CASE REPORT

# Sleep-disordered Breathing in an Adult with Mucopolysaccharidosis Type I (Hurler–Scheie Syndrome): A Case Report

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## Abstract

**Aim and background:** Hurler–Scheie syndrome, also known as mucopolysaccharidosis (MPS) type I, is one of the lysosomal storage diseases, resulting in the accumulation of glycosaminoglycans in various organs. The patient presents with coarse facial features, musculoskeletal deformities, and umbilical hernia with no signs of intellectual disability or corneal involvement in childhood. This case report aims to create awareness among the clinicians to identify, diagnose, and treat the sleep-disordered breathing (SDB) in adult patients of MPS.

**Case description:** This case report highlights the incidence of a 33-year-old adult, who was diagnosed with MPS type I in childhood, and later presented with SDB in his adulthood. The patient was diagnosed with obstructive sleep apnea (OSA) with polysomnography. He was treated with bilevel PAP support in which post-treatment his apnea–hypopnea index (AHI) showed drastic improvement from AHI of 99.2 to AHI of 2.

**Conclusion:** The SDB and OSA are few of the respiratory complications seen in MPS type I. With the advent of new therapies, these pediatric disorders have better survival rates than the past few years. Adult survivors of MPS, thus pose as a novel challenge to physicians in their management.

**Clinical significance:** This case report highlights a new challenge that physicians face with the treatment of adults' survivors of MPS, who present with SDB.

**Keywords:** Case report, Mucopolysaccharidosis, Obstructive sleep apnea, Polysomnography, Sleep-disordered breathing.

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## Introduction

Mucopolysaccharidosis (MPS) are a category of inherited metabolic diseases caused by hallmark pathophysiology of deficiency of enzymes in the lysosomes that degrade glycosaminoglycans (GAG), causing accumulation of GAG in the body.[1] Mucopolysaccharidosis disorders are caused due to autosomal recessive genes, except for MPS type II.[2] The accumulation of GAGs in various organs causes multiorgan manifestations such as restrictive lung diseases, upper and lower airway obstruction, musculoskeletal deformities, hepatosplenomegaly, corneal clouding, and cognitive impairment in a few subtypes.[3] Sleep-disordered breathing (SDB) is commonly seen in MPS I (also known as Hurler syndrome, Hurler–Scheie syndrome, or Scheie syndrome, based on the severity of disease), causing cardio-respiratory complications in the future.[4] However, the number of MPS children surviving into adulthood has increased in recent years, due to development of novel treatment plants such as enzyme replacement therapy.[5] Hence, adult survivors of MPS require a specialist's treatment with a multidisciplinary approach.

This case report showcases the incidence of a 33-year-old adult who was diagnosed with MPS type I in childhood and later presented with SDB in adulthood with evidence of a split night study and polysomnography findings.

## Case Description

A 33-year-old male came to the Department of Pulmonology and Sleep Medicine of the Multispecialty Tertiary Care Hospital with the chief complaints of cough with expectoration and breathlessness since past few weeks. Breathlessness aggravated on exertion and was classified as MRC grade II. The patient had complaints of snoring with daytime fatigue and somnolence. He also had a mild fever and loss of appetite for the past 4 days. There were no symptoms of chest pain, hemoptysis, or palpitations. No pallor, cyanosis, icterus, lymphadenopathy, or pedal edema were seen. On examination, his pulse was 96/min, blood pressure was 100/70 mm Hg, $spO_2$ was 95% on room air, respiratory rate was 22/min and his body mass index was 21.5. The trachea was central, and the breath sounds

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were normal with S1, S2 heard. Patient was conscious and oriented to time, place, and person.

The patient was born out of a distant consanguineous marriage and was one of the three living male children with two elder brothers. His mother had a past history of three abortions—one spontaneous and two medical termination of pregnancy. The detailed evaluation of family history revealed the existence of the father's brother (paternal uncle), who had developmental delay with psychomotor retardation and died at the age of 12 years. The motor, speech, and social milestones of the patient were appropriate to the age.

Alongside the short stature, patient gave history of thickened wrist, short stout hand and mild claw hand deformity since the age of 2 months in childhood. Limited flexion and extension were seen at the elbow joint. An X-ray of the hands revealed short, dysplastic, proximally tapering metacarpals with short and thin metaphyses. Radiolucency in the bones suggested the presence of lysosomal storage disease. The chest X-ray revealed spatulate, oar-shaped, narrow-necked ribs. On examination, he was found to have exaggerated lumbar lordosis with no kyphoscoliosis. Patient later developed numbness in the distribution of median nerve along with the atrophy of thenar muscles. There was no hepatosplenomegaly seen, but umbilical hernia was noted in childhood. There was no evidence of hyperkinetic or aggressive behavior, with no findings of mental retardation seen.

On further investigation, serum galactosidase and glucuronidase levels were normal, which ruled out the respective enzyme deficiencies. Alder Reily bodies, which are dense granules, resembling toxic granulation in leukocytes as seen in MPS, were absent. Over the course of years, the patient's urine GAG screening test showed excessive excretion of dermatan sulphate along with chondroitin and heparin sulphate. A lysosomal enzyme study proved the deficiency of alpha-iduronidase enzyme level in lysosomes, which was diagnostic for MPS type I. Since there were no symptoms of psychomotor retardation with cognitive impairment and corneal clouding in this patient, he was diagnosed with Hurler–Scheie syndrome in childhood.

With progressing age, the patient developed noisy breathing, snoring, and daytime tiredness in adulthood. Over the years, patients developed cardio-respiratory complications such as pulmonary artery hypertension (PAH). The 2D echocardiography showed the presence of acyanotic congenital heart disease and a bicuspid aortic valve with mild aortic regurgitation with left ventricular ejection fraction (LVEF) of 58%. Later, there was worsening of the respiratory symptoms, hypoxia causing PAH with pulmonary arterial systolic pressure (PASP) 45%, posing high risk of cor pulmonale. There was no history of any upper airway endoscopy or upper airway surgery.

On further evaluation in Pulmonology Department, the Epworth Sleepiness Scale and STOPBANG scores were calculated to be 20 and 5, whereas Mallampati score was 4, suggesting a high probability of obstructive sleep apnea (OSA).

Spirometry was performed, which demonstrated forced expiratory volume (FEV1)/forced vital capacity (FVC) ratio 75.9 favoring a restrictive pattern and FEV1 21%, demonstrating very severe obstructive pulmonary disease. Flow-volume loop was of obstructive pattern. Overall spirometry was mixed picture, due to short stature and crowding of airways, due to facial and musculoskeletal abnormalities consistent with MPS.

Attended in-lab, split night study with video polysomnography (level 1) was performed in accordance with the American Academy of Sleep Medicine (AASM) scoring manual for Scoring of Sleep and Associated Events. Bed wetting, excessive perspiration, and mouth breathing was observed during the study. Total recording time (TRT) of the sleep study was 276.0 minutes and total sleep time (TST) was 236.5 minutes. His sleep efficiency was 85.7%. Patient took 4.5 minutes to fall asleep. He went through different stages of sleep [N1: 0.8%, N2: 49.7%, N3: 39.7%, rapid eye movement (REM): 9.7%]. Patient had total 391 respiratory events (159 Apneas, 232 Hypopneas and 0 RERAs). Patient's apnea-hypopnea index (AHI) was 99.2, REM AHI was 122.6. Full EEG montage demonstrated no seizure activity during the study.

In view of evidence of significant respiratory events (AHI – 99.2 and REM AHI – 122.6) during the diagnostic part of the study, decision was taken to proceed with the titration procedure. Patient was then titrated from a baseline initial continuous positive airway pressure (CPAP) pressure of 4 cm $H_2O$ to bilevel pressure 19.0/12.0 cm $H_2O$. Lower pressures were associated with respiratory events and snoring. His excessive daytime sleepiness (ESS) score was found to be 20 (more than 10) out of 24.

He was later started on Bilevel PAP support with Max IPAP (CWP): 14, Min IPAP (CWP): 8, Max EPAP (CWP): 8, Min EPAP (CWP): 4, Pressure support (CWP): 4, Respiratory rate (/min): 16 and Tidal volume (mL): 260. Post treatment with the Bilevel PAP, the patient's AHI was found to be 2. Post-PAP therapy, though AHI was corrected to optimum, but patient had complaint of ESS and hence, modafinil was used to manage this effectively.

## Discussion

Mucopolysaccharidosis is a group of lysosomal storage diseases (LSD) due to mutations in genes causing deficiency of the lysosomal enzymes that are responsible for deterioration of GAG.[5] Mucopolysaccharidosis is an inherited disorder, classified into seven different subtypes based on the enzymatic deficiency of one of the 11 enzymes. Kobayashi's study explains the subtypes of MPS, namely MPS I (Hurler, Hurler–Scheie, and Scheie syndrome), MPS II (Hunter's syndrome), MPS III (Sanfilipo syndrome), MPS IV (Morquio syndrome), MPS VI (Maroteux–Lamy syndrome), etc., based on their enzyme deficiency and clinical phenotype.[1]

The enzyme deficient in MPS type I is a-L-iduronidase enzyme, which results in accumulation of GAGs such as dermatan sulphate and heparin sulphate.[1] Accumulation of these GAGs causes multisystemic manifestations. Each individual has different phenotypic variation, causing a severe or attenuated presentation based on the activity of residual enzymes. Along the spectrum, severe MPS I (Hurler syndrome) is diagnosed within the first year of life; however, attenuated forms, namely Hurler–Scheie and Scheie syndrome are diagnosed within age of 3–10 years. Attenuated forms have normal intelligence with no psychomotor retardation, and no corneal clouding.[3]

Khan et al. in his epidemiological study stated that the birth prevalence of MPS varies in each country based on ethnic variations.[6] The combined prevalence of MPS tends to be higher in Norway, Australia, and Netherlands, whereas MPS Type I was found to be prevalent in Norway.[1] Updated version of the epidemiological study published in 2020 showed that the prevalence of MPS was highest in Saudi Arabia, followed by Portugal, Brazil, the Netherlands, and Australia.[2] In India, a cross-sectional study evaluated 1,110 children in 2013, where MPS contributed to 22% of the children in the study, in which MPS I-Hurler and Hurler–Scheie syndrome was confirmed in 2.52%.[7]

Earlier children with MPS had a limited life expectancy; however, the recent advances in treatments have caused an increase in the survival rate. Muenzer et al. study on MPS II showed the increasing survival rate of MPS type II patients over the years.[8] There is an increasing trend of survival of MPS children into adulthood, which poses a new challenge to the management strategies in adults.[8] Another South Asian continent study in Taiwan showed increase in patients' life expectancy, though this increase was gradual ($p < 0.01$).[5]

The implementation of newborn screening programs and recent novel treatments such as enzyme replacement therapy and hematopoietic stem cell transplant have increased the survival of MPS patients in adulthood.[4] A growing percentage of children are now living from childhood into adulthood, which pose a new challenge to physicians in their management. The adults with MPS face numerous complications such as growth impairment, cardiac and respiratory complications such as upper or lower respiratory tract obstruction, restrictive lung disease, SDB, valvular insufficiency, PAH and cor-pulmonale, musculoskeletal deformities, ocular corneal clouding, hepatosplenomegaly, umbilical hernia, and central nervous system (CNS) involvement such as behavioral problems and cognitive decline.[9] Hence, adults with MPS require multidisciplinary treatment with various specialists.

Sleep-disordered breathing and OSA are the major respiratory complication seen in MPS.[4] Pal et al. proved that the pretreatment prevalence of OSA in MPS was 81% with a mean AHI of 10.4.[10] Patients with MPS I are most significantly affected, with 75% suffering with moderate to severe OSA (mean AHI, 16.6). Obstructive sleep apnea least affects MPS III.[4,10] Snoring, daytime somnolence, excessive fatigue, early morning headache are common symptoms of OSA. Adult pulmonologists need to be alert, as these respiratory symptoms can go unmasked due to physical inactivity due to musculoskeletal deformities. Patients with MPS also suffer from complications of upper airway obstruction or tracheobronchial malacia, which can be difficult to treat in cases of emergency intubations or planned anesthetic procedures. Upper airway obstruction can be treated with tracheostomy, but no guidelines exist for the management of lower airway malacia or stenosis, except for a few recently published cases of a new technique of tracheal stenting.[11]

Evaluation by pulmonary function tests and spirometry can be difficult in MPS patients due to disease-induced cognitive impairment. Polysomnography (Level 1) and upper airway evaluation is recommended in all patients of MPS presenting with SDB symptoms.[12]

Continuous positive airway pressure can be used to prevent airway collapse while asleep, thus improving the symptoms.[13] In this case, the patient was treated with Bilevel PAP support, in which post treatment his AHI showed drastic improvement from AHI of 99.2 to AHI of 2. If CPAP is not providing effective control over SDB, non-invasive ventilation (NIV) may also be advised as a backup option.[4] Laronidase (Aldurazyme) was licensed by the U.S. food and drug administration (FDA) in 2003 as a therapy for MPS I. In particular, patients with the Hurler and Hurler–Scheie variants of MPS I as well as those with the Scheie type who have moderate to severe symptoms may be treated with this enzyme replacement treatment.[14]

## Conclusion

Sleep-disordered breathing and OSA are few of the respiratory complications seen in MPS Type I. With the advent of new therapies, these pediatric disorders have better survival rates than the past few years. Adult survivors of MPS, thus pose as a novel challenge to physicians in their management.

### Clinical Significance

This case report highlights a new challenge that physicians face with the treatment of adults' survivors of MPS who present with SDB. It aims to create awareness among the clinicians to identify, diagnose, and treat the SDB in adult patients of MPS. It is also important that clinicians identify that adult survivors of MPS require a multidisciplinary approach in their management.

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