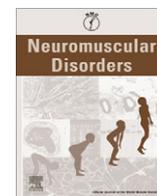




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Workshop report

Respiratory management of congenital myasthenic syndromes in childhood: Workshop 8th December 2009, UCL Institute of Neurology, London, UK

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1. Introduction

A workshop on the respiratory management of congenital myasthenic syndromes (CMS) in childhood was held on 8 December 2009 at the UCL Institute of Neurology, UK. The workshop was sponsored by the Muscular Dystrophy Campaign and attended by 20 participants from 9 centres (8 in UK and 1 in Europe). The aim of the workshop was to review respiratory management of childhood CMS in major UK specialist centres and develop recommendations for standards of care to help anticipate and treat respiratory complications.

The congenital myasthenic syndromes are a heterogeneous group of genetic disorders which result in impaired neuromuscular transmission and fatigable weakness. Advances in molecular genetic diagnosis have led to the identification of distinct genotypes [1] which are associated with particular patterns of respiratory decompensation.

Many CMS children present with respiratory difficulties at birth and most are at risk of ventilatory failure with intercurrent respiratory illnesses. However, recurrent, life-threatening episodic apnoea in infancy and childhood (often precipitated by infection or even stress) is a particular feature of the presynaptic CMS caused by mutations in CHAT and postsynaptic CMS due to mutations in RAPSN. Other phenotypes, such as the synaptic CMS due to mutations in COLQ and the slow channel syndromes caused by mutations in the acetylcholine receptor subunits, cause an end plate myopathy which results in progressive respiratory muscle weakness and respiratory failure requiring long term ventilatory support. The fast channel syndromes are associated with recurrent and particularly severe respiratory crises in infancy and childhood. Other genotypes have diverse respiratory presentations, for example the post-synaptic CMS caused by mutations in DOK7 may be associated, in severe cases, with respiratory failure requiring ventilation at birth, or congenital stridor due to vocal cord palsy often necessitating tracheostomy, without any evidence of the limb gir-

dle weakness which develops later. Progressive respiratory failure may occur in childhood or adulthood.

In recent reviews of 46 CMS children seen at two large regional centres [2,3] we reported the frequency and diversity of respiratory complications in childhood CMS, highlighting the genotype/phenotype correlation which facilitates proactive anticipatory respiratory care. We reported the usefulness of non-invasive ventilation (NIV) for emergency use in children with episodic apnoea, in addition to resuscitation training for all parents and the need to monitor carefully certain genotypes in view of their specific risks. We suggested that all CMS children should be under the care of a specialist respiratory centre and should undergo regular respiratory surveillance. It is important to note that before the identification of CMS in the index cases, several families had suffered the death of one or more children from unexplained respiratory illnesses, very likely to have been associated with undiagnosed CMS.

Significant advances have been made in the respiratory management of most neuromuscular disorders [4], with recommendations for the care of adults, excluding neuromuscular junction disorders [5] and in standards of care documents for childhood disorders such as SMA and Duchenne Muscular Dystrophy [6,7]. However there are no detailed published guidelines regarding respiratory management in the congenital myasthenic syndromes.

This workshop was convened to share information on the respiratory management of childhood CMS in major UK specialist centres, with the aim of improving awareness and devising recommendations for the monitoring and management of respiratory complications. In view of the rarity of CMS and the absence of randomised controlled trials, these recommendations are, of necessity, based on expert opinion and non-analytic studies of small case series.

2. Session 1

2.1. Overview of the congenital myasthenic syndromes (Georgina Burke)

Dr. Georgina Burke (Southampton and Oxford, UK) opened the meeting by giving a comprehensive overview of the known genetic mechanisms underlying pre-synaptic, synaptic and post-synaptic congenital myasthenic syndromes. Currently at least 12 genes have been identified in which mutation events result in abnormal neuromuscular transmission and fatigable muscle weakness. Genetic

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¹ On behalf of [all] participants (see end of report).

mutation data from 268 CMS patients analysed by the UK National Commissioning Group (NCG) service in Oxford illustrated the relative frequency of post-synaptic CMS (92%): AChR deficiency, predominantly *CHRNE* (41%), *DOK7* (19%), *RAPSN* (19%), kinetic AChR defects (12%) compared with pre-synaptic CMS: *CHAT* (3%) and synaptic: *COLQ* (5%) forms. Most CMS are autosomal recessive, apart from the slow channel syndromes which are usually autosomal dominant.

In addition to fatigable weakness, other distinctive phenotypic features may serve as clues to a CMS diagnosis and guide mutation analysis. Pre-synaptic CMS with defective acetylcholine synthesis due to mutations in *CHAT* are usually characterised by onset of CMS symptoms at birth, with life-threatening respiratory crises precipitated by infections, fever or stress. In between crises, infants may be relatively well; CMS symptoms are improved by pyridostigmine and the frequency of crises tends to improve with age. Endplate acetylcholinesterase deficiency, due to mutations in the collagen-like tail subunit gene *COLQ* usually result in a severe CMS, unresponsive to, or worsened by, treatment with pyridostigmine. Weakness is often progressive, with axial involvement resulting in scoliosis and progressive respiratory failure, necessitating nocturnal non-invasive ventilation. Failure to thrive commonly complicates the course of the condition. Clues to the diagnosis include a delayed pupillary response to light and a double CMAP response to a single nerve stimulus. Treatment with ephedrine or salbutamol may improve muscle strength. Post synaptic CMS due to mutations in the acetylcholine receptor subunit genes may result in receptor deficiency and/or kinetic abnormalities of the AChR channel, the slow and fast channel syndromes. *CHRNE* CMS is relatively stable, characterised by ophthalmoplegia in addition to ptosis, fatigable bulbar and limb weakness. Response to pyridostigmine is generally good. By contrast, the rare fast channel syndromes respond less well to pyridostigmine and are subject to frequent, severe respiratory crises which occur rapidly. Onset is usually at birth and may be accompanied by arthrogryposis. The slow channel syndromes are variable in their onset and severity and are unresponsive to pyridostigmine, but improved by quinidine or fluoxetine. Weakness tends to progress, with the occurrence of chronic respiratory failure requiring NIV. Mutations in *DOK7* and *RAPSN*, genes encoding proteins involved in the localisation and maintenance of AChR at the endplate, account for an increasing number of CMS cases, particularly in childhood. *DOK7* CMS is characterised by the onset of limb girdle weakness, often after normal motor milestones, mild ptosis and occasional ophthalmoplegia (usually of up gaze), tongue wasting with 'furling' and a tendency to gradually worsen over time, often with the need for nocturnal NIV. Pyridostigmine may help only initially, if at all and often worsens symptoms. However, weakness may improve with ephedrine or salbutamol. The CMS due to mutations in *RAPSN* may present as an early onset form with weakness from birth, often with arthrogryposis and distinctive episodic apnoeic attacks precipitated by intercurrent infections, fever and stress. Both the apnoeic attacks and the severity of CMS symptoms tend to improve with age. A milder, late onset *RAPSN* phenotype may be difficult to distinguish from 'seronegative' myasthenia gravis in adults.

Rarer CMS genotypes (*LAMB2*, *AGRN*, *MUSK*, *SCN4A* and *PLEC1*) and phenotypes such as limb girdle CMS with tubular aggregates were briefly presented, with the caveat that many CMS cases remain to be genetically characterised, so that further CMS genes are likely to be identified.

2.2. Introduction to respiratory problems in CMS (Stephanie Robb)

Dr. Stephanie Robb (London, UK) introduced the spectrum of respiratory problems affecting CMS children and the importance

of specialist respiratory referral and emergency management with reference to illustrative cases.

Case 1, with *RAPSN* mutations had weakness, respiratory difficulty, mild arthrogryposis and recurrent apnoeic episodes from birth with subsequent acquired microcephaly. The CMS diagnosis was made after she failed extubation following an episode of respiratory failure with an intercurrent chest infection at 4 months. Despite pyridostigmine at 7 mg/kg/day, she went onto have frequent, severe respiratory crises, initially requiring intubation, later successfully managed with NIV, rescue (AMBU) bag and parental training in CPR. Incidental tonsillar hypertrophy resulted in upper airways obstruction, necessitating nocturnal NIV, but with complete resolution following emergency tonsillectomy. Now aged 6 years, she attends mainstream school, her episodic apnoeas are less frequent and she is able to ask for her non-invasive ventilator if she has warning of impending weakness.

Case 2, with *CHAT* mutations, also presented with recurrent apnoea in infancy and had been treated with carbamazepine for suspected epilepsy, despite a normal EEG. Although a CMS was later suspected after demonstrating decrement following prolonged RNS at 10 Hz, response to pyridostigmine was incomplete. Genetic diagnosis was confirmed after he presented with profound apnoea associated with influenza A infection at age 4 and required tracheostomy to be weaned from the ventilator. He failed to respond to the addition of 3,4-diaminopyridine to his pyridostigmine, but has been helped by the addition of ephedrine, and subsequently, salbutamol. His tracheostomy was successfully decannulated with the aid of NIV at age 6 years and NIV was required thereafter for infrequent respiratory crises. With growth in adolescence, he developed increasing weakness and fatigue, with borderline nocturnal hypoventilation, the need for supplemental feeds via gastrostomy and powered wheelchair use in. It is noteworthy that aged 12 years after a 2 years apnoea free interval, he had a respiratory arrest in association with an upper airways infection at home and was successfully resuscitated by his father with no neurological sequelae. This emphasises the need to continue regular resuscitation updates for parents even though the incidence of apnoeic episodes declines with age. Case 3 (severe slow channel syndrome due to a heterozygous mutation in *CHRNA1* with symptoms from birth) and case 4 (with homozygous mutations in *COLQ*) were presented to illustrate the progressive nature of these CMS, with gradual onset of nocturnal respiratory insufficiency necessitating use of NIV at night, together with the need for gastrostomy feeding and spinal fusion before the age of 10 years. Finally, attention was drawn to the incidence of neonatal stridor (often due to bilateral vocal cord palsy) accompanied by feeding difficulty as an early presenting feature of *DOK7* CMS, which predated the onset of weakness in 6 of 11 *DOK7* cases seen at Great Ormond Street Hospital for Children [8].

2.3. CMS respiratory problems – Royal Brompton Hospital Review (Anita Simonds)

Dr. Anita Simonds (London, UK) presented a detailed analysis of a sub-group of CMS patients referred to RBH for ventilatory assessment. The group was part of a cohort of CMS children reported by Kinali et al. [2]. Of those 46 CMS children, 33/46 had genetic mutations identified (10 *RAPSN*, 7 *COLQ*, 6 *CHRNE*, 8 *DOK7*, 1 *CHRNA1* and 1 *CHAT*). Twenty-four children needed acute or long term respiratory support, with non-invasive ventilation (NIV). Eleven CMS children have their current respiratory management at RBH (4 *COLQ*, 1 *CHAT*, 1 *CHRNE* fast channel, 2 *RAPSN* and 3 unclassified). Details were presented of their clinical course, ventilatory assessment, pulmonary function tests and sleep studies. The principles of management for the children were that they started on NIV if diurnal hypercapnia, or nocturnal hypoventilation was identified,

or started on acute application of NIV for myasthenic crisis, or that NIV was not indicated. In addition, all families were trained in basic life support and in physiotherapy for airway clearance. The results grouped for genotype were as follows:

COLQ: 4 patients were referred at ages 2, 10, 10 and 8 years old. O₂/CO₂ sleep study results: mean TcCO₂ 8 ± 1 kPa; mean SaO₂ 96 ± 1%; nadir SaO₂ 76 ± 7%.

All use NIV at night and 3 use NIV in the day for rests.

CHAT: 1 child, presenting in infancy with a history of acute apnoeic episodes/respiratory crises in response to infection. Referred aged 5 years post ITU stay with tracheostomy in situ. O₂/CO₂ sleep study results: mean TcCO₂ 7.5 kPa; mean SaO₂ 97%; nadir SaO₂ 90%. The tracheostomy was decannulated, he uses NIV when unwell and acutely for severe acute cyanotic/apnoeic episodes.

CHRNE: Presentation at birth with stridor due to bilateral vocal cord palsy, referred aged 6 months with a history of acute respiratory episodes/crises with infection and reflux. O₂/CO₂ sleep study: mean TcCO₂ 6.5 kPa; mean SaO₂ 98%; nadir SaO₂ 80%. She uses NIV acutely for severe acute cyanotic/apnoeic episodes.

RAPSN: One presentation at 15 months following respiratory arrest with tonsillitis.

O₂/CO₂ sleep study post tonsillectomy: mean TcCO₂ 6.2 kPa; mean SaO₂ 97%; nadir SaO₂ 93%. Mild phenotype and has not required NIV use.

One presented at birth, followed by apnoeic episodes/crises in infancy. O₂/CO₂ sleep study: mean TcCO₂ 7.0 and 7.5 kPa; mean SaO₂ 97%; nadir SaO₂ 79 and 81%. NIV used nocturnally and also acutely for severe cyanotic/apnoeic episodes.

Overall the results showed that in this small group of children with mixed genotypes, NIV was used together with cardiopulmonary resuscitation with AMBU bag to successfully manage episodic apnoea/myasthenic crises in six children, from as young as 6 months of age. NIV successfully corrected nocturnal hypoventilation in all 4 COLQ patients and 2 with unclassified mutations. Two patients did not require NIV for episodic apnoea as no further episodes occurred. Ten of 11 patients required supplementary feeding with PEG for bulbar/swallowing problems. All patients who received NIV had battery provision. A correlation was noted between growth spurts and temporary worsening nocturnal hypoventilation.

Predisposing factors and management of myasthenic crises. Factors associated with myasthenic apnoeic crises included: heat, tonsillar hypertrophy resulting in obstructive sleep apnoea (OSA), gastro-oesophageal reflux, emotional stress and temper tantrums. Patients who presented at birth or early in life with apnoea, vocal cord palsy or bulbar/feeding issues were more likely to have myasthenic respiratory crises. Our cases of pre-synaptic and synaptic CMS were more likely to have nocturnal hypoventilation. As expected, the need for NIV during acute apnoeic decompensation was not predicted by sleep study.

Practicalities of management. The ventilator should be small, ideally a bilevel device, portable with easily attachable battery, adjustable settings and easy to connect to mains electricity supply.

Ventilator settings may be higher than expected, e.g. inspiratory positive airway pressure (IPAP) 14–18 cm H₂O and expiratory positive airway pressure (EPAP) 4 cm H₂O with age appropriate breaths per minute back-up rate (BPM) to support weak respiratory muscles and overcome upper airway obstruction. Children and families using NIV for occasional apnoeic episodes need regular acclimatisation to the device and refitting of the mask as they grow. Resuscitation training should be given to parents, with regular refresher courses. Training is also needed for community nurses and school staff, teachers and assistants. Class sessions are helpful to educate and reassure other pupils and friends.

Summary of Brompton experience

- In this group the ventilatory course in COLQ patients tended to be progressive whereas in RAPSN, CHRNE and CHAT sudden apnoeas/crises predominate.
- Respiratory management has not previously been specified but based on our findings we would recommend:
 - i All parents should be taught CPR at diagnosis and AMBU bag/mask ventilation for those susceptible to sudden apnoea.
 - ii NIV should be considered, especially in patients with COLQ mutations/nocturnal hypoventilation.
 - iii NIV for episodic use should be available and is a valuable addition for emergencies, even in children who are relatively well between myasthenic crises. Apnoeic events may reoccur after a long period without a crisis in some patients.
 - iv Remember other sensible measures: flu and pneumococcal vaccination.

2.4. NCG CMS respiratory cases in Oxford (Jeremy Hull)

Dr. Jeremy Hull (Oxford, UK) presented details of six CMS children followed by his service. These were RAPSN (2), CHRNE slow channel (1), CHRNE fast channel (2) and DOK7 (1). The child with slow channel syndrome, aged 15 years 8 months had required nocturnal non-invasive ventilation for sleep hypoventilation from the age of 7 years. The child with DOK7 CMS had needed a tracheostomy at 3 months of age because of recurrent respiratory crises and bilateral vocal cord palsy and required nocturnal ventilation for sleep hypoventilation. The two children with fast channel syndrome had respiratory crises managed with invasive ventilation (1 episode in one aged 2 years 7 months, whose parents were resuscitation trained and had an AMBU bag and eight episodes in the second, aged 2 years 10 months, who also had use of NIV at home for crises). Of the 2 RAPSN cases, one aged 5 years 5 months had three hospital admissions for episodes of respiratory distress and one episode requiring invasive ventilation, but had no episodes for the last 3 years and did not require active respiratory management. The younger RAPSN patient, aged 2 years 2 months had three episodes of invasive ventilation, parents had resuscitation training and provision of an AMBU bag. Dr. Hull commented that the fast channel syndrome child who required multiple hospital admissions for ventilation was the most challenging of the CMS children to manage. The problem of recurring, severe respiratory crises in fast channel syndrome patients is evident from a case series seen in Oxford, currently being prepared for publication.

2.5. CMS service in Scotland (Robert McWilliam)

Dr. Robert McWilliam (Glasgow, UK) presented the group of children with myasthenia under his care and that of the respiratory team. Most did not yet have a molecular genetic diagnosis. Although often geographically isolated from specialist centres, local emergency medical services were usually highly skilled in managing acute respiratory difficulties.

2.6. CMS cases in Newcastle upon Tyne (Tracey Willis)

Dr. Tracey Willis (Newcastle upon Tyne, UK) described the congenital myasthenia service in Newcastle upon Tyne. Sixteen patients (eight children) are followed in the 3 monthly myasthenia clinics. Nine are molecularly characterised (1 CHAT, 3 CHRNE, 3 DOK7 and 2 RAPSN). The child with the CHAT mutation presented with an acute life-threatening illness aged 5 months and had a tracheostomy at 7 months. Currently at age 5 years she still has a tracheostomy and

receives ventilation via this when she has a respiratory tract infection or cold. One child with DOK7 has stridor when fatigued, which is reproducible in clinic after exercise. One adult has been successfully treated with nocturnal NIV for 35 years.

2.7. CMS service at the Evelina Children's Hospital (Elizabeth Wraige and Debbie Clarke)

Dr. Elizabeth Wraige and Ms Debbie Clarke (London, UK) gave an overview of their CMS service, which provides care for children from South Thames and South East England. There are currently 16 CMS children (*RAPSN 5*, *COLQ 2*, *PLEC1 1* and 7 unclassified). Three require ongoing respiratory support with nocturnal NIV (*COLQ 2* and 1 unclassified) and these have been included in the Royal Brompton Series, presented earlier by Anita Simonds. Debbie Clarke discussed the role of the nurse specialist in supporting families, as a contact point for advice about respiratory problems and in liaising with local services, notably around discharge planning from hospital.

2.8. Weaning from tracheostomy to NIV (David Kilner)

Dr. David Kilner (London, UK) spoke about the specific difficulties to be considered in weaning CMS children from tracheostomy to NIV. This is relevant to those children who may have had a tracheostomy in infancy, often before the diagnosis of CMS was established and who, on confirming the diagnosis then receive specific treatment. This has been the case particularly in children who present with stridor due to vocal cord palsy, many of whom have DOK7 CMS. Pharmacological treatment may improve vocal cord mobility and respiratory muscle strength, potentially allowing the children to manage with NIV.

2.9. Competency training with NIV/AMBU bag for parents and schools (Michelle Chatwin)

Dr. Michelle Chatwin (London, UK) presented procedures used for competency training of parents and carers in the management of respiratory failure at the Royal Brompton Hospital. As there have been no randomised controlled trials in this area, the information presented is based on clinical experience of the management of CMS children at the Brompton. The first priority is to teach basic life support (BLS), according to the recommendations of the Resuscitation Council (UK), with specific attention to the advice for rescue breaths in children over 1 year of age and in infants. It is important to ensure annual updates, ensure school nurses and any other carers involved are trained and ensure that the ambu-

lance service is aware of the fact the child has life-threatening episodic apnoea.

NIV is used if the child is demonstrated to be hypercapnic at night and the settings are titrated in hospital to correct hypercapnia. For daytime episodic apnoea only, it is important to ensure parents are competent in mask fitting and reassess masks at clinic as children may grow out of them if having a long period of stability. Parents are instructed to set the ventilator in order to see good chest wall movement during apnoea it may be necessary to increase the pressure to achieve this. Therefore ventilator settings may need to be higher than expected (e.g. IPAP 14–18 cm H₂O and EPAP 4 cm H₂O and age appropriate breaths per minute back-up rate). Parents need to bring out and test the ventilator regularly to ensure they remain competent. An update in ventilator use is arranged annually and school nurses and any other carers involved are trained. Parents are instructed on the management of acute respiratory failure according to the flow chart in Fig. 1.

Parents/carers should be trained in basic life support (BLS). This will familiarise them with the essentials of ensuring safety of the rescuer and child, identifying whether the child is responsive, summoning help, assessing the airway and breathing, and establishing whether there are signs of circulation. In most short lived apnoeic episodes, circulation is maintained, unless the episode becomes protracted. Parents are shown how to give rescue breaths by mouth to mouth but also provided with an AMBU (rescue) bag and instructed in its use to deliver breaths, emphasising that its use should complement, rather than replace their BLS training.

Parents need to have a good understanding of the aims of providing a ventilator: i.e. overnight use if hypercapnic, emergency use if the child is fatigued or floppy, liberal use if unwell, particularly with a chest infection and to recover from an apnoeic episode. Ventilators need to be portable with battery backup as apnoeic episodes may occur unexpectedly when the child is away from home. It may be necessary to provide a full-face mask for apnoea episodes, an oxygen saturation monitor and suction equipment if secretions are a problem. In addition, it is important to ensure that respiratory physiotherapy is taught. The necessary competencies are examined and signed off before the child's discharge from hospital (Table 1).

3. Session 2

3.1. Stratification of respiratory risk

This session began with emphasis on the importance of early recognition of CMS symptoms and referral for expert neurophysio-

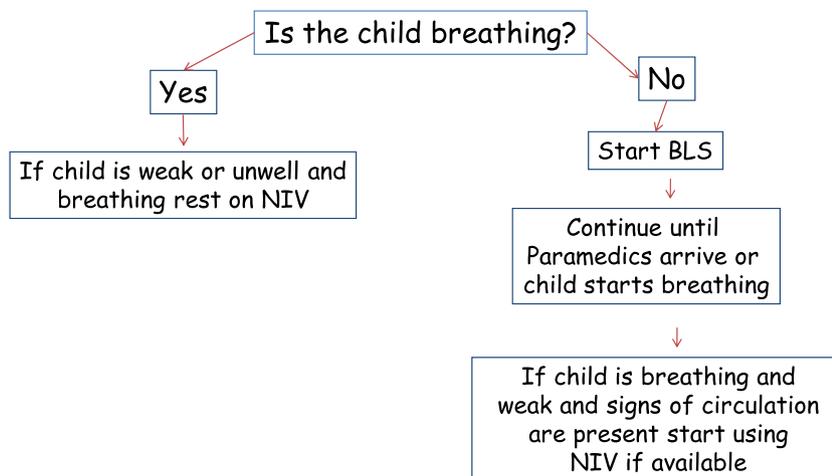


Fig. 1. Procedures to be followed by parents/carers in the acute management of respiratory failure in a CMS child.

Table 1

Respiratory management of CMS children: parent and carer competencies to be signed and agreed.

<input type="checkbox"/> BLS taught and competent
<input type="checkbox"/> Able to turn ventilator on and off
<input type="checkbox"/> Able to put mask on and off
<input type="checkbox"/> Understand I need to see chest wall movement and if I don't I need to increase IPAP
<input type="checkbox"/> Can change filters, tubing and wash mask and head gear
<input type="checkbox"/> Can attach battery/Handy mains
<input type="checkbox"/> I have contact details and know how to call in the event of a breakdown
<input type="checkbox"/> Reassessed year _____
<input type="checkbox"/> BLS refreshed
<input type="checkbox"/> Setting check
<input type="checkbox"/> Parents still competent with ventilator use
<input type="checkbox"/> School had update

logical diagnosis. Although susceptibility to bulbar and respiratory decompensation with intercurrent illness occurs in most CMS children and adults, a precise genetic diagnosis is crucial to predict more specific patterns of respiratory involvement associated with individual genotypes. In the UK DNA samples are referred for genetic analysis to the UK NCG service for CMS in Oxford. Where phenotypic features are unclear, patient referral to Oxford for clinical assessment helps target genetic diagnosis.

3.2. General measures for all CMS children

The following recommendations were suggested

- All confirmed or suspected CMS children should have fast track access to their local paediatric service in the event of illness or in an emergency. Respiratory failure may develop in a matter of hours, even in those with a relatively 'low risk' genotype, so that early assessment is important whenever a CMS child is unwell. Informing the ambulance service for those children subject to very rapid decompensation/episodic apnoea is important with the fast track letter emphasizing that even though the child may look relatively well, based on previous history or genotype he or she needs urgent admission. A documented plan for respiratory management, with contact details of the specialist centre is recommended. The letter should also list current medication and dose, with recommendations, for those children treated with pyridostigmine, for the equivalent dose of IM neostigmine that should be used if they are unable to take, or absorb, their medication by the oral route.
- Parents of all CMS children should receive training in basic life support (BLS), including the management of choking. Training should be updated annually.

3.3. Escalate priority for those at high risk

- CMS children with genotypes associated with sudden, rapid decompensation (such as *CHAT*, *RAPSN* and fast channel syndromes), those associated with progressive respiratory failure (*COLQ*, *DOK7*, severe slow channel syndromes) and others with a history of respiratory illness or bulbar insufficiency should be referred to their regional paediatric respiratory centre for assessment including formal sleep study and management and to formulate a respiratory care plan.

3.4. Recommendations for respiratory assessment and management

- Parents need to be aware of the warning signs indicating impending respiratory crises. Training in recognizing this should be mandatory in those families with at-risk genotypes and in those where children have already had a respiratory illness. Awareness of fluctuation in respiratory muscle strength in

relation to medication and time of day and the effects of intercurrent illness, particularly vomiting and diarrhoea (when medication may not be absorbed), were discussed, highlighting the importance of seeking advice sooner than later.

- The unpredictable nature of many respiratory crises was emphasized, so that parents and carers need to be vigilant and, for those with episodic apnoea, carry their AMBU bags and or ventilator with them outside the home.
- Screening CMS children for respiratory risk involves taking a meticulous history of previous respiratory episodes and an overnight sleep study with O₂ and CO₂ monitoring. More complex respiratory function tests may not be necessary, particularly in younger children.
- The use of non-invasive ventilation for pre-crisis management has been very successful in the Royal Brompton Hospital series, but in the face of a normal overnight sleep study is not yet part of the recognized orthodoxy of treatment. Likewise, although small rises in nocturnal pCO₂ (e.g. to 6.5 kPa) may be tolerated by some patient groups, a lower threshold for treatment may be necessary in this group of children.
- Careful liaison with all team members and perioperative High Dependency Unit or Intensive Care is advisable for CMS children undergoing elective surgical procedures, so that impact of anaesthetic drugs, adjustment of medication and ventilatory support is fully available.
- More detailed knowledge of the natural history of individual genotypes will be important to ensure appropriate monitoring over time. Adults may be more at risk of hypoventilation as episodic crises reduce with age whilst end plate myopathy progresses.
- In communicating these risks to the parents of children newly diagnosed with CMS, it is important to emphasise that training in BLS and respiratory crisis management is crucial to keep their child safe, whilst acknowledging that some may never need to use their skills.
- It was suggested that a questionnaire/checklist (Table 2) may be helpful in ensuring recommendations are implemented and to audit their effectiveness.
- General measures, such as flu and pneumococcal vaccination, training in chest physiotherapy, a supply of powdered antibiotics at home for use 'out of hours' and monitoring and management of other contributing factors such as bulbar weakness, tonsillar hypertrophy (which, even if moderate may be significant in the face of respiratory muscle weakness), gastro-oesophageal reflux and oral secretions were also recommended.
- For those children under the care of a specialist respiratory centre, a checklist of parental/carer competencies in recognizing alarm signs, BLS and ventilator use, should be completed before the child is discharged after respiratory assessment.

3.5. Weaning the ventilated CMS infant and child

- Based on their personal experience, the group felt that few CMS infants required long term ventilation in the absence of bilateral vocal cord palsy. In CMS infants or children already ventilated, appropriate treatment with pyridostigmine, 3,4-DAP, fluoxetine, salbutamol or ephedrine according to genotype [9] with optimal timing and dosage of medication is used to maximize respiratory and bulbar muscle strength. NIV may be useful in the transition phase and may be needed long term at night for some children, as guided by the results of sleep studies. Occasionally NIV may be required for periods during the day either to deal with apnoeic episodes, during chest infections or teenage growth spurts when respiratory muscle strength may be outstripped by rapid skeletal growth and ventilator demands increase.

Table 2
Proposed checklist for CMS respiratory management.

<p>CMS genotype (if known): Stratification of risk based on: previous history <input type="checkbox"/> genotype <input type="checkbox"/> both <input type="checkbox"/> High risk of: episodic apnoea <input type="checkbox"/> hypoventilation <input type="checkbox"/> Low risk genotype: <input type="checkbox"/> Specialist Paediatric Respiratory Centre referral: Respiratory history: Neonatal: stridor <input type="checkbox"/> vocal cord palsy <input type="checkbox"/> respiratory failure <input type="checkbox"/> Neonatal O₂ <input type="checkbox"/> CPAP <input type="checkbox"/> IPPV <input type="checkbox"/> Tracheostomy <input type="checkbox"/> Details of how long needed: Previous chest infections <input type="checkbox"/> Previous IPPV <input type="checkbox"/> frequency: Previous episodic apnoea <input type="checkbox"/> frequency: Morning headache <input type="checkbox"/> Poor appetite <input type="checkbox"/> Daytime somnolence <input type="checkbox"/> Medication: Pyridostigmine <input type="checkbox"/> 3,4-diaminopyridine <input type="checkbox"/> ephedrine <input type="checkbox"/> Salbutamol <input type="checkbox"/> fluoxetine <input type="checkbox"/> quinidine <input type="checkbox"/> other <input type="checkbox"/> Bulbar problems: Prolonged mealtimes <input type="checkbox"/> swallowing difficulty <input type="checkbox"/> cough <input type="checkbox"/> choking <input type="checkbox"/> Aspiration <input type="checkbox"/> nasal escape <input type="checkbox"/> underweight for height <input type="checkbox"/> Excessive secretions <input type="checkbox"/> Videofluoroscopy <input type="checkbox"/> age and findings: Respiratory assessment: FVC result: Sleep study result: Respiratory management: BLS taught: parents <input type="checkbox"/> carers <input type="checkbox"/> AMBUC bag <input type="checkbox"/> NIV emergency use only <input type="checkbox"/> NIV at night <input type="checkbox"/> Tracheostomy <input type="checkbox"/> Parent/carer competency check <input type="checkbox"/> Fast track access to local hospital <input type="checkbox"/> Letter for ambulance service <input type="checkbox"/> Flu/pneumovax vaccination <input type="checkbox"/> Powdered antibiotics at home <input type="checkbox"/></p>

3.6. Screening neonates with stridor and vocal cord palsy for CMS

- Recognition of congenital VCP as an early symptom of CMS is very important, as successful treatment may improve vocal cord mobility and hence respiratory prognosis. A high index of suspicion in infants with neonatal stridor due to VCP and neurophysiology by an experienced operator may enable an early CMS diagnosis in the neonatal period so that, in some cases tracheostomy may be avoided [9].

3.7. Monitoring infants and children at home

- The panel discussed whether provision of a home oximeter monitor was useful for parents, bearing in mind that normal SpO₂ may give false reassurance despite a significant rise in pCO₂ which will go undetected. It was agreed that an oximeter may be helpful for experienced parents to use when their child is only mildly unwell, particularly at night, to guide the need for non-invasive ventilation and/or hospital admission.

3.8. Trials of medication

- Treatment with pyridostigmine (and neostigmine) may cause deterioration with apnoea in some CMS genotypes. The panel recommended that trial of medication in CMS is better deferred if possible until the genotype has been confirmed. However in those CMS children with significant weakness, it may be necessary to consider a trial of medication before the genetic diagnosis is available. It was agreed that such a trial should always be com-

menced in hospital, with the availability of full resuscitation facilities. Medication should be given in low dose and gradually increased. Where the phenotype is more suggestive of COLQ or DOK7 CMS a trial of salbutamol or ephedrine is more appropriate, but it must be recognized that the time scale for improvement is much longer, over weeks and months. In urgent circumstances the Oxford NCG DNA lab may be able to provide rapid screening for DOK7 and COLQ in those infants at risk, so that medication may be reasonably deferred until these genotypes are confirmed or excluded. A clinical referral to the NCG service in Oxford specifically for medication trial may be considered.

3.9. Family support networks

- Finally, the burden for parents of recurrent respiratory crises, with the need for constant vigilance, ensuring the availability of non-invasive ventilation at home, at school and even on family outings was acknowledged. Support from the local community nursing and paediatric teams, the local children with disabilities service as well as the regional neuromuscular and respiratory centres are crucial. Patient support networks such as the Myasthenia Gravis Association and particularly the recently established support group for children and young people in the UK (Myasthenickids.org) are an important source of advice.

Workshop participants

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