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Workshop report

117th ENMC Workshop: Ventilatory Support in Congenital Neuromuscular Disorders — Congenital Myopathies, Congenital Muscular Dystrophies, Congenital Myotonic Dystrophy and SMA (II) 4–6 April 2003, Naarden, The Netherlands

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Eighteen participants from Australia, Austria, Denmark, Finland, France, Germany, The Netherlands, the UK, and the USA met in Naarden, representing a variety of disciplines with experience in the respiratory management of patients with neuromuscular disorders (NMD). The aims of the workshop were to agree upon and report minimum recommendations for the investigation and treatment of respiratory involvement in congenital muscular disorders, and to identify areas where further research is needed. The workshop specifically excluded patients with Duchenne muscular dystrophy where evidence for the need for and efficacy of the treatment of respiratory failure is better established. All participants contributed to the review and assessment of published evidence in the field, and current practice amongst the group was also compared. Despite the individual rarity of the conditions under consideration in this workshop, the accumulated experience of the group represented the care of more than 545 patients with these disorders, of whom around one-third were receiving mechanical ventilation.

1. Session 1—Assessment methodologies in childhood respiratory impairment

The first session addressed the rationale for commonly performed measurements of various aspects of respiratory

function in order to generate recommendations for assessment of respiratory function in children with NMD (Appendix A).

1.1. Lung and respiratory muscle function

The literature on the assessment of lung function and respiratory muscle function was reviewed by Dr Laier-Groeneveld (Erfurt, Germany). Routine measurements of respiratory function include static lung volumes, flows and indices of gas exchange. If respiratory muscle weakness is suspected because of the underlying disease or abnormalities in the initial investigation, measurements may be completed by direct tests of the respiratory muscle function. In children with NMD monitoring of respiratory status is particularly important because respiratory malfunction is often progressive and a major cause of morbidity and mortality.

However, data on the natural history of lung and respiratory muscle function in children with congenital NMD are scarce and some of the techniques to assess respiratory muscle function lack validation and normal values.

Apart from the well-validated measurement of vital capacity (VC) and blood gas tensions the following non-invasive techniques are available to assess the respiratory muscles in children. Based on their feasibility they are of different importance in routine clinical use:

- Maximum inspiratory pressure (P_{Imax}) and maximum expiratory pressure (P_{Emax}) measured at the mouth can be

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obtained at approximately 6–7 years of age. Pressures increase with age and are higher in boys than in girls [1, 2]. The variability of normal values and the dependence on cooperation by the child makes the assessment of the individual child difficult and requires some practice and experience with the technique.

- Nasal sniff pressures (P_{sn}) is an established test of inspiratory muscle strength in adults and has been applied to children. It is a simple and non-invasive measure, particularly of the diaphragm, and normal values for children are available [3,4].
- Mouth occlusion pressure ($P_{0.1}$) is measuring the pressure generated by the inspiratory muscles during tidal breathing and allows estimation of the respiratory drive and the ratio $P_{0.1}/P_{\text{Imax}}$ is representing the load of respiratory muscles. It has been shown that these measures are closely correlated with angle of scoliosis, VC and gas exchange and may indicate respiratory muscle fatigue [5–8]. The technique requires specifically trained personnel and special equipment; it may play a role in scientific questions. Normal values for children are available [2,9].

There are further, more invasive or sophisticated techniques, e.g. phrenic nerve stimulation, measurement of oesophageal pressure, electromyography to assess the respiratory muscle function. However, their applications may be restricted to the research setting and have not been described in children with NMD.

On the basis of data obtained from adults with various conditions including NMD the ATS/ERS Statement on respiratory muscle testing [10] concluded among others that:

- Respiratory muscle weakness reduces VC.
- Expiratory muscle weakness can increase residual capacity.
- Reduction of chest wall and lung compliance, as a consequence of muscle weakness, reduces lung volumes, notably VC.
- A fall in VC in the supine position, compared with when upright, suggests severe diaphragm weakness or paralysis.
- Reduced maximal flows in NMD may reflect poor respiratory muscle coordination.
- PaO_2 and PaCO_2 are affected by muscle weakness.
- Respiratory muscle weakness may cause desaturations and hypercapnia during REM sleep.

The ability to cough depends on VC, expiratory muscle strength and bulbar muscle function. Therefore peak cough flows (PCF) are an indirect indicator of lung and respiratory muscle function; PCF can be measured with a simple asthma peak flow meter and in adults a minimum PCF above 200 l/min can usually clear airway secretions adequately [11].

1.2. Sleep-disordered breathing

Dr Mellies (Essen, Germany) reviewed the techniques available for the detection and assessment of sleep-disordered breathing (SDB) and its significance in NMD. SDB is common in NMD [12,13]. The principal cause is disease-related loss of respiratory muscle function, which in the setting of sleep-induced reduction of respiratory muscle tone and drop of central drive results in limited capacity to compensate for sleep-related drop of alveolar ventilation. SDB is particularly prevalent in REM sleep [14–16], a period of maximal muscle atonia, and in the presence of diaphragm dysfunction [6]. It can manifest in different ways, depending on the relative contribution of upper airway or diaphragm dysfunction. Hypopneas with desaturations in REM sleep are most common, particularly in the early stages. As the disorder progresses, hypercapnic alveolar hypoventilation, first in REM, then in non-REM sleep prevails as the predominant marker of decreasing respiratory muscle force. For adults with myopathies and children with various NMD it has been shown that the degree of ventilatory restriction impacts directly on pattern and severity of SDB and that SDB-onset, nocturnal hypoventilation and respiratory failure can be reliably predicted from simple spirometry [7,17].

Because nocturnal hypoventilation is likely to advance to the development of cor pulmonale and daytime respiratory failure and may impact unfavourably on survival, timely recognition is important [18–21].

Unfortunately, SDB is rarely apparent on daytime presentation. Symptoms may be subtle and non-specific and recently it has been shown that a structured symptom questionnaire failed to predict SDB in children with advanced NMD [16]. A high index of suspicion is required and if diagnosis cannot be confirmed by simple tests such as overnight pulse oximetry additional polysomnographic evaluation may be indicated [22].

1.3. Conclusions

The guidelines developed through discussion (Appendix A) were agreed as the minimum necessary to be able to predict safely the development of respiratory failure. The recommendations focus on detecting change in respiratory muscle strength, ability to cough, overnight oximetry and the presence of subtle symptoms of SDB. VC is a key investigation which should be performed regularly in all of these patients as VC below 60% expected is a good predictor of the onset of SDB and VC below 40% is a good predictor of nocturnal hypoventilation.

PCF less than 160–200 l/min may be also ineffective in children and patients are at risk for recurrent chest infections and respiratory failure. Absence or presence and severity of nocturnal desaturations reflect respiratory reserve and can be detected with overnight oximetry in most cases. Deterioration in these key parameters should

be the indication for further more specialised investigations including polysomnography and arterial or capillary blood gas estimation.

2. Session 2—Treatment of respiratory impairment in congenital neuromuscular diseases

The whole impetus of investigations is to highlight patients who will respond to treatment modalities. This session reviewed the evidence for the range of treatments available, including physiotherapy techniques to enhance respiratory muscle function or cough and techniques of assisted ventilation. The recommendations of the group in this area are summarised in Appendix B.

2.1. Respiratory muscle training and assisted coughing techniques

Dr Eagle (Newcastle upon Tyne, UK) reviewed the literature on respiratory muscle training in NMD. The purpose of such training is theoretically to overcome the decreased lung compliance that is a feature of these disorders. Studies tended to include mixed groups of patients, making it hard to draw any clear conclusions [23–26]. Overall, patients with severe disease appeared to be unable to benefit from respiratory training, so it is likely that any major benefits would be seen in patients with only moderately affected respiratory muscle strength [27–29]. A further problem with the published data is the lack of functional endpoints, so that there was no idea of any practical outcome resulting from observed differences in tests of respiratory function.

Within the group of experts assembled at the workshop, there was little experience in the use of respiratory muscle training, and it was agreed that no recommendations could be made as to the efficacy of these techniques. Further trials could be limited by the small gains likely [30,31], the fact that effects are short-lived [32] and that the exercises necessary may be time consuming and boring for the children. However, advances in technology could potentially reduce problems with compliance, [33] and the targeting of this technique to particular patients, for example those about to undergo surgery could still be an area for further study.

In contrast to a lack of enthusiasm about respiratory muscle training, the group was very positive about the use of assisted coughing for these patients, reviewed by Dr Eagle, Dr Simonds (London, UK) and Dr Mellies. Much of what little evidence there is in this area has been published by Dr John Bach or his colleagues [34–48]. While inspiratory muscle weakness predisposes the individual to ventilatory failure, expiratory muscle weakness causes cough impairment, retention of secretions and often chronic atelectasis. In some neuromuscular conditions inspiratory and expiratory muscle strength tend to decline in parallel, in others e.g. spinal muscular atrophy there may be early expiratory muscle weakness before the development of inspiratory

insufficiency. Patients who have a cough peak flow rate (PFR) above 4.5 l/s can usually clear bronchial secretions adequately and are not at risk of developing respiratory decompensation during upper respiratory tract infections. Once cough PFR falls below this level, cough efficiency is impaired. It has been suggested that a cough PFR of 2.7 l/s (160 l/min) is the minimum required to clear airway debris [36], although this figure has not been extensively evaluated. So ineffective cough in patients with NMD may be a combination of inspiratory muscle weakness causing reduction in total lung capacity and reduction in PCF. Expiratory muscle weakness causes a reduction in the pressure available to drive the cough. These factors combine to cause retention of secretions and increased susceptibility to chest infections.

Various measures exist to assist chest clearance by percussion and vibration techniques in association with manually assisted coughing. These techniques can be made more effective by the addition of some means of increased insufflation with or without exsufflation. These vary in their sophistication from glossopharyngeal breathing taught to patients to allow increased accumulation of breath, use of an Ambu-bagTM to inflate the lungs manually, or use of some kind of device to provide increased airflow, such as a mechanical ventilator, an IPPB-device or the mechanical insufflator–exsufflator (Emerson Cough-assistTM) which in addition to assisting inspiration also adds support in exhalation. Data now exist to support the use of these techniques in the steady state in patients with NMD. Sivasothy and co-workers [49] compared manually assisted and mechanical insufflation in 29 subjects (9 normals, 8 COPD, 4 with respiratory muscle weakness and scoliosis, 8 with respiratory muscle weakness without scoliosis). Subjects with COPD and respiratory muscle weakness with scoliosis did not show any benefit, but those with respiratory muscle weakness alone demonstrated an increase in cough peak flow with both techniques.

Marchant and Fox [50] describe the postoperative use of a cough-assist device in avoiding prolonged intubation as use of a cough in-exsufflator facilitated weaning in a DMD patient postscoliosis surgery.

Chatwin and co-workers [51] describe the controlled comparison of spontaneous cough, physiotherapy assisted cough, NIV assisted cough and in-exsufflation in adults with steady state NMD and children with severe NMD. There was a significant increase in cough peak flow with in-exsufflation, which was well tolerated and was just as effective in patients with scoliosis. Dohna and Mellies (submitted) showed nearly doubling of assisted cough flows in children with NMD using an IPPB device. Treatment was equally effective in patients with and without scoliosis.

2.2. Mechanical ventilation

The use of non-invasive ventilation (NIV) in NMD was reviewed by Dr Simonds. Individuals with NMD have been

in the vanguard of the growth in NIV. Negative pressure techniques were life saving in the polio epidemics, and over 30 years ago Rideau and Delaubier [52] applied positive pressure nasal mask ventilation in Duchenne muscular dystrophy patients. Subsequent rapid developments in mask technology and bilevel pressure support ventilators in the 1980s and 1990s, consequent on the explosion in CPAP therapy for sleep apnoea syndromes, have allowed the technique to be extended to a range of congenital NMD, including successful use in the paediatric age range. However, unlike the use of NIV in acute exacerbations of COPD, there have been no randomised controlled trials of NIV in hypercapnic NMD. There are though several major published case series [53,20] showing survival, physiological and quality of life gains in NMD patients and most would accept that in patients with non- or slowly progressive conditions associated with chronic hypercapnia and cor pulmonale withholding of NIV in a controlled trial would be unethical. There is a growing database in progressive conditions such as ALS [54]. A meta-analysis [55] of nocturnal mechanical ventilation for chronic hypoventilation in NMD and chest wall disorders included four randomised trials in a heterogeneous group of patients. Improvement in nocturnal and diurnal arterial blood gas (ABG) tensions occurred, with survival advantage at 1 year. It was not possible to examine secondary outcomes, or outcome in different diagnostic groups or different ventilatory strategies because of small numbers and heterogeneity of the group. A consensus conference [18] has suggested that NIV is indicated in symptomatic NMD patients with one or more of (a) $\text{PaCO}_2 > 6.0 \text{ kPa}$, (b) nocturnal desaturation $< 88\%$ for $> 5 \text{ min}$, (c) for progressive conditions maximum inspiratory pressure $< 60 \text{ cmH}_2\text{O}$ or forced vital capacity (FVC) $< 50\%$ predicted.

Respiratory problems are the dominant cause of mortality and morbidity in congenital NMD affecting the respiratory muscles or chest wall development. The respiratory problems in NMD are multifactorial and to a certain extent may vary from disease to disease. Pulmonary difficulties are due to inspiratory muscle weakness leading to atelectasis and nocturnal hypoventilation, expiratory muscle weakness which impairs cough efficiency, thoracic scoliosis which restricts chest wall and lung expansion, chest deformity and spinal rigidity which increases the work of breathing. Patients with early onset scoliosis (age less than 5 years) [56] and curves involving the cervico-dorsal region tend to have greater respiratory impairment. Bulbar problems may cause aspiration and obstructive apnoeas during sleep. SDB usually precedes ventilatory decompensation [7], and the occurrence of recurrent slow-to-resolve chest infections coupled with progressive SDB usually heralds diurnal respiratory failure. Intercurrent events such as surgery for scoliosis or other orthopaedic procedures may tip the balance into respiratory failure in borderline cases. Rapid growth spurts in adolescence can also cause decompensation. While the natural history of

respiratory decline is relatively predictable in some conditions such as Duchenne muscular dystrophy or Type I SMA, in other conditions such as congenital muscular dystrophy (CMD) or congenital myopathies there may be wide phenotypic variation and the factors contributing to ventilatory limitation (inspiratory and expiratory muscle weakness, type of scoliosis, bulbar involvement) will differ from individual to individual. Other determinants such as need for surgery, weaning, nutritional status and presence of cardiomyopathy may also influence the time to introduce ventilatory support. It is therefore not possible to suggest ventilatory management plans based on a diagnostic label (e.g. CMD, Type I/II SMA) alone.

It should also be recognised that ventilatory care is only part of a respiratory care package which should ensure appropriate use of influenza and pneumococcal vaccination, antibiotics, physiotherapy, speech, swallowing, seating and physiotherapy assessment, and provide support for the family on end-of-life decision-making [57], advance directives and symptom palliation.

Prof Estournet reviewed the huge experience of her centre with the provision of ventilation in NMD, based on a combination of non-invasive and tracheostomy ventilation. The indications for tracheostomy ventilation in summary are that an individual who meets the criteria for NIV has uncontrollable secretions despite the use of expectorants, impaired swallowing and aspiration, persistent symptoms of respiratory failure after NIV or failure to tolerate NIV: other indications include the need for 24 h ventilatory support or patient and carer preference for tracheostomy ventilation.

Dr Kampelmacher reviewed the current practice of home mechanical ventilation (HMV) in The Netherlands by the four centres for HMV, which serve clearly defined regions with approximately four million inhabitants each. In July 2002, a total of 950 ventilator users with NMD (64%), chest wall deformities (20%), pulmonary disorders (12%) and various other problems (4%) were under supervision. Most of them (61%) were using non-invasive ventilation and approximately 15% were ventilated more or less continuously.

Candidates for HMV, who are often presented during multidisciplinary consultations at rehabilitation centres, are invited for a discussion about the pros and cons of HMV in their specific situation. Next, an appointment is made in the outpatient department for assessment of lung and respiratory muscle function. If nocturnal hypoventilation is suspected, candidates are referred to a respiratory unit for confirmation of nocturnal hypoventilation by nocturnal blood gas analysis (either capillary or arterial), end-tidal CO_2 measurement, pulseoximetry, and observation of sleep during 1–4 nights. For this purpose the Utrecht centre uses a respiratory unit located within a rehabilitation centre, which combines the merits of specialised respiratory care and rehabilitation for both children and adults in very comfortable surroundings.

Once nocturnal hypoventilation is demonstrated, HMV is set up non-invasively by nasal or facial mask (about 75% commercially made) or mouthpiece. There is a tendency to use coughing techniques and to postpone invasive ventilation as much as possible, but now and then tracheostomies are needed. Under supervision of a nurse from the centre for HMV, patients are discharged from the respiratory unit to their home (67%), living congregation (28%) or nursing home (5%). Children are usually cared for by their parents and relatives, and only in special circumstances is professional home care needed. Much effort is given to the instruction of health care professionals, non-health caregivers, school personnel, taxi drivers and volunteers in HMV care, particularly with respect to suctioning and cannula care.

At least twice a year, the effectiveness of the ventilation is checked by a full night of pulseoximetry and capnometry in the home setting. In addition, all HMV users are routinely visited at home by a nurse one to four times per year. Additional home visits are made if needed, for instance to repair a custom-made nasal mask or to adjust the ventilator settings. Once a year, HMV users are invited to the outpatient department. Obviously, the centres for HMV offer permanent accessibility and continuous availability. If needed, ventilators are replaced within 2 h. Together with the home care company, which sells and services all equipment, holidays abroad are prepared and organised with respect to HMV. Finally, all HMV centres work in close cooperation with an orthopaedic surgeon, ENT-surgeon and a pediatric pulmonologist.

2.3. Conclusions

The guidelines for treatment of respiratory involvement in childhood NMD (Appendix B) reflect the need for intervention in the acute situation as well as long term. It was the unanimous recommendation of the group that the complexity of management in these patients requires, where possible, the involvement of specialised centres. Although there is a lack of series specifically addressing the individual disorders in question, there is a clear indication to treat the respiratory complications of congenital muscle disorders, and various effective treatments are available. In the current situation, even less data exist on the need for and efficacy of ventilatory support in other congenital muscle disorders, such as congenital fibre type disproportion, but we recommend that these patients also be closely monitored for respiratory function.

Respiratory tract infections are the commonest cause of hospital admission and death in patients with NMD involving the respiratory muscles [41]. The various studies reporting positive results in assisting such patients to achieve a better cough are reflected in the recommendations of the group, though as yet none of these assisted insufflation techniques can be recommended above the others, and the choice may also depend on availability of

equipment and personal preference (Appendix B). While there is clear evidence that physiotherapy-assisted coughing is also a key part of the management of intercurrent acute chest infections in these patients, the relative usefulness of these techniques in the acute situation has not been evaluated and could be the focus of further study.

The reviews of the literature and experience of the group brought about a clear consensus that ventilatory support is effective in this group of patients and this is reflected in our recommendations (Appendix B).

3. Session 3—Specific issues relating to the natural history of respiratory involvement in these disorders

The next session of the meeting focused on the disease subgroups under discussion and specific features of their natural history suggesting that recommendations for management should be more specific than those for the group as a whole. The burden of the respiratory complications in these diseases is summarised in Table 1.

3.1. The congenital muscular dystrophies

Prof Voit (Essen, Germany) reviewed the literature on respiratory impairment and treatment in the congenital muscular dystrophies. This group of disorders is now much better characterised at the molecular level, and the respiratory phenotypes of the specific subgroups are becoming clearer. Even before this subdivision there was clear evidence of respiratory impairment in these disorders. McMenamin and co-workers [58], in 1982, reviewed 24 patients with CMD and observed that 6/24 died from respiratory failure with marked weakness of intercostal and diaphragmatic muscles. The diaphragm was involved in two autopsy cases. Heckmatt and co-workers [59] reported cuirass ventilation in a 6-year-old, non-ambulant CMD patient. Dick and co-workers [60] reported a CMD patient who required ventilatory support from birth but eventually became ambulant. Khan and co-workers [61] gave a comprehensive review of sleep studies and ventilatory treatment in patients with congenital NMD. Their series also comprised two patients with CMD and two with rigid spine syndrome. That patients with rigid spine syndrome are particularly prone to develop respiratory compromise was observed in 1990 already by Morita and co-workers [62]. In these conditions the degree of weakness may be highly variable, but respiratory and facial muscles can be involved, and contractures plus scoliosis are consistent features. Pulmonary hypoplasia may complicate the picture. Although generalised weakness may be static, respiratory decompensation can occur during childhood or adolescence due to a progressive scoliosis and fall in respiratory muscle strength. In a series of CMD children treated by Barois and co-workers [63] one-third had sufficient limb strength to continue walking, but diaphragm weakness was common.

NIV was used in the majority of patients aged 2–10 years, a few patients required tracheostomy. In a series [61] of patients with CMD seen at the Royal Brompton/Hammersmith Hospital, respiratory failure occurred at an average age of 11.6 years. Symptoms and ABG tensions were controlled using nocturnal ventilatory support, allowing the individuals to continue normal activities during the day long term.

More recently, respiratory insufficiency was reported in the initial descriptions of the individual disorders for RSMD-1 [64], for MDC 1B [65], for MDC 1C [66] and for UCMD [67]. A review of current experience from Essen in 27 patients with CMD was presented (10 MDC 1A, two partial MDC 1A, two MDC 1B, four MDC 1C, three RSMD-1, two CMD with rigid spine syndrome, four Ullrich CMD; age 11.4 ± 5.7 years).

Severe restrictive ventilatory defect (IVC <40%) was found in 15 patients. Two patients had moderate restriction (IVC 40–60%), four mild restriction (IVC 60–80%) and three normal lung function. In patients with severe restriction five presented with daytime hypercapnic respiratory failure, eight with nocturnal hypoventilation and two without hypoventilation. In patients with moderate restriction to normal lung function none showed diurnal hypercapnic failure but one girl had nocturnal hypoventilation. Parameters of diurnal and nocturnal gas exchange correlated with IVC and PIP. Patients with frequent chest infections ($n = 12$) had significantly lower IVC and worse gas exchange (daytime PaO_2 and PaCO_2 , mean nocturnal saturation, $P < 0.05$ for all). A clear relation between motor capacities and respiratory function could be observed in patients with primary or secondary laminin- α -2-deficiency: all wheel-chair bound patients had a severe restrictive defect and 9/10 showed nocturnal or diurnal hypoventilation compared to mild restriction or normal lung function and no hypoventilation in ambulatory patients. In patients with the rigid spine syndrome or Ullrich CMD the group found a mismatch between peripheral and respiratory muscles. Respiratory failure in two RSMD-1 and nocturnal hypoventilation (RSMD-1, Ullrich CMD) in three patients occurred despite maintained ambulation.

Data presented by Dr Manzur (London, UK) showed a similar pattern of problems in the different groups. Of 21 children with MDC 1A 11 were ventilated and one had refused. The mean age of starting ventilation was 11.6 years and the earliest 4 years. Most had failure to thrive and required gastrostomy before symptomatic ventilatory insufficiency required the institution of NIV. Over time, respiratory failure is probably invariable in these patients. In MDC 1C, of three patients two are alive aged 5 and 9 not in respiratory failure. One had died aged 7 during an intercurrent URTI. Of 10 patients with RSMD-1 nine are ventilated at an average age of 10 (the earliest at 3), and a key feature in these patients is diaphragmatic weakness, which is seen early clinically and respiratory failure typically occurs in these patients while they are still

ambulant. In 23 patients with Ullrich's CMD, the severity of motor impairment was very variable, but intercostal muscle and diaphragmatic involvement was common, as was spinal rigidity. In this group, respiratory failure typically occurred after the loss of ambulation.

Prof Estournet's data showed very positive results from the use of long-term ventilation in the CMD group. Thirty-one patients with MDC 1A were ventilated, some for many years. Eight patients with MDC 1C were ventilated and six with RSMD-1, with the same observations as the other groups that these patients had a specific predilection for diaphragmatic failure and respiratory impairment while still ambulant. UCMD patients showed the most heterogeneity.

The overall conclusions of the group were that the RSMD-1 and UCMD subgroups of CMD are at specific risk of respiratory failure even while ambulant and should be monitored for diaphragmatic impairment. Respiratory compromise in this group may also be complicated by nutritional problems and assessment of these children should take this into account, with swallowing and dietetic assessment and timely use of gastrostomy vital to overall management.

3.2. Spinal muscular atrophy

The specific focus of this part of the workshop was those children with Type II SMA who often require ventilatory support in the first two decades, while individuals with Type III SMA develop respiratory insufficiency in the second, third or fourth decades, depending on the extent of respiratory muscle involvement and the severity of scoliosis. The natural history of respiratory impairment was reviewed by Prof Iannaccone (Dallas, TX), who described the relatively stable forced VC observed in these patients with age, reflecting a progressive reduction in the predicted value for age and height.

Children with SMA over the age of 2 years have been treated with NIV (mean age 10 years), as have nine children under the age of 2 years (mean age 15.5 months). A tracheostomy was subsequently performed in a minority of patients [68]. A combination of mask ventilation and augmented coughing techniques (e.g. cough insufflator/exsufflator) may be sufficient to support children in the grey area between non-invasive and invasive ventilatory support, say categories 1.7–2.5. Children with Type II SMA show comparable outcome to CMD and congenital myopathy patients. In a London series of Type II SMA patients the average age at initiation of NIV was 5.7 years and long-term survival and quality of life have been encouraging. Only very occasional hospital admission is required and most children are completing schooling and attending university.

The experience of the Hammersmith group (Dr Manzur) shows that of 107 patients with Type II SMA, 12 are currently ventilated, all non-invasively, at a range of ages from 1 to 24 years. Two groups of children could be identified. In the first group, NIV was required before

the age of 7 years, and the indication was often frequent chest infections. In the second group, ventilation was required between 10 and 24 years of age with the indication of symptomatic sleep hypoventilation.

Just as with the congenital muscular dystrophies, difficulties with swallowing and nutrition may complicate the picture and require attention at the same time as ventilatory issues. Similar conclusions were presented by Prof Estournet, who emphasised the importance of holistic respiratory management with respiratory physiotherapy, periodic hypersufflation, use of the percussioneaire, and orthopaedic treatment especially of scoliosis with bracing, surgery and head control.

3.3. *The congenital myopathies and congenital muscular dystrophy*

The natural history of the congenital myopathies (nemaline myopathy, central core disease, myotubular myopathy and multicore myopathy) was reviewed by Dr Wallgren-Pettersson (Helsinki, Finland). These disorders may present with specific problems at different ages. In the neonatal period, severe respiratory insufficiency is common especially in myotubular myopathy but is also seen in some cases of nemaline myopathy and other congenital myopathies. No reliable prognostic indicators have been identified. Although mortality is high in patients lacking spontaneous respiration at birth [69–73], there is even intrafamilial variability [74], and some infants are able to establish spontaneous respiration after an initial period of ventilation [69,72–78].

In the preschool years, respiratory infections may be common [70,73,79]. During the prepubertal period, respiratory infections often become less frequent, but the risk of respiratory failure increases during the period of rapid growth [70,73,79]. In many patients, chest deformity, scoliosis and wheelchair dependency may supervene. In youth and adulthood, the risk of respiratory failure continues even in ambulant patients with otherwise stable muscle strength [70,73,76–86]. In all of these patients the cause of death is almost invariably respiratory. Several studies show a good response to night-time NIV [80,86–90].

These findings were reflected in the experience of the group (presented by Dr Ryan, Dr Manzur, Prof Bushby, Prof Estournet). Relatively few patients with central core disease had respiratory impairment while in the other conditions it was common. As already reported for the allelic condition RSMD-1, respiratory impairment in multicore myopathy commonly occurs while the patients are still ambulant and diaphragmatic involvement plays a major role in the development of these problems in these patients.

The respiratory impairment in congenital myotonic dystrophy was reviewed by Dr Ryan (Sydney, Australia). Significant respiratory involvement is present in at least 50% of infants, with respiratory involvement reflecting lung hypoplasia and immaturity with decreased intrauterine

breathing movements. These infants typically have elevation of the right hemidiaphragm, probably exacerbated by recurrent aspiration. There are also some reports of pulmonary hypertension. There is also a possible role for central respiratory failure. These problems are all exacerbated by the prematurity which is also common in this condition. Respiratory function was an important predictor of long-term survival [91] in 14 infants, 10 of whom were ventilated from birth. If ventilation was required beyond the age of 4 weeks the children died <15 months. Various smaller series show similar results of poor prognosis if ventilation is required for longer than 4 weeks with a significant incidence of sudden death in survivors, even with no preceding respiratory disease apparent. Survivors are also likely to have a very low IQ.

4. Session 4—Discussion and opportunities for further study

The final session of the workshop allowed time to debate various issues of specific importance and milestones in these diseases. For neonates with a need for prolonged ventilatory support, discussion with centres with experience in these disorders is imperative before decisions about continuing or discontinuing treatment are made. In neonates and at all ages, very clear discussion of the endpoint of ventilation will allow appropriate management of the terminal stages of these disorders.

Dr Bullock (Newcastle upon Tyne, UK) led a discussion on the experience of children with these diagnoses who are already undergoing ventilatory support undergoing surgery, for example for scoliosis. The experience of the group was that with very careful preoperative assessment and management of the surgery and postoperative period, surgery is not necessarily contraindicated in these patients, but should be done in experienced centres.

The workshop participants agreed to set up clinical trials that address the impact of ventilatory support in congenital NMD. Two trials have priority:

1. A prospective randomised trial on the impact of early non-invasive ventilation in children with SDB but still compensated diurnal respiratory status. This international multicentre study will focus on the outcome parameters morbidity, health-related quality of life and cost efficiency.
2. A prospective case-control trial on the efficiency of different assisted coughing techniques and its impact on respiratory morbidity.

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Appendix A. Assessment of respiratory function in congenital neuromuscular disorders

NMD presenting in childhood represent a group of disorders in which the involvement of respiratory muscles and subsequent progressive respiratory impairment are common complications. In these patients respiratory failure is a major cause of significant morbidity and early death. Some children with muscle disease are at risk of respiratory complications even in the presence of otherwise stable muscle function and maintained ambulation.

In the literature there are several studies suggesting that ventilatory support, mainly in the way of NIV, consistently improves respiration, symptoms, quality of life and survival, and NIV therefore is considered as effective treatment of chronic respiratory failure due to NMD. Evidence of benefit is based on non-randomised studies only and remains scant in the paediatric setting, particularly in congenital neuromuscular disorders other than Duchenne MD.

The following recommendations are based on literature reviews and on the accumulated experience of the workshop participants with more than 500 patients (see workshop report). The timing of the decline in respiratory function may vary depending on the natural history of the underlying disease, but there are generic guidelines, which can be applied to the group.

A.1. Guidelines

The management of patients with congenital NMD may be complex, it requires special expertise and technical equipment and therefore should be *coordinated* where possible by specialised centres.

The regular *assessment* of respiratory function in children with NMD should be performed by the physicians caring for these patients (neurologist, pulmonologist, paediatric neurologist, etc.) and should include techniques to assess *lung function, nocturnal respiration, cough and symptoms*.

A.1.1. Assessment

Lung function

- It is recommended that *forced vital capacity (FVC in % predicted) in the sitting position* should be performed annually. When FVC is abnormal (<80%) an additional measurement in the *supine position* should be performed to detect potential diaphragm weakness (indicated by >20% drop from baseline).
- FVC <40% and/or diaphragm weakness constitute a significant risk of nocturnal hypoventilation. With FVC >60% there is a low risk of nocturnal hypoventilation.

Nocturnal respiration

- *Continuous recording of overnight pulse oximetry* (and end-tidal or transcutaneous CO₂ if available) *during sleep* should be performed annually when FVC is <60%, more often when FVC is <40%.
- In patients less than 5-years-old in whom FVC cannot be measured, nocturnal pulseoximetry (and end-tidal or transcutaneous CO₂ if available) should be performed at least annually.

If continuous recording of overnight pulse oximetry is not available, the patient should not be left unassessed, but referred to a specialised centre.

Cough

- PCF should be measured annually during a steady state and at any episode of chest infection to determine whether assisted coughing techniques and chest physiotherapy are indicated.

Symptoms

Features of respiratory impairment may include the following, which should be specifically sought and documented.

- Diaphragmatic involvement (suggested by >20% drop in supine FVC or dyspnoea in the supine position, or paradoxical breathing)
- Frequent chest infections
- Bulbar dysfunction
- Feeding difficulties
- Failure to thrive

SDB is typically present in these patients before frank respiratory failure. Symptoms of SDB should be sought and documented at every appointment. These may include:

Night

- Frequent nocturnal awakening
- Nightmares, scary dreams
- Frequent need for turning
- Night sweating

Morning

- Drowsiness
- Difficulty getting going
- Anorexia for breakfast
- Nausea
- Headache

Day

- Drop in energy levels
- Need for a rest after school/frequent naps during the day
- Concentration levels at school dropping
- Loss of appetite
- Bad mood

However, SDB may be present in the absence of symptoms.

Further investigations should be initiated at a centre with adequate expertise if pulse oximetry is abnormal and/or there are symptoms suggesting SDB. Further investigations should include:

Blood gas analysis from arterial puncture or arterialised ear lobe blood in

- patients with symptoms suggesting current respiratory failure;
- patients presenting with current or recurrent lower airway infections;
- patients with abnormal overnight pulse oximetry and/or capnometry;
- FVC <40% predicted.

Polysomnography including capnometry is also indicated if overnight pulse oximetry is not diagnostic in the presence of symptoms suggestive for SDB such as obstructive and non-obstructive apnea, hypopneas or hypoventilation. Polysomnography should be performed according to the guidelines of the American Sleep Disorders Association [99].

Peak inspiratory and peak expiratory muscle pressure

May be used to monitor the severity and course of respiratory muscle weakness.

Appendix B. Ventilatory support in congenital neuromuscular disorders

B.1. Management of acute respiratory infections

- There should be a low threshold for prescription of antibiotics for upper respiratory infections.
- Children should have fast track access to hospital services with experience in these disorders.
- Oxygen therapy may be helpful in the acute situation but needs to be used with caution while monitoring CO₂-tension, because of the risk of hypercapnia, and should *not* be administered as a long-term isolated therapy measure.
- Hospitalised patients require measurement of blood gases.
- Chest physiotherapy and assisted coughing is mandatory. Use of devices to improve insufflation such as the Ambubag™, insufflator/exsufflator (Cough-assist™) or an IPPB-device may be useful.
- Failure to respond to conventional management may necessitate institution of ventilation, usually non-invasively.
- Children already using nocturnal ventilation are likely to require increased use of their ventilator.

B.2. Prevention and management of chronic respiratory failure

- Children should be offered pneumococcal and influenza vaccination.
- Where there are recurrent infections the source of pathogen should be sought and treated appropriately. Recurrent chest infections are defined as three or more

episodes per year of lower airway infections causing significant symptoms and necessitating medical attention and antibiotic treatment.

- Symptoms of bulbar insufficiency also need to be sought.
- There was no evidence for respiratory muscle training being useful in these patients from the studies reviewed, however, definitive controlled trials have not been performed.
- It was accepted that assisted coughing in order to achieve a more effective cough is likely to be useful in these patients in achieving enhanced clearance of secretions and also to prevent chronic atelectasis. Where there is evidence of ineffective coughing (e.g. PCF < 200 l/min) all patients should be taught one of these techniques.

Various methods have been shown to be effective in different settings.

These include:

- Physiotherapy-assisted coughing
- Assisted insufflation, e.g. by Ambu-bag™, IPPB-device or a volume-cycled ventilator
- The insufflator/exsufflator (Cough-assist™)
- Percussionaire

There is a need to conduct trials to determine the usefulness of these different techniques in different settings, e.g. during acute infections, and in terms of the long-term effect on forced VC and susceptibility to chest infections.

B.3. Ventilatory support

- Acute deterioration of chronic respiratory failure is an indication for mechanical ventilation. Whenever possible it should be applied with a non-invasive technique. Patients who require invasive ventilation should be weaned to non-invasive ventilation as soon as possible.
- Symptomatic daytime hypercapnia is a clear indication for non-invasive mechanical ventilation. SDB, gas exchange, symptoms, quality of life and survival are improved by this treatment.
- Mechanical ventilation for symptomatic nocturnal hypoventilation in the absence of daytime hypercapnia appears to be helpful. A CO₂-tension of 6.7 kPa (50 mmHg) for 50% of the sleep time or worse defines nocturnal hypoventilation [22].
- The presence of symptoms such as failure to thrive or recurrent chest infections >3 per year will also influence the decision to ventilate.
- Non-symptomatic nocturnal hypercapnia or hypo-pnoeas require close follow up as these patients are at risk of deterioration. The patient and parents need to be educated about the symptoms and risks. Although published data is lacking, NIV may be

considered on an individualised basis in this group of patients.

Tracheostomy and invasive ventilation should be considered when ventilatory support is indicated in patients

- with severe bulbar involvement and/or recurrent aspiration
- in cases of extreme ventilator dependency
- unable to tolerate NIV
- ineffective NIV
- severe retention of secretions that cannot be cleared by non-invasive techniques

B.4. Disease-specific groups

B.4.1. Congenital muscular dystrophy

Increasing use of specific genetic tests for the subtypes of CMD means that this previously undifferentiated group of patients can be subdivided on the basis of the underlying molecular pathology.

All types of CMD predispose to the development of respiratory failure. Patients with rigid spine muscular dystrophy and Ullrich's CMD are at specific risk of diaphragmatic failure while still ambulant.

B.4.2. Spinal muscular atrophy

Detailed criteria for respiratory care of patients with SMA Types II and III have already been produced [100]. Children with SMA Type II are at particular risk of respiratory impairment and may present with recurrent chest infections or failure to thrive as well as the more classical symptoms of nocturnal hypoventilation. It is important to recognise that failure to thrive in SMA Type II may be multifactorial and is an indication for nutritional assessment, ventilatory assessment and swallowing assessment.

B.4.3. Congenital myopathies

The respiratory involvement in these disorders varies depending on the precise diagnosis (see Table 1). Even patients who are very stable from the muscle perspective may be at risk of respiratory failure, and they and their doctors need to be educated about this risk. NIV is a very effective treatment for these patients.

In those patients with non-specific features of myopathy, even in the absence of a precise diagnosis, surveillance of respiratory function (including erect and supine FVC) is indicated.

Patients with particular types of congenital myopathies may have problems at various ages:

Neonatal period

Myotubular myopathy and nemaline myopathy may present in the neonatal period with failure to establish spontaneous respiration. Careful counselling by experienced clinicians is necessary for neonates requiring

Table 1

Disease	Respiratory involvement (in chronological order)	% of patients in whom abnormalities likely	Age/severity range at onset of respiratory impairment	Treatments used	References
SMA type II	Poor cough, low VC, SDB, NH. Often FTT, recurrent chest infections in early years. May be additional swallowing problems	Probably 100% with time. FVC in SMA is relatively stable in absolute measure but relative to predicted deteriorates with time	Correlates with severity of muscle disease	Assisted cough, NIV, tracheostomy ventilation	Barois and Estournet (1997) [68]; Samaha et al. (1994) [92]; Gozal (2000) [93]; Bach and Wang (1995) [94]; Wang et al. (1994) [95]; Tangsrud et al. (2001) [96]
MDC1A	Poor cough, low VC, SDB, NH. Often FTT, recurrent chest infections in early years. May be additional nutritional problems	Probably 100% with time in total LAMA2 deficiency. Partial deficiency patients may have less respiratory disease	When patients are wheelchair bound	Assisted cough, NIV, tracheostomy ventilation	
MDC1C	Poor cough, low VC, SDB, NH	Probably 100% with time	With severe muscle disease	Assisted cough, NIV, tracheostomy ventilation	Brockington et al. (2001) [66]
Ullrich's CMD	Poor cough, low VC, SDB, NH; Diaphragmatic involvement may be prominent feature from early age	Probably 100% with time	More severely affected patients from muscle perspective show respiratory involvement when WCB. Some mildly affected patients may have diaphragmatic involvement when still ambulant	Assisted cough, NIV, tracheostomy ventilation	Camacho et al. (2001) [67]
RSMD1 and multicore myopathy	Diaphragmatic involvement may be prominent feature from early age	Probably 100% with time	May supervene when patients are still ambulant	NIV	Mogadaszaheh et al. (1998) [64]; Swash and Schwartz (1981) [81]; Rimmer and Whitelaw (1993) [83]; Jungbluth et al. (2000) [90]; Ferreira et al. (2000) [79]
Central core disease		Rare respiratory complications	Very variable; Require respiratory follow-up		
Nemaline myopathy-severe neonatal form	May never establish independent respiration. Others develop spontaneous respiration after a period of ventilation	Most	No reliable prognostic indicators identified; Treatment decisions to be taken in casu, consultation with expert recommended	Full-time ventilation	Wallgren-Pettersson and Clarke (2002) [69]; Roig et al. (1987) [77]; Banwell et al. (1994) [78]; Ryan et al. (2001) [73]
Typical nemaline myopathy	Often present neonatally with floppiness, respiratory and feeding difficulties. Subsequently, recurrent chest infections, poor cough, low VC, often nocturnal hypoventilation	Most will develop problems with time	Decrease in chest infections with increasing age; Need life-long follow-up of respiration	May require some support in the neonatal period. Assisted cough. May require NIV	Maayan et al. (1986) [87]; Wallgren-Pettersson (1989) [70]; Heckmatt et al. (1990) [88]; Howard et al. (1996) [89]; Falga-Tirado et al. (1995) [85]; Jungbluth et al. (2001) [86]; Ryan et al. (2001) [73]
X-linked myotubular myopathy	May never establish independent respiration. Others develop spontaneous respiration after a period of ventilation	Most	No reliable prognostic indicators identified, although, some missense mutations are associated with a better prognosis; Treatment decisions to be taken in casu, consultation with expert recommended	Most require ventilation, NIV or tracheostomy	Wallgren-Pettersson et al. (1995) [71]; Barth and Dubowitz (1998) [74]; McEntagart et al. (2002) [72]
Congenital myotonic dystrophy	50% require ventilation at birth. Others develop respiratory failure in teens/twenties	Probably most	Correlates with severe hypotonia in neonatal period. Later respiratory problems may supervene when still ambulant	NIV/IV	Rutherford et al. (1989) [94]; Hageman et al. (1993) [97]; Roig et al. (1994) [98]

ventilatory support. There are no clear prognostic indicators as to which infants will subsequently become independent of ventilatory support, although in X-linked myotubular myopathy some missense mutations have been associated with a more favourable prognosis. Further studies are required to determine firmer evidence of longer term outcomes, but preliminary data suggest that in myotubular myopathy of those children who survive 30% will require full-time long-term mechanical ventilation.

Preschool years

Surveillance for and treatment of respiratory infections is important in this age range. Surveillance by speech and language therapists and identification of failure to thrive are also important issues.

Puberty

Risk of respiratory failure may be significant in this age group, even in ambulant patients.

Youth and adulthood

It is particularly important to note that these patients, who may remain very stable and with continued ambulation, are at continued risk of respiratory failure.

B.4.4. Congenital myotonic dystrophy

Fifty percent require ventilation at birth and prognosis for weaning after 4 weeks' ventilation is poor. Poor prognosis is also predicted by >2000 CTG repeats in the DMPK gene, prematurity and pulmonary hypertension.

Survivors tend to improve and become ambulant but will develop respiratory failure later. Learning difficulties are invariable in this group.

Specific scenarios

- Severely affected neonates, such as for example children with severe Type 1 SMA or severely affected children with congenital myopathies, where the prognosis is very poor, require very careful family counselling with an expert on these disorders, with full explanation of all the implications of the treatment options.
- At the institution of ventilation there is a responsibility to discuss the end point and the issue of termination of treatment, especially in progressive conditions. Clear guidance as to the prognosis and patient autonomy are necessary features of counselling in this situation. Experience of long-term follow up in these conditions where the natural history has been altered by ventilation is still accumulating.
- Although ventilation is a very effective treatment for respiratory failure in these patients, patients who are ventilated are at very high risk in the wrong hands. Surgery is not necessarily contraindicated but any surgery should be performed in experienced centres.

Patients with these conditions are also at risk of scoliosis, and scoliosis surgery may well be indicated for progressive scoliosis in terms of posture and quality of life. Scoliosis surgery is unlikely to improve respiratory function, except in terms of improving postural effects and preventing loss of lung function due to worsening scoliosis. Where patients are stably ventilated prior to surgery, there will not necessarily be an increase in ventilatory requirement postoperatively. Preoperative assessment is very important and must include full respiratory assessment and assessment of cardiac function. All respiratory therapies must be optimised including ventilation, treatment of co-existent asthma, rhinitis, and treatment of chronic infections. For children with impaired ventilatory function but not yet ventilated, it can be helpful to introduce mask ventilation prior to surgery to facilitate postoperative management.

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