JIM
JIM 2025; 2 (2): e924
DOI: 10.61012_20255_924
Category: *Case Report*

A DIAGNOSTIC X-RAY IN A NEWBORN WITH SKELETAL ABNORMALITIES: A RARE CASE OF MUCOLIPIDOSIS TYPE 2

E. MAINES[1], M.C. CARDELLINI[2], D. D'ONOFRIO[2], S. ZARDINI[3], F. RIVIERI[4], F. ANTONIAZZI[5], T. ZOLLER[5], C. MICHOT[6], M. SOFFIATI[1], R. FRANCESCHI[1,7]

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[1]Division of Pediatrics, S. Chiara General Hospital, Azienda Provinciale per i Servizi Sanitari, Trento, Italy
[2]Division of Neonatology, S. Chiara General Hospital, Azienda Provinciale per i Servizi Sanitari, Trento, Italy
[3]Division of Obstetrics and Gynecology, S. Chiara General Hospital, Azienda Provinciale per i Servizi Sanitari, Trento, Italy
[4]Division of Medical Genetics, S. Chiara General Hospital, Azienda Provinciale per i Servizi Sanitari, Trento, Italy
[5]Regional Center for the Diagnosis and Treatment of Children and Adolescents with Rare Skeletal Disorders, Pediatric Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy
[6]Centre de Référence des Maladies Osseuses Constitutionnelles, Necker-Enfants Malades Hospitals, Paris, France
[7]Centre for Medical Sciences (Cismed), University of Trento, Trento, Italy

Corresponding Author
Evelina Maines, MD; e-mail: evelina.maines@apss.tn.it

***ABSTRACT* – Background:** The aim of this study is to highlight the characteristic radiographic features observed in newborns affected by mucolipidosis type 2 (MLII).

Case Report: A preterm male neonate was admitted to the Neonatal Intensive Care Unit due to prematurity and respiratory distress. The antenatal ultrasound revealed unspecified skeletal abnormalities and intrauterine growth retardation. At birth, he presented with coarse facial features, gingival hyperplasia, shortening of both upper and lower limbs, joint limitation, hip dislocation, and chest deformity. The diagnosis of mucolipidosis type 2 (MLII) (OMIM #252500), a rare autosomal recessive lysosomal disorder, was immediately suspected with a total body x-ray because of the distinctive radiographic features of the disease. X-ray highlighted severe generalized osteopenia, shortening of the proximal segments of both the upper and the lower limbs, extensive cloaking of the right femur, abnormally large and cup-shaped metaphyses with irregular demineralization, resorption of the clavicle, bowing of long bones, vertebral body rounding, altered hip morphology and stippling of the talocalcaneal bones.

Conclusions: The clinical diagnosis of MLII can be challenging in newborns due to phenotypic overlap with other lysosomal disorders, including mucopolysaccharidosis type 1 (MPS I, Hurler disease), gangliosidosis type I (GM I), infantile galactosialidosis, infantile sialidosis (MLI, mucolipidosis I), and infantile free sialic storage disease. Cloaking of the femora is an early, almost diagnostic, radiographic abnormality observed in newborn patients affected by MLII. Recognizing the specific association of anomalies of MLII helps rule out differential diagnosis and establish appropriate diagnosis, care, and parental counselling.

Keywords: Skeletal diagnostic findings, Mucolipidosis type 2, Cloaking of the femora.

INTRODUCTION

Mucolipidosis type 2 (MLII) (OMIM #252500) is a rare autosomal recessive lysosomal disorder with a birth prevalence ranging from 1 in 123,500 live births in Portugal[1] to 1 in 625,000 live births in the Netherlands[2].

MLII belongs to the larger group of metabolic disorders associated with osteochondrodystrophic changes termed dysostosis multiplex[3]. It is caused by a deficiency of N-acetylglucosamine-1-phosphotransferase (GlcNAc-1-phosphotransferase), encoded by the *GNPTAB* gene. GlcNAc-1-phosphotransferase catalyzes the formation of the mannose-6-phosphate (M6P) marker, essential for directing the lysosomal acid hydrolases into the lysosomes. The defect leads to intracellular deficiency of several lysosomal enzymes and increased extracellular levels (serum and plasma), which results in the accumulation of their multiple substrates[4].

Mutations in *GNPTAB* lead to a phenotypic spectrum ranging from a neonatal-infantile presentation of MLII to a mild condition with childhood-onset called mucolipidosis type 3 (MLIII)[5]. In neonatal cases, symptoms can appear shortly after birth or, in the most severe instances, even during the prenatal phase. Regardless, the disease advances quickly and is often fatal due to its severity[5].

Radiographic features are usually distinctive and may allow for a prompt diagnosis[5].

CASE PRESENTATION

A preterm male neonate was admitted to the Neonatal Intensive Care Unit at the Hospital of Trento (Italy) because of prematurity and respiratory distress at birth. He was the first sibling of two consanguineous healthy parents.

The antenatal ultrasound revealed unspecified skeletal abnormalities and intrauterine growth retardation.

At birth, he presented with coarse facial features, gingival hyperplasia, shortening of both upper and lower limbs, joint limitation, hip dislocation, and chest deformity. We performed a total body x-ray (Figure 1) after starting invasive ventilation, and the diagnosis of mucolipidosis type 2 (MLII) was immediately suspected.

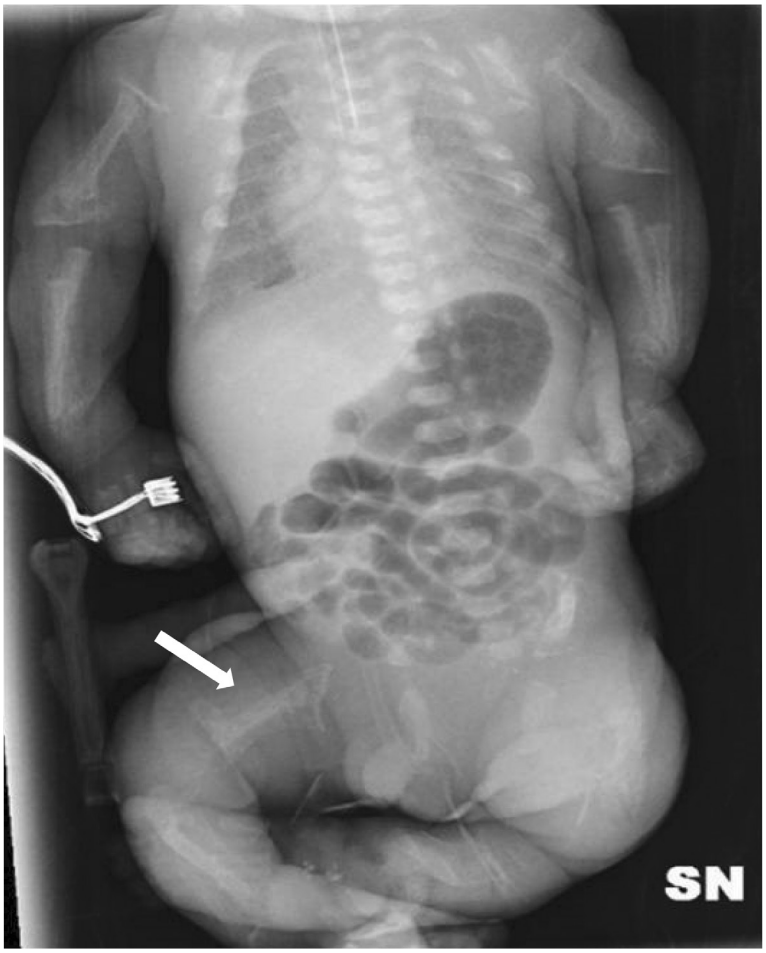

Figure 1. Total body X-ray of the patient. The radiograph shows extensive cloaking of the right femur (white arrow); the figure also shows common skeletal signs of MLII, such as, severe generalized osteopenia, talocalcaneus stippling, irregular demineralization of metaphyses of long bones and cupped physeal-metaphyseal junctions resembling those of rickets, bowing of long bones, vertebral body rounding, altered hip morphology, including acetabular dysplasia, femoral head abnormalities, and an altered acetabulum-femoral head relationship.

X-ray highlighted severe generalized osteopenia, shortening of the proximal segments of both the upper and the lower limbs, extensive cloaking of the right femur, abnormally large and cupped-shaped metaphyses with irregular demineralization, resorption of the clavicle, bowing of long bones, vertebral body rounding, altered hip morphology, and stippling of the talocalcaneal bones.

The patient's diagnosis was confirmed through biochemical and molecular genetic testing. Biochemical studies showed increased activity of several lysosomal enzymes in the serum (arylsulfatase A 1249 nmoL/mL, n.v. 20-200; total hexosaminidase 19,108 nmoL/mL, n.v. 100-1,300; hexosaminidase B 4434 nmoL/mL, n.v. 50-100). The excretion of urinary sialyl oligosaccharides was also increased.

Serum biochemistry revealed markedly elevated activities of alkaline phosphatase (ALP) (1,556 U/L, n.v.: 150-420), hypophosphatemia (3.7 mg/dL, n.v.: 4.5-6.5 mg/dL), hyperparathyroidism (PTH 557 pg/mL, n.v.: 7-65 pg/mL), normal levels of calcium (8.6 mg/dL) and low levels of 25-hydroxyvitamin D (7 ng/mL, n.v.: 20-60 ng/mL).

Mutation analysis of the *GNPTAB* gene identified the homozygous variant c.232_234delGTT (p.Val78del) previously reported in the literature.

The child died at two months of age from acute and severe pulmonary hypertension.

DISCUSSION

Few neonatal MLII cases have been reported in the literature. The neonatal skeletal abnormalities differ from those seen at a later age because they reflect a more severe disturbance in bone development and growth[6].

The neonatal skeletal features usually show marked osteodystrophy, including severe generalized osteopenia, irregular demineralization of metaphyses of long bones and cupped physeal-metaphyseal junctions resembling those of rickets, bowing of long bones, extensive cloaking of the femora, punctate ossification at the talocalcaneus, resorption of scapula, clavicula, and mandible, narrow thorax, vertebral body rounding, sacrococcygeal or generalized vertebral body sclerosis and intrauterine pathological fractures[6,7]. Among the relevant signs, altered hip morphology, including the abnormal interplay between the acetabulum and the femoral head, is also frequently observed[8].

Among biochemical features, transient neonatal hyperparathyroidism has been reported in the literature[9], which was also observed in the present case.

The clinical diagnosis of MLII can be challenging in newborns due to phenotypic overlap with other lysosomal disorders, such as mucopolysaccharidosis type I (MPS I, Hurler disease), gangliosidosis type I (GM I), infantile galactosialidosis, infantile sialidosis (MLI, mucolipidosis I), and infantile free sialic storage disease[10].

Although in the perinatal and neonatal period, MLII has similar clinical features to those found in several mucopolysaccharidoses and mucolipidoses, there are distinctive diagnostic radiographic features. The diagnosis of MLII should be strongly suggested by cloaking of the femora in combination with one or more of the following radiographic criteria: talocalcaneal stippling, sacrococcygeal or generalized vertebral body sclerosis, vertebral body rounding, or rickets-hyperparathyroidism-like changes. These findings are not found in the other two forms of mucolipidosis (MLIII and MLI) nor mucopolysaccharidoses[6]. In particular, cloaking of the femora refers to a highly characteristic (almost diagnostic), early but transient radiological sign characterized by a hazy, cloud-like appearance around the femoral bones[11]. This abnormality is observed in three-quarters of affected newborn patients[6].

The only differential diagnosis of the early radiographic changes of MLII is Pacman dysplasia, but it is unclear whether these are separate entities[12].

MLII could also be considered prenatally in fetuses presenting with reduced femoral length[13] and intrauterine pathological fractures[6,7] in association with characteristic radiographic features of the pathology.

CONCLUSIONS

Our case highlights the characteristic radiographic features observed in newborns affected by MLII. In particular, cloaking of the femora is a characteristic, almost diagnostic, radiographic abnormality observed in newborn patients affected by MLII. Recognizing the specific association of anomalies of MLII helps rule out differential diagnosis and establish appropriate diagnosis, care, and parental counselling.

Acknowledgments:
The authors are grateful to the Laboratory of Fondazione Mondino (Pavia, Italy) for gene analysis, to Dr. Fiorella Piemonte and Dr. Michela Semeraro of Ospedale Pediatrico Bambino Gesù in Rome (Italy) for supportive biochemical studies, and to all colleagues who contributed to case management.

Authors' Contributions:
Conceptualization, EM, MCC, DDO; methodology, FA, TZ, CM; investigation, MCC, DDO, FR, SZ; writing–original draft preparation, EM; writing–review and editing, RF; supervision, MS. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Material:
All data from this study are included in the article.

Conflicts of interest:
The authors declare that they have no conflict of interest

Consent to participate:
Written informed consent for participation and for publication of the clinical details and clinical image was obtained from the parents of the patient.

Ethics approval:
The latest revision of the Helsinki declaration, as well as the Oviedo declaration, were the basis for the ethical conduct of the study. The study protocol was designed and conducted to ensure adherence to the principles and procedures of good clinical practice and to comply with the Italian laws.

Funding:
No funding is declared for this article.

ORCID ID:
Evelina Maines: 0000-0002-0445-2974
Franco Antoniazzi: 0000-0003-1405-1792
Roberto Franceschi: 0000-0002-2230-7148

REFERENCES

1. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, Pinto E, Silva E, Rocha S, Marcão A, Ribeiro I, Lacerda L, Ribeiro G, Amaral O, Sá Miranda MC. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet 2004; 12: 87-92.
2. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999; 105: 151-156.
3. Spranger JW, Brill PW, Poznanski A. Bone Dysplasias: Atlas of Genetic Disorders of Skeletal Development. 2 ed. New York, NY: Oxford Univ Press; 2002. pages 295-299.
4. Leroy JG, Cathey SS, Friez MJ. GNPTAB-Related Disorders. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1828/
5. Aggarwal S, Coutinho MF, Dalal AB, Mohamed Nurul Jain SJ, Prata MJ, Alves S. Prenatal skeletal dysplasia phenotype in severe MLII alpha/beta with novel GNPTAB mutation. Gene 2014; 542: 266-268.
6. Lai LM, Lachman RS. Early characteristic radiographic changes in mucolipidosis II. Pediatr Radiol 2016; 46: 1713-1720.
7. Herman TE, McAlister WH. Neonatal mucolipidosis II (I-cell disease) with dysharmonic epiphyseal ossification and butterfly vertebral body. J Perinatol 1996; 16: 400-402.
8. Ammer LS, Oussoren E, Muschol NM, Pohl S, Rubio-Gozalbo ME, Santer R, Stuecker R, Vettorazzi E, Breyer SR. Hip Morphology in Mucolipidosis Type II. J Clin Med 2020; 9: 728.
9. Leyva C, Buch M, J Wierenga K, Berkovitz G, Seeherunvong T. A neonate with mucolipidosis II and transient secondary hyperparathyroidism. J Pediatr Endocrinol Metab 2019; 32: 1399-1402.
10. Nur BG, Erdogan Y, Curek Y, Akcakus M, Oygur N, Bircan I, Mihci E. Mucolipidosis ii infants presenting with skeletal deformities mimicking rickets and a new mutation in GNPTAB gene. Genet Couns 2016; 27: 373-380.
11. Burgac E, Kaplan İ, Köseci B, Kara E, Kor D, Bulut FD, Atmış A, Pişkin F, Tuğ Bozdoğan S, Urel Demir G, İncecik F, Önenli Mungan N. Early diagnostic clues of mucolipidosis type II: Significance of radiological findings. Am J Med Genet A 2024; 194: e63545.
12. Saul RA, Proud V, Taylor HA, Leroy JG, Spranger J. Prenatal mucolipidosis type II (I-cell disease) can present as Pacman dysplasia. Am J Med Genet A 2005; 135: 328-332.
13. Costain G, Inbar-Feigenberg M, Saleh M, Yaniv-Salem S, Ryan G, Morgen E, Goh ES, Nishimura G, Chitayat D. Challenges in Diagnosing Rare Genetic Causes of Common In Utero Presentations: Report of Two Patients with Mucolipidosis Type II (I-Cell Disease). J Pediatr Genet 2018; 7: 134-137.