

Prenatal Diagnosis of Restrictive Dermopathy

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We report three cases of Restrictive dermopathy from unrelated families. All were small for gestational age with small eyes and open mouth. Taut, stretched skin caused restriction of movements. Clavicular hypoplasia was a consistent radiological feature. Molecular diagnosis in the parents facilitated prenatal diagnosis from chorionic villous sample (CVS) in the subsequent pregnancy.

Key words: India, Mutation, Prenatal diagnosis, Restrictive dermopathy.

Restrictive dermopathy is a rare lethal genodermatosis(1) resulting in fetal hypokinesia due to tight and adherent skin. Neonates present with distinctive facies, multiple joint contracture, dysplastic clavicle and pulmonary hypoplasia. Three babies—two neonates and a stillborn fetus—with features of restrictive dermopathy are presented. Molecular diagnosis, performed in two families, identified the same mutation.

CASE REPORTS

Case 1: An opinion was sought for a sick neonate weighing 1.1 kg born at 32 weeks at a tertiary hospital. She was the first born of a nonconsanguinously married healthy South Indian couple. The family pedigree revealed unexplained neonatal deaths in the maternal and paternal side. Baby had small eyes and nose, low set ears and open mouth. The head was dolicocephalic with open sutures and wide open anterior fontanelle. The skin was taut, parched and peeling in patches. The taut skin resulted in shallow respiration. Joints and limbs were stiff with restriction of movements (**Fig. 1(a)**). Extension of neck resulted in laceration that required suturing. X-ray chest revealed dysplastic clavicles.

Ultrasound abdomen was normal. Skin biopsy revealed mildly thickened epidermis without hyperkeratosis or parakeratosis. The epidermis was flattened and there were no rete pegs; sweat glands were absent. Subcutaneous tissue was normal. The final impression was consistent with restrictive dermopathy. Baby expired on the second day. Parents were counseled. Extensive search led us to a research laboratory at the Washington University School of Medicine, which offered to proceed with carrier screening for the couple. Molecular analysis revealed carrier status in the parents. The ZMPSTE24 gene was sequenced for Exon 6 and the couple was found to be heterozygous for c691G >T (Glu231X) mutation.

The carrier status of the couple was re-established in the Indian laboratory and certified by the researcher. Prenatal diagnosis in their subsequent pregnancy was performed and the fetus was found to be homozygous for the c691G >T (Glu231X) mutation. Hence, the pregnancy was terminated and autopsy was done, revealing a male fetus of 14-15 weeks gestation without any structural anomaly.

The same exercise was repeated in her third pregnancy. Though the fetus was found to be

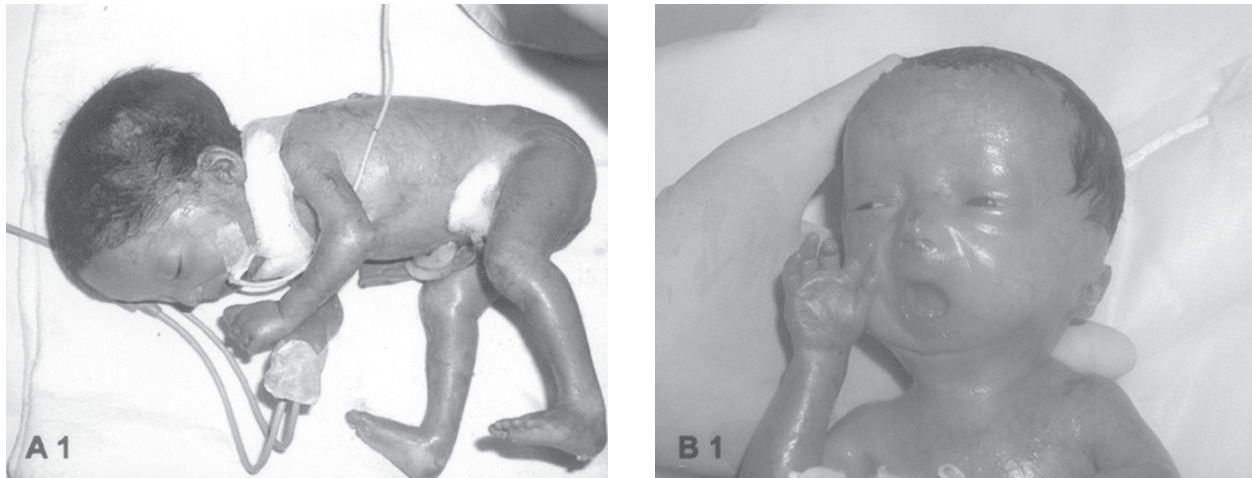


FIG. 1 (a) and (b), Neonates with features of restrictive dermopathy.

homozygous for the mutation and hence affected, the mother wanted to continue the pregnancy, whatever be the outcome. Fetal growth, movements and liquor were normal till 28 weeks. At 30 weeks, reduced fetal movements and polyhydramnios was noted. At 32 weeks, following progressive polyhydramnios and maternal distress, baby was delivered by caesarean section and had all the features of Restrictive dermopathy.

Case 2: The second neonate was referred for opinion to identify the genetic problem. The mother was known to have a single kidney and was on treatment for pregnancy induced hypertension from 28 weeks of gestation. In view of premature rupture of membranes and meconium stained liquor, baby was delivered by emergency caesarian section, at 33–34 weeks of gestation. The baby (**Fig.1(b)**) weighed 1 kg with tight dry and parched skin, small eyes, nose and mouth. There were joint contractures, fluid collections in the scrotal sacs and in the subareolar region. X-ray chest revealed hypoplastic clavicles. Diagnosis of Restrictive dermopathy was made.

Blood sample from the baby was sent to the same laboratory in India. Using the same probe used in the previous case, the baby was confirmed to be homozygous for the mutation detected in the first family - c691G>T (Glu231X) mutation. The couple was counseled about the condition; the need for prenatal diagnosis in every pregnancy was insisted.

Case 3: A fetus was sent for autopsy following intrauterine demise at 36-37 weeks. The fetus had all clinical, radiological and histopathologic features of Restrictive dermopathy.

DISCUSSION

Restrictive dermopathy or tight skin contracture syndrome is a rare lethal condition, first described in 1929(1). Prenatal diagnosis by antenatal ultrasound is difficult as polyhydramnios and growth retardation are late nonspecific markers. Even a fetal skin biopsy at 24 weeks has not been able to pick up this problem(2). Fetal skin development is not complete till 20 weeks(3) and hence, the skin biopsy before 20 weeks, as in the affected fetus in our case, definitely cannot pick up this problem. Hence, a more specific prenatal diagnostic test is the need.

The conversion of Prelamin A to Lamin A requires ZMPSTE 24, a Zinc metalloproteinase(4). Mutations in ZMPSTE 24 cause accumulation of Prelamin A, a cytotoxic precursor, which is associated with laminopathies(5). New mutations are being identified through research; c691G>T (Glu231X) mutation of ZMPSTE24 is postulated to be specific for Indian population. The two unrelated families were found to have the same mutation.

Identification of mutation is essential for prenatal diagnosis of this problem. This being a rare condition, it may not be possible to set up

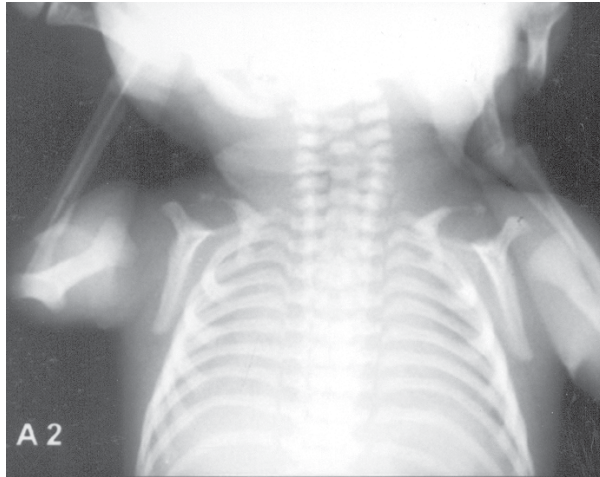


FIG. 2 Xray chest showing dysplastic clavicles.

laboratories in every country for these conditions. However, cooperation and sharing of information across international borders goes a long way in helping families with rare disorders.

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IS performed the antenatal scans. LM performed the autopsies and skin biopsy in these cases.

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REFERENCES

1. Verloes A, Mulliez N, Gonzales M, Laloux F, Hermanns-Le T, Pierard GE, *et al.* Restrictive dermopathy, a lethal form of arthrogyrosis multiplex with skin and bone dysplasias: three new cases and review of the literature. *Am J Med Genet* 1992; 43: 539-547.
2. Hamel BCJ, Happle R, Steylen PM, Kollee LAA, Schuurmans Stekhoven JH, Nijhuis JG, *et al.* False negative prenatal diagnosis of restrictive dermopathy. *Am J Med Genet* 1992; 44: 824-826.
3. Elder DE, Elenitsas R, Johnson BL, Murphy GF. *Lever's Histopathology of Skin*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
4. Navarro CL, Cadiñanos J, De Sandre-Giovannoli A, Bernard R, Courier S, Boccaccio I, *et al.* Lamin and ZMPSTE 24 (Face-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Molec Genet* 2005; 14: 1503-1513.
5. Moulson CL, Gloriosa G, van der Wal A, Smitt JHS, van Hagen JM, Miner JH. Homozygous and compound heterozygous mutations in ZMPSTE 24 cause the laminopathy restrictive dermopathy. *J Invest Dermatol* 2005; 125: 913-919.