STUDENTS' CORNER
CASE REPORT

# A rare encounter mucolipidosis type II alpha/beta: A case report

Khadija Anwar[1], Darshan Kumar[2]


## Abstract

Mucolipidosis type II alpha/beta (ML II) (OMIM # 252500), alternatively referred to as Inclusion Cell (I-cell) Disease, is a relatively rare lysosomal storage disorder that is autosomal recessive in inheritance due to the mutation of the GNPTAB (N-acetylglucosamine-1-phosphate transferase sub-units alpha and beta) gene present on chromosome 12q23.3. Currently, there is no cure for this disorder; treatment is both symptomatic and palliative. This report describes the case of a five-year-old patient with ML II with pathogenic variant (t c.3335+1G>A) who presented with aspiration pneumonia and renal insufficiency. The child was born to a consanguineous couple and had a sibling with a similar clinical presentation who passed away at age four due to cardiovascular complications. The patient was treated with continuous positive airway pressure (CPAP) and IV Tazobactam, Piperacillin, and Vancomycin. On follow-up, she was started on Spironolactone 20mg and Captopril 12.5mg daily for mitral regurgitation.



**Keywords:** Mucolipidosis Type II alpha/beta, Inclusion cell (I-cell) disease, Mitral regurgitation, Clinical homozygosity, Case report.

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## Introduction

Mucolipidosis type II (ML II) (OMIM # 252500), alternatively referred to as Inclusion Cell (I-cell) Disease, is a relatively rare lysosomal storage disorder that is autosomal recessive in inheritance and was first described and differentiated from lipidoses and mucopolysaccharidoses by Leroy and DeMars in 1967.[1] The GNPTAB (N-acetylglucosamine-1-phosphate transferase sub-units alpha and beta) gene situated on chromosome 12q23.3 encodes the sub-units α and β of the enzyme N-acetylglucosamine-1-phosphotransferase, also known as GlcNAc-phosphotransferase, the two α and β sub-units each combine with a pair of γ sub-units; encoded by the GNPTG gene (N-acetylglucosamine-1-phosphate transferase sub-unit gamma) to create the active hexameric configuration of the enzyme. The enzyme GlcNAc-phosphotransferase catalyses the initial step in the synthesis of mannose-6-phosphate tag that marks roughly 60 lysosomal proteins for transportation; mutation of this enzyme results in lysosomal storage disorders such as mucolipidosis.[2-4] This disorder is characterised by the absence of the lysosomal enzyme GlcNAc-phosphotransferase, which prevents mannose phosphorylation, due to which the transportation of lysosomal hydrolases to the lysosome is impaired.[3] This eventually causes lysosomal dysfunction prompting non-degraded biomolecule substrates to accumulate, which exacerbates lysosomal dysfunction and the creation of enormous inclusion bodies in fibroblasts, hence the name Inclusion Cell (I-Cell) Disease.[5] Clinically mucolipidosis type II is similar to mucopolysaccharidoses, although radiographically it presents earlier than mucopolysaccharidoses and other forms of mucolipidosis. Mucolipidosis type II alpha/beta usually presents as rickets due to similar clinical features and radiological findings of osteopenia, bone resorption, fractures, and metaphyseal irregularities which may lead to late diagnosis.[6] Clinical characteristics include coarse facial features with metopic prominence, shallow orbits, craniosynostosis, thickened alveolar ridges, depressed nasal bridge, and gingival hypertrophy.[7,8] Orthopaedic abnormalities include hip dislocation, scoliosis, hand contractures, and bowed limbs with statural growth failure occurring completely before or by the age of 24 months.[8] Patients have delayed developmental milestones, especially motor development, mobility is limited ranging from some patients being unable to sit even with support and some walking unaided.[8] Most patients can make vocal sounds with some being able to speak poorly pronounced words, while receptive skills and cognitive development ideally fit into moderate intellectual disability.[8] Patients are poor feeders; mitral and aortic valve thickening on echocardiography, hypertrophy of ventricular walls, hepatosplenomegaly, abdominal diastasis, inguinal hernia, corneal hazing, recurrent otitis media and respiratory infections are the common features of ML II.[7]


[1]4th Year MBBS Student, Dow International Medical College, Karachi, Pakistan; [2]Department of Medicine, Dow University Hospital, Ojha Campus, Karachi, Pakistan.

**Correspondence:** Darshan Kumar. e-mail: Darshan.kumar@duhs.edu.pk
ORCID ID: 0009-0002-2951-6310



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## Case Report

A five-year-old Pakistani female patient, the fourth child of a first-generation consanguineous couple, presented in the emergency room (ER) of Dow University Hospital, Ojha Campus, Karachi, Pakistan on April 29, 2024, with continuous high-grade fever of 103ºF, decreased oxygen saturation of less than 90%, shortness of breath, and decreased urinary frequency for the past two days. The patient was diagnosed with aspiration pneumonia based on her medical history and clinical investigations conducted. The patient's DNR (do not resuscitate) had been signed and she was kept on pharma code. The patient was noted to have a homozygous pathogenic variant (t c.3335+1G>A) in the GNPTAB gene due to a splice mutation and was diagnosed with autosomal recessive mucolipidosis type II alpha/beta.

The patient had a brother with similar facial features and clinical presentation eighteen years ago, who remained undiagnosed, and who passed away due to cardiovascular complications at the age of four.

The patient was incompletely vaccinated; the last vaccination was administered at 14 weeks of age which included oral polio vaccine (OPV), inactivated polio vaccine (IPV), Pentavalent-3, and 10-valent pneumococcal conjugate vaccine 3 (PCV-10)[3]. The patient's development was severely delayed, and the patient had not developed gross motor and speech skills; she could sit with support, grasp objects and transfer them from one hand to another, and hear and respond via sign language. The patient was diagnosed with ML II at age three after her parents and her paediatrician noted her poor development. The patient had an episode of aspiration pneumonia and otitis media a year ago for which she was treated accordingly with antibiotics and mechanical ventilation.

Physical examination revealed short stature (measured to be 94cm in length) with a weight of 8kg and frontal orbital circumference of 43cm, the anterior fontanelle was completely closed, the patient had coarse facial features with craniosynostosis, flattened face and nose bridge, puffy eyes with mild bilateral exophthalmos, macroglossia. Kyphosis could also be noted. The patient's hands were short and broad, and mild hepatosplenomegaly was noted. She had severely restricted joint movement with muscle hypotonia, bilateral crepts in the chest were audible on auscultation, and subcostal recessions were positive on examination. The patient did not have clouding of the cornea or dislocation of any joints.

Haematological and biochemical investigations were all normal except that the patient had a raised total leucocyte count (TLC), moderate hypochromic microcytic anaemia, raised CRP (C-Reactive Protein) and troponin I levels, the patient's blood culture revealed no bacterial growth, as shown in (Table).

The following radiological investigations were performed: chest X-ray (Figure). Anterior Posterior (AP) view showed unilateral consolidation at the upper lobe of the right lung as shown in (Figure), ultrasound KUB (kidney ureter bladder) revealed a non-obstructing calculus measuring 0.3cm in the left kidney.

The patient was diagnosed with aspiration pneumonia and was treated with intravenous (IV) Ceftriaxone for four days after which it was discontinued and IV Tazobactam and Piperacillin were administered for two days; the patient was also started on IV Vancomycin on day two of admission which continued till discharge. She was also mechanically ventilated with CPAP (Continuous Positive Airway Pressure) for four days due to which her oxygen saturation increased to 96%. A nasogastric (NG) tube passed on day two of admission was removed on day five.

On follow-up, two weeks later, the patient's chest auscultation was clear. Echocardiography disclosed mildly,

**Table:** Laboratory findings of the patient

| Lab | Patient value | Reference range |
|---|---|---|
| TLC | 24.2 mEq/L | 4.0-10.0 |
| Hb | 8.5 gm/dL | 11-14 |
| PLT | 233 x10^9/L | 200-490 |
| Cr | 0.25 mg/dL | 0.6-1.1 mg/dL |
| cTnI | 21.46 mg/L | <10 mg/L |
| Na | 144 mEq/L | 136-146 mEq/L |
| K | 4.4 mEq/L | 3.5-5.1 mEq/L |
| Cl | 106 mEq/L | 98-107 mEq/L |
| $HCO_3$ | 24.2 mEq/L | 23-29 mEq/L |

TLC: Total Leucocyte Count. Hb: Haemoglobin, PLT: Platelets, Cr: Creatinine, cTnI: cardiac troponin I, Na: Sodium, K: Potassium, Cl: Chloride, HC03: Bicarbonate.

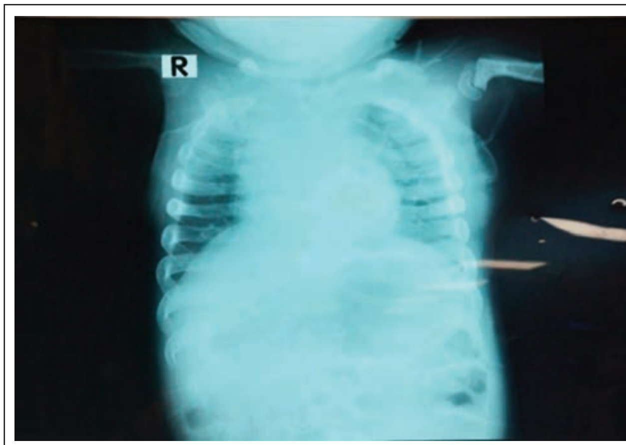


**Figure:** Chest X-ray AP (anterior-posterior) view showing right upper lobe consolidation and cardiomegaly.

myxomatous valves with mild prolapse of both PMVL (posterior mitral valve leaflet) and AMVL (anterior mitral valve leaflet), and mild pulmonary arterial hypertension (PAH) was also noted. The patient's PSPG (pulmonary systolic pressure gradient) was 40mm of Hg. The patient was started on spironolactone 20mg and captopril 12.5mg daily for mitral regurgitation.

## Discussion

This report describes a rare case of a five-year-old girl with mucolipidosis type II presenting with aspiration pneumonia. The patient was noted to have a homozygous pathogenic variant (t c.3335+1G>A) in the GNPTAB gene due to a splice mutation. Mucolipidosis type II and type III are extremely rare disorders of lysosomal storage that are autosomal recessive in inheritance caused by the mutation of the GNPTAB gene located on chromosome 12q23.3. A total of 287 mutations have been reported to date, of which 27 splice mutations have been documented within the gene.[9] According to The Human Gene Mutation Database (HGMD) professional 2023.4, the GNPTAB variant c.3335+1G>A has been reported as disease-causing.[9,10] Based on the classification provided in the patient's CENTOGENE genetic testing report, which follows the ACMG (American College of Medical Genetics and Genomics) variant interpretation guidelines, the GNPTAB variant (c.3335+1G>A) was categorised as likely pathogenic (class 2). All children suffering from ML II have skeletal and craniofacial abnormalities and diagnosis is usually made from the age of three weeks to 2.5 years of life. Diagnosis is established based on clinical features, developmental delays including both motor and intellectual delays, radiographic findings, measuring the plasma activity of several lysosomal hydrolases, and genetic testing.[8] To date, there is no curative treatment for ML II and management is a combination of symptomatic and palliative care; however, considering the rapid advancement of medical interventions for monogenic inborn disorders of metabolism, interventions like gene therapy might become accessible in the next few years. There have been reports of patients with ML II seeking potential life-extending procedures such as stem cell transplantation (SCT), tracheostomy, surgery for craniosynostosis, gastric tube placement, cardiac interventions such as valve replacement, drainage of pericardial effusion and coronary artery bypass, and the correction of spinal abnormalities.[22]

## Conclusion

Mucolipidosis type II alpha/beta (OMIM # 252500) is a lysosomal storage disorder that is autosomal recessive in inheritance and presents with unique clinical and radiographic findings. The disorder has a poor prognosis as there is no cure and management is symptomatic. This case highlights a patient suffering from a rare splice mutation of the GNPTAB gene present on chromosome 12q23.3.

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**Abbreviations:** ML II (mucolipidosis type II alpha/beta), KUB (kidney ureter bladder), AMVL (anterior mitral valve leaflet), PMVL (posterior mitral valve leaflet), pulmonary arterial hypertension (PAH), PSPG (pulmonary systolic pressure gradient), GNPTAB (N-acetylglucosamine-1-phosphate transferase subunits alpha and beta), GlcNAc-phosphotransferase (N-acetylglucosamine-1-phosphotransferase), GNPTG (N-acetylglucosamine-1-phosphate transferase subunit gamma), oral polio vaccine (OPV), inactivated polio vaccine (IPV), 10-valent pneumococcal conjugate vaccine 3 (PCV-10)3, HGMD (The Human Gene Mutation Database), ACMG (American College of Medical Genetics and Genomics), AP (anterior posterior)

**Consent:** Informed consent was obtained from the patient's guardian to publish this case.

**Disclaimer:** Human subjects: consent for the patient's participation in this case report was obtained from the patient's guardian.

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**Author Contribution:**

**KA:** Drafting, case study, discussion, conclusion, development, final approval and agreement to be accountable for all aspects of the work.

**DK:** Critically reviewed, editing, final approval and agreement to be accountable for all aspects of the work.