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CASE REPORTS

# Progression of Polysomnographic Abnormalities in Mucolipidosis II (I-Cell Disease)

William I. Wooten III, MD[1]; Marianne S. Muhlebach, MD[2]; Joseph Muenzer, MD, PhD[3]; Ceila E. Loughlin, MD[2]; Bradley V. Vaughn, MD[4]

*[1]Department of Pediatrics, Division of Pulmonology, Brody School of Medicine at East Carolina University, Greenville, NC; [2]Department of Pediatrics, Division of Pulmonology, University of North Carolina at Chapel Hill; [3]Department of Pediatrics, Division of Genetics and Metabolism, University of North Carolina at Chapel Hill; [4]Department of Neurology, Division of Sleep Medicine, University of North Carolina at Chapel Hill*

Mucolipidosis II (Inclusion cell or I-cell disease) is an autosomal recessive lysosomal storage disorder clinically comparable to the mucopolysaccharidoses (MPS), characterized by progressive respiratory and neurologic deterioration. Sleep problems, especially obstructive sleep apnea (OSA) and disrupted sleep architecture, are observed in other lysosomal storage diseases but have not been described in mucolipidosis II. We report the progression of polysomnographic abnormalities in a child with mucolipidosis II, demonstrated by worsening sleep-related hypoventilation, OSA, and sleep state fragmentation despite advancing PAP therapy. Background slowing and reduction in spindle activity on limited EEG may reflect progressive CNS disease affecting thalamic neurons.

**Keywords:** mucolipidosis, I-cell disease, obstructive sleep apnea, polysomnography, non-invasive ventilation, hypoventilation, sleep architecture, lysosomal storage disorder

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## INTRODUCTION

Mucolipidosis II (Inclusion-cell or I-cell disease) is a rare lysosomal storage disorder with clinical features similar to the mucopolysaccharidoses (MPS), due to impaired intracellular enzymatic degradation of substrates and accumulation of these undigested substrates within cell bodies.[1] Obstructive sleep apnea (OSA) and hypoventilation have been reported, presumably due to progressive airway obstruction and central nervous system disease as seen in MPS.[2] Progression of OSA and disrupted sleep architecture have been described in MPS; however, details of polysomnography and clinical course of sleep abnormalities have not been previously characterized in mucolipidosis.[3–6]

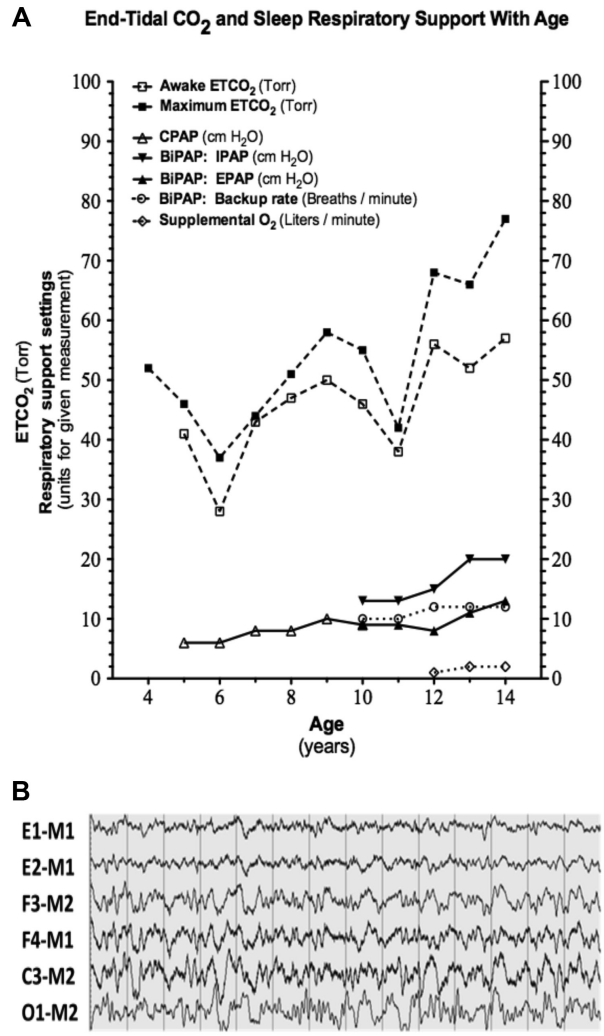
## REPORT OF CASE

We report a 15-year-old male with mucolipidosis II who is followed in our pediatric airway and sleep centers. When diagnosed at 19 months of age, he exhibited typical disease characteristics including coarse facial features with a prominent forehead, short stature, kyphosis, and hepatomegaly. His disease course has been characterized by growth delay, recurrent otitis media and heart disease involving mild left ventricular hypertrophy and mild aortic/mitral valvular stenosis. Progressive kyphoscoliosis led to multiple spinal surgeries during childhood. Polysomnography at 3 years of age revealed severe OSA with an apnea-hypopnea index (AHI) of 43 events per hour, nadir pulse oximetry of 70%, and maximum end-tidal $CO_2$ ($ETCO_2$) of 60 torr. Flexible bronchoscopy demonstrated adenoid hypertrophy with diffuse upper and lower airway mucosal edema. Adenoidectomy was performed at 3.5 years of age and repeat polysomnography 10 months later demonstrated residual sleep apnea, consisting of both obstructive and central events (AHI of 11.1, OAI of 5.0, and CAI of 1.9). The patient began continuous positive airway pressure (CPAP) at 5 years of age. Because of respiratory irregularity with central apnea and hypoventilation on CPAP (AHI of 6.9, OAI of 1.3, CAI of 3.9 with maximum $ETCO_2$ of 58 torr), he was transitioned to bilevel positive airway pressure (BiPAP) with backup rate of 10 breaths/min at 10 years of age. Hypoventilation improved as evidenced by reduction in awake and maximum sleep-related $ETCO_2$, however these measures again worsened over the following years despite increasing ventilatory support (**Figure 1A**). Serial echocardiography revealed normal right ventricular function without pulmonary hypertension to explain the need for supplemental oxygen. Sleep architecture was consistently abnormal with poor sleep continuity, excessive state fragmentation, and REM duration < 15% of total sleep time. Sleep EEG was notable for paucity of sleep spindles, hypersynchronous slowing following arousals, and presence of background EEG slowing (**Figure 1B**).

## DISCUSSION

This case demonstrates progression of multifactorial sleep disturbance during childhood in mucolipidosis II, characterized by worsening OSA, hypoventilation and sleep architecture

**Figure 1**




**(A)** PSG findings of end-tidal $CO_2$ ($ETCO_2$) and respiratory support settings over time/age. Squares indicate $ETCO_2$ measured at onset of PSG and maximum during sleep. Other symbols represent respiratory support settings used during PSG to control respiratory events. **(B)** Limited EEG montage during PSG in NREM sleep. Background slowing and paucity of sleep spindles suggest altered thalamocortical function and may be a consequence of disease deposits within thalamic neurons.

changes. Apnea and hypoventilation worsened with advancing age, similar to what we observed in our cross-sectional study of mucopolysaccharidosis II.[5] As in the mucopolysaccharidoses, airway narrowing from soft-tissue deposits within the upper airway, along with craniofacial abnormalities such as flat face and depressed nasal bridge, are presumed to yield an increased risk of OSA. In lysosomal storage diseases, hypoventilation may also occur as a result of skeletal limitations, lung parenchymal changes or central neural regulatory changes. Scoliosis and decreased thoracic elasticity may contribute to restrictive lung disease and reduced respiratory reserve during apneic episodes. An increasing gap between baseline and maximum $ETCO_2$ suggests worsening sleep-related hypoventilation, either from progression of primary pulmonary disease or a state-dependent central nervous processing issue. The latter is supported by the presence of central apnea despite elevated $CO_2$.

Notable electroencephalographic changes were apparent including reduction in sleep spindles and increase in background slowing on EEG (**Figure 1**). Background slowing was noted even during wakefulness, which may reflect thalamocortical dysfunction from the mucolipidosis. Despite the lack of clear structural changes on brain MRI, the absence of sleep spindles suggests dysfunction within thalamic neurons. This reduction of spindle activity during non-REM sleep is an unusual finding, described in a few neurological disorders such as Parkinson disease and Lewy body dementia.

Our patient's course suggests that sleep-related breathing disorder evolves through childhood in mucolipidosis II. Gas exchange alterations and disrupted sleep architecture may reflect cumulative effects upon the airway and central nervous system, while changes in sleep neural regulatory processes may be related to mucolipidosis II involvement of central neural regulatory pathways. Frequent clinical and PSG based monitoring is necessary in these patients to avoid secondary complications arising from sleep apnea and hypoventilation. Polygraphic sleep parameters also bear potential utility to indicate therapeutic response as novel therapies become available for this category of disorders.

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## SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: William I. Wooten III, MD, 600 Moye Boulevard, 2MA-216, Greenville, NC 27834; Tel: (252) 744-8285; Fax: (252) 744-3829; Email: wootenw@ecu.edu

## DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Muenzer was the principal investigator for both the MPS II phase I/II enzyme replacement clinical trial and the MPS II natural history studies at UNC and has been a consultant to Shire, Genzyme, and BioMarin. The article submitted is not related to these relationships. Dr. Vaughn has been involved in Medical Education Resources (Speaker's Bureau) and ABIM (Chair of the Exam and Policy Committee for Sleep Medicine). The article submitted is not related to these relationships. The other authors declare no conflicts of interest.