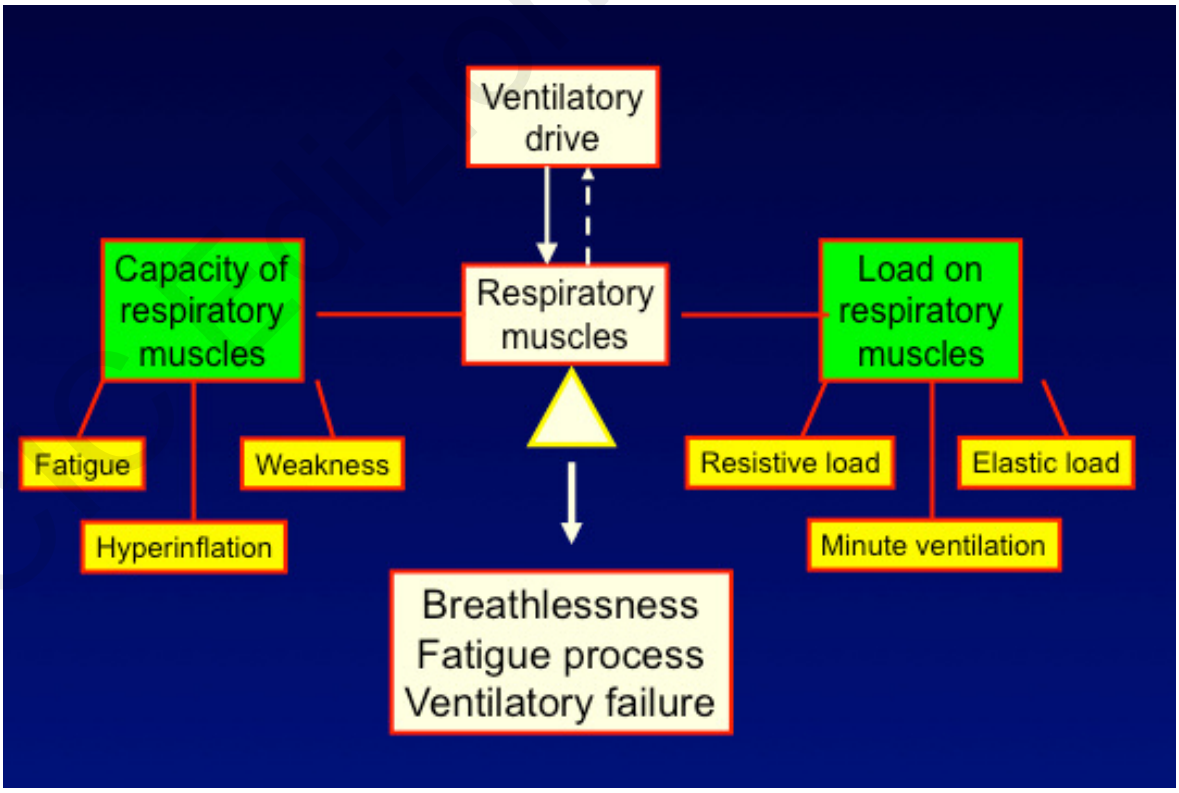

Figure 1 - Mechanisms of breathlessness, fatigue, and hypoventilation in patients with neuromuscular disorders.

Table 1 - Likelihood of respiratory involvement and starting point of pulmonary observation in the different forms of neuromuscular disease.

Neuromuscular diseases	Likelihood of respiratory involvement/ start of pulmonary observation
Muscular dystrophies	
Duchenne muscular dystrophy	**inevitable**/to be checked regularly when in wheelchair at latest
Becker muscular dystrophy	**inevitable**/to be checked regularly when in wheelchair at latest
Limb-girdle muscular dystrophy	**frequent** /to be checked six monthly
Myotonic dystrophy	**rare**/to be checked by symptoms
Fascioscapulohumeral muscular dystrophy	**rare**/to be checked by symptoms
Congenital muscular dystrophy	**frequent**/to be checked six monthly
Metabolic disease of the muscles	
Pompe disease	**frequent**/to be checked six monthly
Mitochondrial myopathies	**rare**/to be checked by symptoms
Other myopathies	
Polmyositis	**rare**/to be checked by symptoms
Thyroid conditions	**occasional**/to be checked by symptoms
Corticosteroid induced	**occasional**/to be checked by symptoms
SLE	**rare**/to be checked by symptoms
Diseases of neuromuscular junction	
Myasthenia gravis	**occasional**/to be checked by symptoms
Eaton-Lambert syndrome	**rare**/to be checked by symptoms
Botulism	
Disease of peripheral nerve	
Charcot-Marie-Tooth disease	**rare**/to be checked by symptoms
Guillen-Barré syndrome	**frequent/**to be checked on diagnosis
Disease of the motoneuron	
Amyotrophic lateral sclerosis	**inevitable**/to be checked first on diagnosis
Postpolio syndrome	frequent
Spinal muscular atrophy type I	**inevitable**/to be checked first on diagnosis
SMA type 2	**occasional/** to be checked by symptoms
SMA3	
Other diseases involving the spinal cord	
Traumatic injury	**frequent**/to be checked by symptoms
Syringomyelia	
Multiple sclerosis	**occasional**/ to be checked by symptoms

tory failure. Probably the most important co-morbidity among NMD patients is obesity. Obesity can cause a restrictive defect on one hand increasing the ventilator load and reducing endurance of the respiratory muscles. Obesity is also predisposing factor for sleep related breathing disorders which further may worsen the endurance of both inspiratory and expiratory musculature during NMD (5).

Cardiac involvement is not rare in NMD, for example in advanced stage of Duchenne dystrophy. Left ventricular failure with attendant pulmonary congestion may cause decreased pulmonary compliance and further mismatching in ventilation-perfusion rate. Cardiac involvement is also frequent in myotonic dystrophy (5). Changes in circulation could be added factor in emergence in all forms of hypoventilation.

Malnutrition is a common problem in neuromuscular disease as low protein intake further reduces muscle including respiratory muscle quantity. In these cases not only body weight should be measured carefully but in the early stages of the disease the whole body composition including fat portion, body water, and protein rate should be measured. Even patients with normal or high BMI could be in lack of protein while in excess of fat. The extra non muscle type of weight this way also can raise the respiratory working load (5). In Table 1 there is a list of the different forms of neuromuscular disease with the probability of respiratory involvement and with a suggestion with the starting point of regular pulmonary follow up.

Tests for the evaluation of respiratory muscle function

Before turning to the detailed description of the several different tests which are currently available for patients suffering of neuromuscular disease we have to state that these conditions need careful care by a multidisciplinary staff (5). Close collaboration with a group

Lung function test in neuromuscular patient shows a restrictive pattern: total lung capacity and vital capacity reduced while functional residual capacity maintained or even decreased while residual volume is increased when expiratory muscles are weak.

of dedicated doctors, physiotherapists, lung function technicians, ventilator therapists, dieticians are needed. Part of multidisciplinary staff includes neurologist and chest physician (both adult and in case of necessity paediatrician), cardiologist, somnologist and intensive care specialist. This is important because in NMD acute respiratory failure is not rare and needs focused approach both in coughing augmentation techniques and non-invasive respiration and invasive respiration mode as well. Patients' education is extremely important in this group of patients as the condition are in most of the cases rare and needs specialised nurse or technician to help to cope with the deteriorating condition mentally and socially as well as arranging the regular follow up at within the group of specialised doctors (6).

The clue of the care is the regular follow up. When respiratory capacity is normal the lack of the symptoms does not mean that the respiratory muscles are not yet involved in the disease. It is important to accept that even in symptom free intervals, a "hidden" involvement of the central respiratory drive slowly deteriorate the response to the changed respiratory load.

As respiratory defects are characterised by different pattern even in one type of neuromuscular diseases the timing with other type of evaluation, such as neurologic examination, six minute walk test (6MWT), strength test of skeletal muscles, should be carefully monitored as progression could be an important signal for closer evaluation, such as in the case wheelchair need, as sitting type of life from moving type of life changes adaptation significantly.

Simple, cheap lung function test both in sitting and supine condition, early morning arterial blood gas analysis in contrast to daytime, maximal inspiratory and expiratory pressure (MIP and MEP) can be performed 6 monthly. Night time cardiorespiratory polygraphy (CRPG), polysomnography (PSG) are both expensive procedures, so they should be reserved for use in a yearly base. However in child's case there is no indication of solely CRPG but PSG advised to be performed (6). In adults there are evidences for the usefulness of PSG over CRPG (7, 8), especially in case of neurocognitive changes such as hypersomnolence or alteration in concentration ability or slight changes in personality.

In this population non invasive respiratory measurement techniques are recommended on a regular basis. Using these simple, repeatable and comparable tests next therapeutic steps can be determined over the time if follow up results are available.

Table 2 - Symptoms of respiratory involvements of NMD.

Dyspnoea
- orthopnoea
- stress dyspnoea
- resting dyspnoea
- shallow breath
- tachypnoea
Headache
Daytime somnolence
Intellectual deterioratin
Depression

Test for respiratory muscle strength

Sleep study should be performed in the case of typical complaints such as headache, daytime sleepiness, nicturia, insomnia and changed cognitive function.

1. The importance of physical examination

In the initial phase of the disease the physical examination can be normal. One of the first symptoms is tachypnoea. At later stages of the disease dyspnoea becomes common on minimal exercise or at rest, up to usual rapid shallow breathing. In later phase we can observe higher shoulder attitude, a visible work of the accessory respiratory muscles can also be seen. In certain diseases, e.g. acid maltase deficiency, there is a trend to have a narrower neck during the progression of the disease. It is unavoidable to check the throat by Mallampatti criteria in order to assess probability of upper airway obstruction (6). It is also unavoidable to check the rib cage and the spine as well as thoracic abdnormality can further deteriorate both.

2. Lung volumes and expiratory flow rate

Monitoring breathing pattern: respiratory rate (Fr), the tidal volume (Vt) and minute ventilation. The raised rapid shallow breathing index (Fr/Vt) is reflected on the enlarged respiratory work load (7, 8) rather than the muscle weakness. Slow component of the lung function test such as total lung capacity (TLC) and at the same time the vital capacity (VC) rely on the integrated muscle pump of the respiratory musculature, so over the time there are good guides of the deterioration of the pumping function including the muscle work. Lung function test in neuromuscular patient shows a restrictive pattern: total lung capacity (TLC) and vital capacity (VC) reduced while functional residual capacity (FRC) maintained or even decreased while residual volume (RV) is increased when expiratory muscles are weak (9). On rapid lung function technics forced expiratory volume in 1 second (FEV1) as well as forced vital capacity (FVC) is reduced in a proportionate way.

In condition when diaphragm is involved in the degenerative process, comparison of the sitting at the supine position is reflected best on the degree of the diaphragm weakness. Normally the drop is less than 10% in the supine position, while in bilateral diaph-

Table 3 - Respiratory follow up of patients with NMD.

Test	Frequency
History, physical examination	Six monthly and **in** acute conditions
Lung function test (FVC, FEV1,	Six monthly and **after** acute conditions
VC – upright and supine	
MIP, MEP	Six monthly and **after** acute conditions
Cough peak expiratory flow	Six monthly and **after** acute conditions
Early morning and daytime blood gas analysis	Six monthly
Polysomnography	At least yearly, symptom oriented and after acute conditions

Table 4 - Indications for non-invasive ventilation in neuromuscular diseases.

- Chronic daytime hypercapnia with $PaCO_2 \geq 45$ mmHg
- Nocturnal hypercapnia with $PaCO_2 \geq 50$ mmHg
- Daytime normocapnia with a rise in $PTcCO_2$ of ≥ 10 mmHg during the night
- A rapid, significant reduction in VC
- MIP < 50 H_2O cm or 60% and FVC < 40%

ragm paralysis the drop is 30% (9).
This maneuver is cheap and easily performed by a trained technician in a general pulmonology department or out patient clinic.

3. Maximal inspiratory (MIP) and expiratory pressures (MEP)

Maximal inspiratory pressure is measured during the "Mueller maneuver" which means it is measured at the airway opening during a maximal static inspiratory effort initiated at either FRC or RV. The type of mouthpiece influences the result: generally for the greater pressure's a phlange-style rather than a tube-style mouthpiece is preferred (Figure 2).
Maximal expiratory pressure (MEP) measured during "Valsalva maneuver". This means that it is measured at the airway opening during the maximal static expiration effort. Expiratory muscles are strongest at high lung volumes while inspiratory muscles are strongest at low pulmonary values. The best way of measuring MIP is to use tube-style mouthpiece or a mask covers the mouth.
This means that MIP reflects best on the strength of the diaphragm, while MEP reflects on the ability of coughing. Generally both elements are reduced in neuromuscular disease, but at the early stage of amyotrophic lateral sclerosis and diaphragm paralysis causes only MIP reduction. Normal values of MIP and MEP have large ranges. It depends on gender and age. As it variable according to patient's effort, the mouthpiece and previous training, it is highly important to be performed by a trained technician, preferably the same over the time (11).

4. Maximal sniff pressure/Sniff test (Pimax)

This technique does not require the use of a mouthpiece. Nasal inspiratory pressure is measured by occluding one nostril by special nasal plug fitted around a catheter during a maximal sniff manoeuvre through the contralateral un-occluded nostril. Because the technique does not require a mouthpiece and sniffing is a usual process for most individual, it has less technical requirement than MIP. Furthermore the correlation VC and sniff Pimax appears to be higher than between VC and MIP in neuromuscular diseases.

Figure 2 - Phlange-style mouthpiece.

5. Cough peak flow rate (CPF)

Muscle weakness results in reduced values of peak flow which can be measured by a simple peak flow meter. Peak flow depends on the breathing effort, which is not independent from the respiratory muscle weakness. CPF can minimise the effort related diversions. It is a very reliable measurement of the expiratory muscles. It should be performed by a simple big cough in a peak flow meter (12). According to different studies cough flow even in bulbar involvement is useful guide of the muscle state. Below 250 ml/min treated as low value (13).

6. Other muscle strength measurement techniques

Trans-diaphragmatic pressure is a reliable method to assess the ability of the diaphragm to generate adequate negative pressure in the thoracic cage. This is an inconvenient technology as two measuring ballo-

ons need to be placed in the stomach and the oesophagus on the two sides of the diaphragm. Similarly to MIP and MEP Mueller and Valsalva maneuver should be performed. The trans-diaphragmatic pressure is calculated by direct measurement. If the technic is combined with phrenic nerve stimulation the peripheral drive could also be tested. Electromyogram (EMG) could also be added to the study. This will show the possible differences of the involvement between the two sides. Magnetic phrenic nerve stimulation may exclude important diaphragm weakness. Nevertheless, this test is rarely available and unusual in the daily clinical practice (Figure 3).

Tests of respiratory muscle endurance

1. The importance of history taking

In neuromuscular conditions in our clinical meeting with the patients should focus on their complaints. Validated tests are of use to assess the clinical conditions, but it is extremely important to be empathic with the patients' personal situation and ask in the proper way. In younger patients who are still studying for example it is advisable to focus on the concentration ability, to ask how the ability to work or study changed recently, in older patients daytime somnolence could be our focus point. It is also important to ask the relatives about the possible changes. The sleeping habits also should be asked carefully. We also have to focus on the appearance of dyspnoea in everyday life and under stressed conditions. Respiratory symptoms of NMD are summarized in Table 2.

2. Maximal voluntary ventilation (MVV)

Maximal voluntary ventilation is a very simple test which was found to be in reduced in neuromuscular diseases even when VC is normal. MVV is the volume of the air breathed when a person breathes as deeply and as quickly as possible for a given time (15 seconds). The result usually extrapolated to what could be breathed over 1 minute (9).

3. Arterial blood gas analysis

Arterial blood gas analysis on its own is not sensitive enough for detecting or follow up neuromuscular disease. Nevertheless it should be performed when VC reduces below 50% or MIP becomes lower than 30%. Patients have normal daytime blood gas even with significant hypercapnia during the night. Therefore early morning, preferably wakening arterial blood gas should be performed. In the test pH and bicarbonate level reflects best on the events during sleep. So in the comparison of daytime and early morning arterial blood gas tests could highlight the deterioration of the respiratory muscle function.

4. Sleep study

Sleep studies as patients most of the cases sleep in supine position when, unlike in upright position when

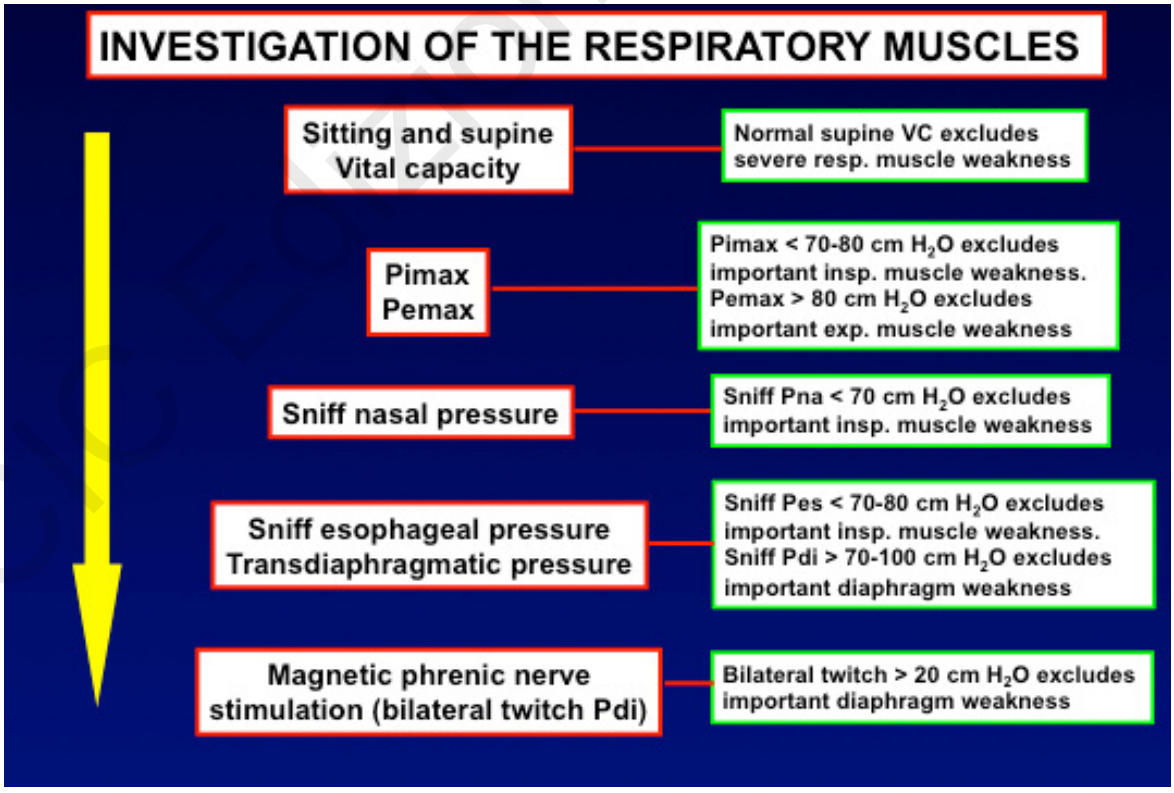

Figure 3 - Tests for the investigation of the respiratory muscles listed according to their complexity.

gravitation is of help in breathing, lying on the bed diaphragm needs extra effort for 6-8 hours to maintain the oxygen need of the body as well through expiration carbon-dioxide should be eliminated. Moreover sleep contains of different sleep stages. There is a relative greatest muscle tone reduction in rapid eye movement (REM) sleep. This means that if diaphragm is involved in a progressive neuromuscular disorder the sleep structure would change. At the beginning of this process, depending on the individual respiratory drive sensitivity, two things may happen:

A. In a relatively early stage of the respiratory involvement in NMD the body tries to avoid REM sleep when the muscle tone is reduced to the threshold when it is not able to provide enough oxygen and/or eliminate carbon-dioxide. In these cases REM phase will be missing or extremely reduced. The result of this is daytime somnolence, deterioration in learning and concentration ability.
B. In a later case reduced or even normal amount or REM sleep can be detected, but hypoxia is also seen on the tracing which shows that respiratory drive moved to a higher hypercapnic threshold.

In very early stages tracings can be seen when the sleep structure is almost kept, but the oxygen level is slowly moving form 95 to 90%. All of these options are signs of hypoventilation. Due to pharyngeal muscle weakness obstructive sleep apnoea could be seen as well, which further aggravates both the night-time and daytime conditions.

Although a number of attempts has been made to clarify those lung function test results which signal the need of sleep study, no clear cut answer was found (10). As a general guideline it is worthwhile indicating PSG when VC is lower than 50% and/or MIP reduced below 30% of normal. If abnormality is seen in daytime blood gas analysis or there is a difference between early morning and daytime blood gas analysis. Sleep study should be performed in the case of typical complaints such as headache, daytime sleepiness, nicturia, insomnia and changed cognitive function and intellectual conditions.

Respiratory management

The basis of respiratory management is – independently from available specific pharmaceutical treatment options – respiratory physiotherapy and training. Respiratory care relies on the clinical data obtained from the test of respiratory muscle strength and endurance. The principle is simple: the earlier the patient becomes familiar with these technics the better he will use them when needed.

Respiratory support maintains not only the respiratory functions but keeps intellectual and learning abilities, therefore it is critical to introduce the non-invasive ventilation in time.

Table 3 gives a short summary on timing and forms of respiratory follow up in patients with NMD.

In case of expiratory respiratory muscle weakness or repeated lower airway infections cough managing techniques should be introduced. This contains self-managed training as well as augmented coughing technics. In case of returning infection accompanied by reduced expiratory muscle function mechanical assistance of cough should be introduced.

In case of deterioration of inspiratory muscle at first place rational muscle training should be introduced (11, 12). There is evidence that regular repeated training does not cause further damage in the muscle (13, 14).

When hypoventilation during the night develops first, non-invasive ventilation (NIV) should be introduced. Several studies clearly suggest benefits from NIV either concerning life expectancy and quality of life, but also blood gas values can be normalized (15, 16). At the first signs of nocturnal hypercapnia, the patient should be offered NIV therapy rather than waiting until the hypercapnia extends into the daytime period. There are no indications for prophylactic mechanical ventilation in the absence of symptoms or hypoventilation. NIV is also indicated prior to elective vertebral column correction surgery when VC < 60% target value and FEV_1 < 40% target value, respectively, or during pregnancy with restricted lung function, as well as palliative care of dyspnea. Respiratory support can maintain not only the respiratory functions but keeps intellectual and learning abilities, therefore it is critical to introduce timely non-invasive ventilation in patients with neuromuscular disorders (17). Finally indication of non invasive ventilation is summarized in Table 4.

The earlier we detect and act, the better is the opportunity for active life and prolonged life expectancy.

Conclusion

Caring for neuromuscular patients with or without a respiratory complication has an important effect on their quality of life and life expectancy. Because of this reason regular respiratory muscle function follow up should be performed even without spectacular respiratory, sleep, cognitive or intellectual symptoms. In the course of these diseases – as there is no rule for the appearance of the breathing problems – special caution is needed. The earlier we detect and act, the better is the opportunity for less deteriorating condition which includes active life and longer life expectancy. For the respiratory pulmonologist it is important to accept the challenge of the follow up of these patients, as acting in time can prolong life time of the patient significantly, in DMD case even for a decade. And it is a real blessing for the patient and the caring staff as well. It is crucial for the pulmonologist to act in coordination with the other team members. His role is critical in unexpected conditions such as before elective surgery or unexpected lower airway infection or acute respiratory conditions. Observation is needed during non-invasive ventilation in order to step up in ventila-

tion forms. Non-invasive ventilation can be used in dependent ventilations with highly assisted mode. In rare conditions diaphragm pacing is a solution. Expert team decision is needed in accordance with the patient's wish in chronic gradual deterioration when mechanical ventilation is unavoidable. Lot of neuromuscular patients are mobile with relatively slow progressing diseases with mechanical ventilation. At the very end stage of some rapidly progressive neuromuscular disease (e.g. ALS), a previous written consent to resuscitation and intubation should be available to guide the medical team's decisions when acute respiratory failure or other life threatening situation occur. A multidisciplinary approach is preferable for these patients and the pulmonologist should accept that they are an integrated part of a medical team caring for neuromuscular patients.

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