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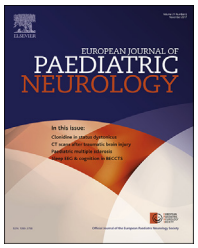

Original article

Sleep in infants with congenital myasthenic syndromes

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ABSTRACT

Background and objectives: Infants with congenital myasthenic syndrome (CMS) are at risk of brief resolved unexplained event (BRUE) and sleep-disordered breathing. The aim of the study was to explore sleep in infants with CMS with a particular focus on heart rate (HR) variability.

Methods: Overnight polygraphy was performed and HR variations associated with respiratory events were analysed. Bradycardia and tachycardia were defined as a variation of HR of ±10 bpm from baseline and analysed as events/hour.

Results: The data of 5 infants with CMS were analysed. Two patients had known mutations (COLQ and RAPSN). One patient had a tracheostomy. The apnoea-hypopnoea index (AHI) was abnormal in all the patients (range 2.8–47.7 events/h), with the highest AHI being observed in the 3 youngest infants. Nocturnal transcutaneous gas exchange was normal in all patients except the tracheostomised patient. Mean HR was 114 ± 23 bpm with a mean HR index of 4.5 ± 4.3 events/h. The amplitudes of HR variations (bradycardia or tachycardia) were around 15–20 bpm, regardless of the type of respiratory event, and comparable between patients. No correlations were found between HR indexes or variations and the type and mean duration of respiratory events. Ventilatory support was initiated in 3

Abbreviations: CMS, congenital myasthenic syndromes; ENMG, electroneuromyography; RNS, repetitive nerve stimulation; Stim-SFEMG, stimulation single fibre electromyography; NIV, non-invasive ventilation; BRUE, brief resolved unexplained event; PSG, polysomnography; SDB, sleep-disordered breathing; HR, heart rate; PG, polygraphy; CSA, central sleep apnoea; OSA, obstructive sleep apnoea; MSA, mixed sleep apnoea; AHI, apnoea-hypopnoea index; $PtcCO_2$, transcutaneous carbon dioxide; DI, desaturation index; ΔDesaturation, maximal variation in SpO_2 desaturation; ΔHR, variations in HR.

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infants immediately after the sleep study because of a high AHI and/or nocturnal hypoventilation.

Conclusions: All 5 infants had an abnormal AHI with younger infants having the highest AHI. Three infants required ventilatory support after the polygraphy, underlining its clinical usefulness. No significant abnormalities of HR were observed during the sleep studies.

1. Introduction

Congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders caused by an abnormal signal transmission at the motor endplate, a special synaptic contact between the motor axon and the skeletal muscle fibre. The molecular defects involved in CMS may be caused by mutations in different genes encoding presynaptic, synaptic and postsynaptic neuromuscular junction proteins,[1] all leading to muscle weakness. Targeted genetic analysis is done if a phenotypic clue points to one or limited number of genes.[2] However, 40–50% of genes involved in CMS are still not identified.[3] Despite important advances in the understanding of molecular pathogenetic mechanisms involved in CMS, diagnostic challenges remain, particularly in childhood, and diagnosis may be delayed because of symptom overlaps and misdiagnosis.[1,3,4] The diagnosis of CMS is therefore based on the association of clinical signs, electroneuromyography (ENMG) and muscle biopsy.[2] Indeed, fatigable weakness especially of ocular and cranial muscles, a positive family history and ENMG studies, with repetitive nerve stimulation (RNS) and stimulation single fibre electromyography (StimSFEMG),[5] can assist the diagnosis. In case of negative diagnostic tests but suggestive symptoms, a therapeutic trial with short-acting cholinesterase inhibitors is recommended.[6]

Infants with CMS may present with respiratory distress, recurrent episodic apnoeas when awake, bulbar weakness, vocal cord palsy, stridor and laryngospasm requiring non-invasive ventilation (NIV) and/or a tracheostomy.[1,2,7–9] Myasthenic crisis causing respiratory failure has been shown to be associated with about 10% mortality.[10] Moreover, 3 studies reported the presence of severe and recurrent brief resolved unexplained events (BRUE) as first symptoms in infants, which investigations led to the diagnosis of CMS.[6,8,9] Even if the role of polysomnography (PSG) was found to be neither sufficiently distinctive nor predictive of BRUE,[11] recent guidelines recommended a systematic PSG in infants who have experienced a BRUE or when there is clinical evidence of sleep-disordered breathing (SDB).[12] A PSG is thus theoretically recommended in all infants with a suspicion of or confirmed CMS, as these infants are at high risk to develop BRUE and/or SDB due to the combination of hypotonia, apnoea and/or laryngospasms.[13]

Surprisingly, very few studies analysed breathing pattern and heart rate (HR) variations during sleep in infants with CMS.[13] As infants with CMS may present with SDB and as respiratory events are associated with variations in HR, we wanted to see if respiratory events were associated with abnormal HR variations, which could precipitate or explain BRUE in these infants. The aim of our study was therefore to analyse respiratory events and HR variability during sleep in infants with CMS.

2. Patients and methods

2.1. Patients

We conducted a retrospective review of the clinical charts and polygraphies (PG)/PSG of infants with CMS younger than 2 years old, who were referred to the Sleep and Noninvasive ventilation Unit of Necker Hospital in Paris or to the Bronchopneumology Unit of Children Hospital Bambino Gesù in Rome between April 2011 and September 2015. PG/PSG was performed because of the suspicion of a neuromuscular disorder or the confirmation of CMS, SDB and/or the presence of BRUE. Diagnosis of CMS was based on characteristic clinical symptoms, with suggestive ENMG and/or muscular biopsy and/or DNA analysis. Clinical data such as family history, clinical symptoms and their evolution, genetic and metabolic studies, ENMG studies, including RNS and StimSFEMG of orbicularis oculi, muscle biopsy, cardiac monitoring, electroencephalography, upper airway examination, pH monitoring, oesophagus-stomach-duodenum contrast, videofluoroscopy, cerebral magnetic resonance imaging (MRI), chest computed tomography scans, coexisting medical conditions, surgical history such as tracheostomy and gastrostomy, use of NIV and evaluation of symptoms of SDB were gathered. The study was approved by the ethical committee (CPP Ile de France II, n° 2014-03-09 SC) and informed consent was obtained from parents.

2.2. Sleep study

Overnight PG/PSG was performed during spontaneous breathing in room air with the recording of nasal flow, respiratory inductive plethysmography, tracheal sound, body position, HR, and pulse oximetry (SpO_2) (Cidelec polysomnograph, CID102L8D, Angers, France; Alice 6LDX Sleepware by Philips-Respironics, Carquefou, France; Compumedics Sleep Monitoring System C510, Charlotte, NC, USA).[14] The sleep study was recorded on videotape with an infrared video camera. Obstructive sleep apnoea (OSA) was defined as a drop in nasal flow amplitude by 90% of baseline for at least two respiratory cycles, with continued or increased inspiratory effort. Central sleep apnoea (CSA) was