A case of neonatal I-cell disease with multiple intrauterine fractures

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Introduction

Mucolipidoses (MLs) are of four types. Among them ML type II, initially called 'inclusion cell disease or I-cell disease', now known as ML II alpha/beta, has an estimated incidence of 0.22 to 2.70 per 100,000 live births[1,2,3]. It is a progressive condition characterized by facial dysmorphism, cardiomegaly, hepatosplenomegaly and musculoskeletal abnormalities[3]. We report a case of I-cell disease in a neonate presenting prenatally as skeletal dysplasia with multiple intrauterine fractures.

Case report

An early term (37+4 weeks of gestation) male infant, born vaginally to a 29-year-old gravida-5, para-4, mother with 2 healthy living children and a history of two infant deaths, was admitted in our neonatal intensive care unit (NICU). Birth weight was 1980g, birth length was 41cm and the head circumference was 31cm, all below the 3rd centile of the World Health Organisation (WHO) growth chart for boys with no family history of early deaths or genetic disorders. The parents were Indians with third degree consanguinity. Baby had Apgar scores of 9 at 1 and 5 minutes and was dysmorphic with coarse facial features and short extremities.

The antenatal scan done at 29 weeks of gestation had revealed severe shortening of the fetal long bones with a depressed nasal bridge raising the suspicion of skeletal dysplasia. Her previous two male infants died at 4 months and at 2 hours of life secondary to pneumonia and birth asphyxia respectively. One of these 2 infants also had dysmorphic features with short limbs and required prolonged ventilation from 1 month of age. This infant was not evaluated. The other 2 siblings are girls and have no morbidities. During this pregnancy, mother was offered antenatal counselling but did not follow up.

Detailed physical examination of the infant revealed microcephaly with a thin, soft skull. Sparse scalp hair and eyebrows were noted. A sloping forehead with a wide nasal bridge, anteverted nostrils, retrognathia, micrognathia, gingival hyperplasia added to the coarseness of face. Examination of trunk revealed a long, narrow bell-shaped thorax with an upper to lower segment ratio of 2:1. In upper extremities, rhizomelic shortening was noted with redundant skin creases and bilaterally stiff elbows. In the lower extremities there was outward bowing of lower one-third (Figure 1). Widening of wrists and ankles was also noted. The rest of the physical examination was normal. Systemic examination revealed hepatosplenomegaly with a normal cardiac examination.

Radiological examination revealed diffuse demineralization of bones, severe thinning of cortex of cranial vault (but no wormian bones), ovoid vertebrae, bell-shaped chest with abnormal shaped ribs on left side, shortened long bones with irregular metaphysis and extensive periosteal reaction of both tibia and femur (Figures 2 and 3). Similar findings of extensive periosteal reaction of humerus, radius, ulna with irregular cupped and splaying of metaphysis were seen. Bullet shaped phalanges with multiple healed fractures of left ulna and left humerus were also noted. Based on these clinical and radiological findings, differential diagnoses included a severe form of skeletal dysplasia, osteogenesis imperfecta, severe neonatal hyperparathyroidism and mucolipidosis.

The neonate had respiratory distress since birth, was initially on high flow oxygen therapy for 10 days and later developed worsening pneumonia requiring mechanical ventilation. He was ventilator dependent thereafter and had multiple extubation failures. He was supported with expressed breast milk fed via a nasogastric tube, with vitamin D, calcium and phosphorous supplementation.

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Figure 1: ***showing coarse facies, loose fold of skin over extremities, abnormal shape of chest and shortening of limbs***
****Permission given by parents to publish photograph***

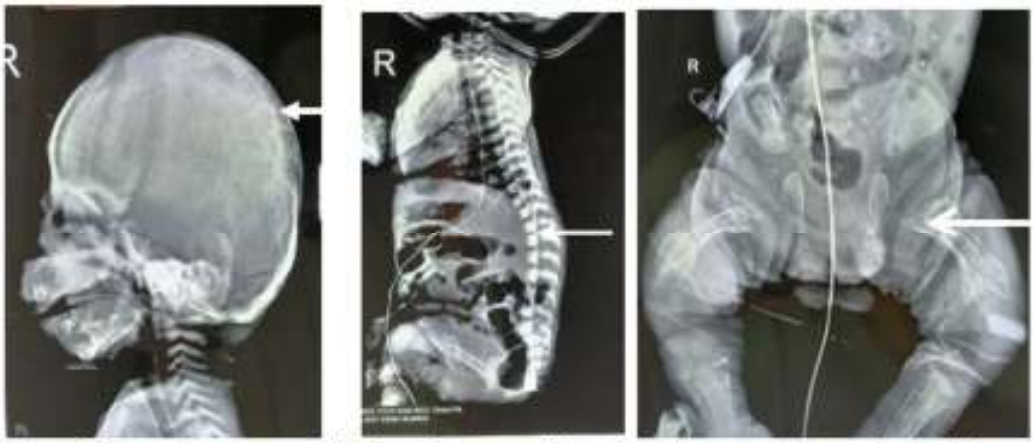

Figure 2: ***Images showing severe thinning of cortex. ovoid shaped vertebrae severe osteopenia of both femur***

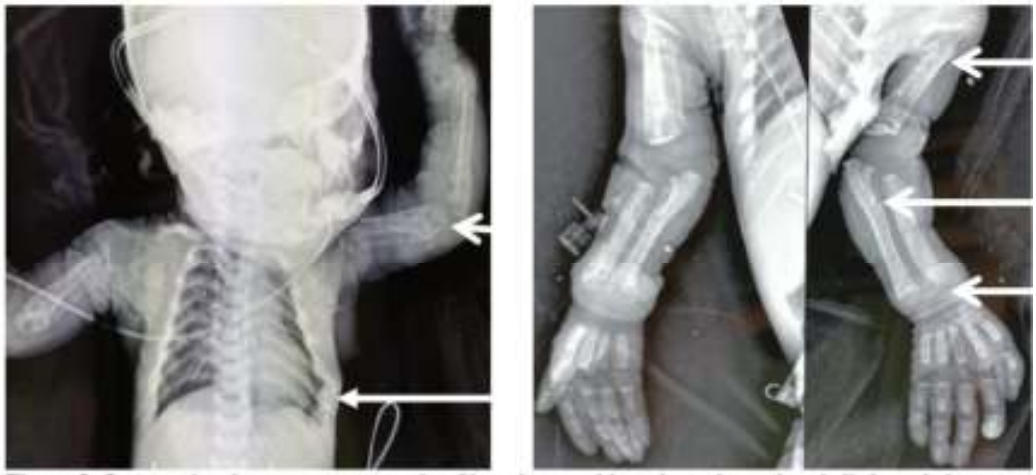

Figure 3: ***Images showing severe osteopenia of long bones with periosteal reaction, bell shaped chest, oar shaped ribs, abnormal metaphysis, fracture left ulna, humerus and bullet shaped phalanges***

The neonate was evaluated by a multidisciplinary team comprising ear, nose and throat specialist, cardiologist, endocrinologist, ophthalmologist, respiratory therapists and occupational therapist. The parents were counselled by a geneticist about the clinical condition and the risk of recurrence in future pregnancies. Based on the family history, clinico-radiological findings and neonatal course in NICU, I cell disease was suspected. The screening blood test, based on pattern of lysosomal enzyme, sulphatase activity in plasma was positive and a diagnosis of I cell disease was made. Confirmatory whole exome sequencing could not be done due to financial constraints of the family. Parents were counselled about the non-availability of any definitive treatment for this disease. The neonate was enrolled for palliative care and supportive care was provided. The baby passed away on day 65 of life.

Discussion

ML type 1 (Sialidosis), ML type II (I cell disease), ML type III (pseudo-Hurler polydystrophy), and ML type IV are the four types of ML[4]. I-cell disease is the most severe type, affects around 1 in 100,000 births and presents at the prenatal or neonatal stage. Mutation in the GNPTAB gene, leading to deficiency of Nacetylglucosamine-1-phosphotransferase (GlcNAc-1-PTase) is responsible for approximately 95% of cases[5,6]. GlcNAc-1-PTase is a hexameric ($\alpha 2\beta 2\gamma 2$) enzyme encoded by two genes: GNPTAB (α and β subunits, located on chromosome 12q23.3) and GNPTG (encoding for soluble γ subunits)[5,6]. This enzyme phosphorylates mannose 6-phosphate (M6P) residues on lysosomal acid hydrolases in the Golgi apparatus, transporting them into lysosomes. Without M6P, the newly synthesized lysosomal enzymes are missorted into the extracellular space and are therefore not able to breakdown their specific substrates in lysosomes[7]. These intra-lysosomal substrates accumulate in connective tissues, cartilage, bones, ligaments, and other tissues and are responsible for the clinical symptoms.

Antenatally, I cell disease can be suspected sonographically by the demonstration of abnormally shortened long bones and intrauterine growth retardation in the setting of a family history[8]. Other antenatal features of I cell disease include periosteal cloaking of the femur and humerus and transient maxillary defects[9]. In our case, the abnormalities found on prenatal ultrasound were severe shortening of long bones, depressed nasal bridge and features of fetal growth restriction, which can be present in skeletal dysplasia. In the absence of a family history, prenatal diagnosis of I-cell disease remains difficult as many other conditions can present with similar findings. In a pregnant lady, with the history of a previous sibling with similar manifestations, chorionic villous sampling followed by estimation of uridine diphosphate-N-acetylglucoseamine-1-phosphotransferase enzyme activity could have been offered to diagnose I-cell disease. In our patient, prenatal diagnosis was not done; hence, the parents were counselled about the risk and were advised to do prenatal testing in a future pregnancy.

In a case series of 516 patients from 34 different countries, mostly non-south east Asian, median age at diagnosis of I-cell disease was 7 months and median age of death was 1.8 years[10]. In a case series of 9 children with mucolipidosis reported from India, 2 neonates had I-cell disease. The cases were diagnosed at 9 months and 15 months[11]. Frequently reported symptoms at birth include dysmorphic facial features in 47.4% and bone abnormalities in 20%[10]. Our patient had coarse facial features with dysostosis multiplex noted at birth which was atypical compared to the general presentation of this disorder.

Lemaitre L, *et al* divided the radiological manifestation of I-cell disease into two groups, stage A and stage B[12]. Stage A included the first 2 months after birth, was typically characterized by storage osteopathy with bone structural and modelling abnormalities, stippling of the epiphyses and components of a storage disorder while Stage B started after the age of 4 months. In our case it was Stage A of the disease based on radiological findings which included metacarpal pointing, bullet-shaped phalanx, oar shaped ribs, and iliac flaring[13].

Most common cause of death is respiratory failure caused by progressive mucosal involvement and the stiffening of the thoracic cage[14]. The cause of death in our patient was respiratory insufficiency, seen as an early manifestation of the severe disease[15].

Due to overlapping features with mucopolysaccharidosis (MPS), the direct measurement of deficient enzymes is ideal but this assay is not available in many centres. ML patients may be diagnosed by the combined pattern of lysosomal enzyme activities in plasma and other biological fluids. Wiesmann U, *et al* in 1971 found a 90-fold increase in arylsulfatase A activity and 30 to 40-fold increase in arylsulfatase B activity in the plasma of ML II patients, compared to those in normal controls[16]. Test in our case was based on the same fact that sulphatase enzymes are nearly 10 to100-fold higher in plasma of infants with ML II. As in our patient, the detection of this enables the diagnosis of I cell disease[17].

Mutations in GNPTAB result in severe and attenuated forms of I-cell disease. Until now, 258 different mutations in GNPTAB have been reported and summarized by Velho RV, *et al*[6]. Forms of

mutation include frameshift mutations (39%), missense mutations (26%), nonsense mutations (23%), splice defects (9%), and deletions/duplications/insertions/deletion-insertions (3%)[6]. The GNPTAB gene contains 21 exons, and the majority of mutations (25%) are located on exon 13. These mutations facilitate the genetic diagnosis of ML[15].

There is no definitive treatment for ML. Patients are given supportive and symptomatic management to prevent life-threatening events and to maintain quality of life. Potential management includes enzyme replacement therapy, enzyme enhancement therapy, substrate reduction therapy, small molecule therapy, haematopoietic stem cell transplantation (HSCT), gene therapy, and clustered regularly interspaced short palindromic repeats-based genome editing[15]. Survival remains at 5 to 9 years even in patients who received HSCT[10].

References

1. Leroy JG, Demars RI. Mutant enzymatic and cytological phenotypes in cultured human fibroblasts. *Science* 1967; **157**: 804–6. https://doi.org/10.1126/science.157.3790.804 PMid: 17842782

2. Cathey SS, Kudo M, Tiede S, Raas-Rothschild A, Braulke T, Beck M, *et al*. Molecular order in mucolipidosis II and III nomenclature. *American Journal of Medical Genetics Part A* 2008; **146A**: 512–3. https://doi.org/10.1002/ajmg.a.32193 PMid: 18203164

3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999; **281**: 249–54. https://doi.org/10.1001/jama.281.3.249 PMid: 9918480

4. Spranger JW, Wiedemann HR. The genetic mucolipidoses. Diagnosis and differential diagnosis. *Humangenetik* 1970; **9**: 113–39. https://doi.org/10.1007/BF00278928 PMid: 4246487

5. Tiede S, Storch S, Lubke T, Henrissat B, Bargal R, Raas-Rothschild A, *et al.* Mucolipidosis II is caused by mutations in GNPTA encoding the alpha/beta GlcNAc1-phosphotransferase. *Nature Medicine* 2005; **11**(10): 1109–12. https://doi.org/10.1038/nm1305 PMid: 16200072

6. Velho RV, Harms FL, Danyukova T, Ludwig NF, Friez MJ, Cathey SS, *et al.* The lysosomal storage disorders mucolipidosis type II, type III alpha/beta, and type III gamma: Update on GNPTAB and GNPTG mutations. *Human Mutation* 2019; **40**: 842–64. https://doi.org/10.1002/humu.23748 PMid: 30882951

7. Braulke T, Bonifacino JS. Sorting of lysosomal proteins. *Biochim. Biophys. Acta* 2009; **1793**(4): 605–14. https://doi.org/10.1016/j.bbamcr.2008.10.016 PMid: 19046998

8. Babcock DS, Bove KE, Hug G, Dignan PS, Soukup S, Warren NS. Fetal mucolipidosis II (I-cell disease): Radiologic and pathologic correlation. *Pediatric Radiology* 1986; **16**: 32–9. https://doi.org/10.1007/BF02387502 PMid: 3080723

9. Chen M, Ke YY, Chang SP, Lee DJ, Chen CH, Ma GC. Prenatal transient alveolo-maxillary defect in a case of mucolipidosis II (I-cell disease). *Ultrasound in Obstetrics and Gynecology* 2010; **36**: 255–6. https://doi.org/10.1002/uog.7620 PMid: 20205156

10. Dogterom EJ, Wagenmakers MAEM, Wilke M, Demirdas S, Muschol NM, Pohl S, *et al.* Mucolipidosis type II and type III: a systematic review of 843 published cases. *Genetics in Medicine* 2021; **23**(11): 2047-56. https://doi.org/10.1038/s41436-021-01244-4 PMid: 34172897

11. Sanjeeva GN. (2014). Mucolipidosis Type II and Type III: Nine cases from one Indian centre. 10.13140/RG.2.1.4613.2245.

12. Lemaitre L, Remy J, Farriaux JP, Dhondt JL, Walbaum R. Radiological signs of mucolipidosis II or I-cell disease. A study of nine cases. *Pediatric Radiology* 1978; **7**: 97–105. https://doi.org/10.1007/BF00975678 PMid: 673536

13. Capobres T, Sabharwal G, Griffith B. A case of I-cell disease (mucolipidosis II) presenting with short femurs on prenatal ultrasound and profound diaphyseal

cloaking. *BJR Case Reports* 2016; **2**: 20150420.
https://doi.org/10.1259/bjrcr.20150420
PMid: 30459979 PMCid: PMC6243348

14. David-Vizcarra G, Briody J, Ault J, Fietz M, Fletcher J, Savarirayan R. The natural history and osteodystrophy of mucolipidosis types II and III. *Journal of Paediatrics and Child Health* 2010; **46**: 316–22.
https://doi.org/10.1111/j.14401754.2010.01715.x
PMid: 20367762 PMCid: PMC4188554

15. Khan SA, Tomatsu SC. Mucolipidoses Overview: Past, present, and future. *International Journal of Molecular Sciences* 2020; **21**(18): 6812
https://doi.org/10.3390/ijms21186812
PMid: 32957425 PMCid: PMC7555117

16. Wiesmann U, Vassella F, Herschkowitz N. "I-cell" disease: Leakage of lysosomal enzymes into extracellular fluids. *New England Journal of Medicine* 1971; 285: 1090–1.
https://doi.org/10.1056/NEJM197111042851923
PMid: 4328711

17. Sheth JJ, Mistri M, Kamate M, Vaja S, Sheth FJ. Diagnostic strategy for mucolipidosis II/III. *Indian Pediatrics* 2012; **49**(12): 975–7.
https://doi.org/10.1007/s13312-012-0247-6
PMid: 22728628