Nager Syndrome Co-Harboring Mutation Consistent with Stickler Syndrome: A Rare Case Report

Abstract

Nager syndrome or preaxial acrofacial dysostosis is a rare malformation syndrome characterized by abnormalities of craniofacial skeleton and limbs. Although most cases are sporadic and some cases have been demonstrated to have autosomal dominant or recessive mode of inheritance, SF3B4 haploinsufficiency is the most common genetic abnormality identified in this syndrome of which only around 100 cases have been reported so far in literature. Classically characterized by ante-mongoloid slant, retrognathia, midface retrusion and proximal limb abnormalities like thumb aplasia or hypoplasia, arachnodactyly and radioulnar synostosis, the major morbidity and mortality in this challenging condition is primarily due to airway abnormalities causing respiratory obstruction. We report a case of genetically confirmed Nager syndrome simultaneously harboring a mutation consistent with Stickler syndrome type II.

Introduction

Nager syndrome, or preaxial acrofacial dysostosis, is an extremely rare malformation syndrome first reported by Nager and de Reynier in 1948. Around 100 cases have been reported so far in literature, few of them have been genetically confirmed [1]. Severe oromandibular hypogenesis and upper limb defects with relative sparing of the lower limbs is the characteristic of this illness. A tenuous airway prone for severe respiratory obstruction, necessitating tracheostomy tube placement by end of infancy, is the major cause of morbidity and mortality in this disorder [2]. We report a neonate born in our institute with gross dysmorphic features which later was proven genetically as a case of Nager Acrofacial Dysostosis, also harboring another mutation consistent with Stickler syndrome.

Case Presentation

The prepositus is a first order neonate who was born in our institute by caesarean section and was referred to Paediatrics department for evaluation of gross craniofacial and limb anomalies. He was born at term with birth weight of 2290 g (<3rd centile), with length 48 cm and head circumference of 33 cm. The morphologic examination of the neonate revealed up-slanting palpebral fissures, malar hypoplasia and severe micrognathia with cleft palate. (**Figure 1**)

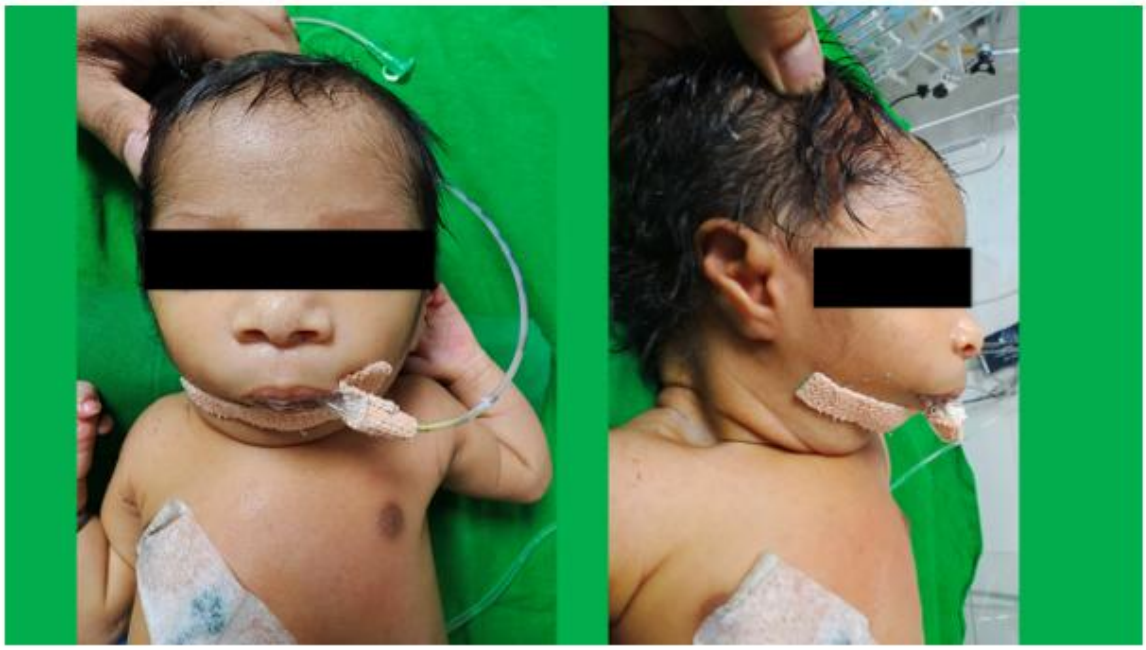

Figure 1: Frontal and Lateral facial profile of the patient showing severe retrognathia

There was right thumb aplasia (type 5) and type 2 thumb hypoplasia on left side with hypoplastic thenar muscles (Blauth classification) [3].(**Figure 2**)

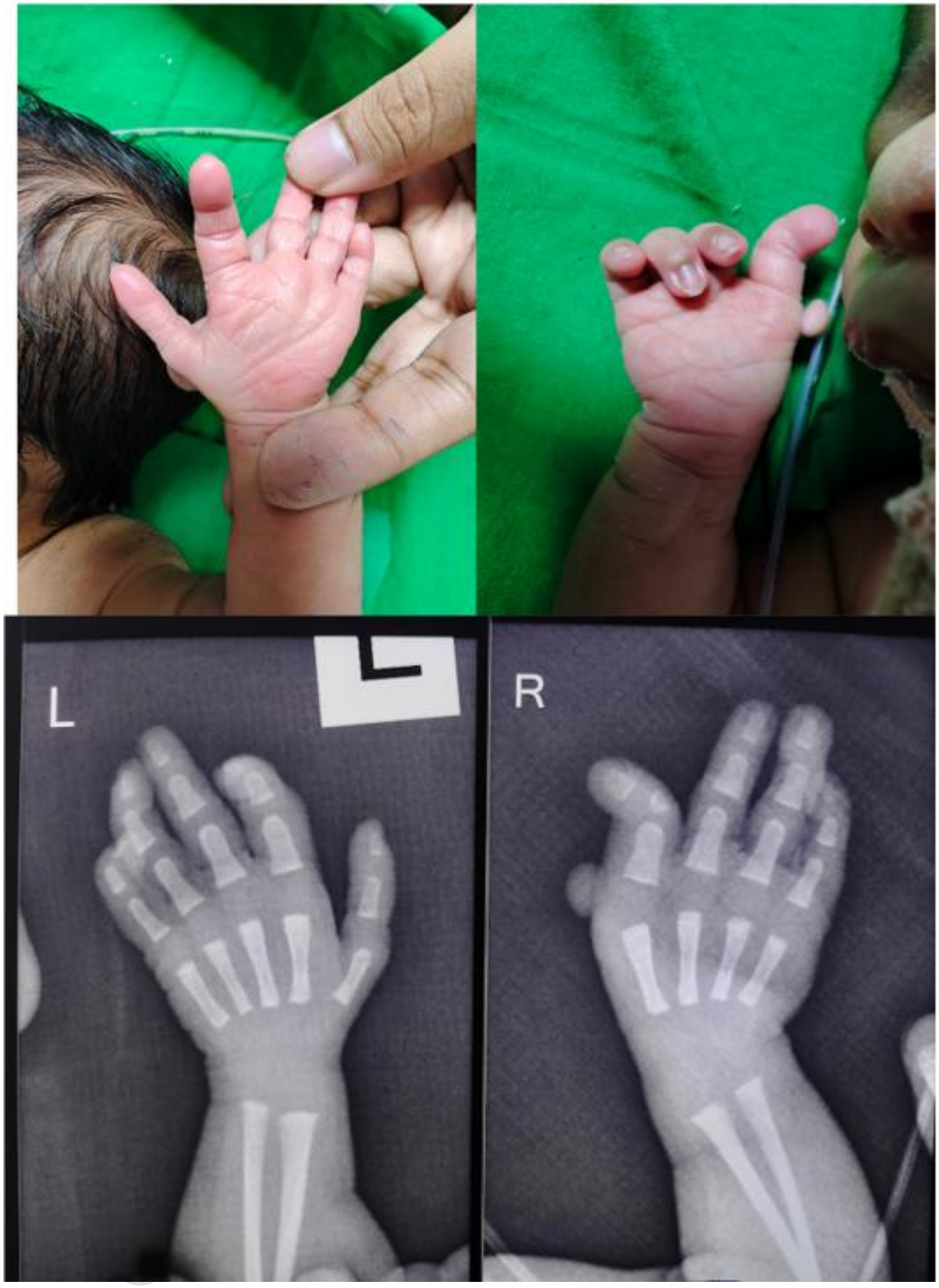

Figure 2: Gross appearance and x-rays of hands showing Thumb Hypoplasia (Left) and Thumb Aplasia (Right)

There was no gross abnormality in bilateral lower limbs and no ocular abnormalities. There was no similar history in any other family members and there was no history of previous pregnancy loss or sibling death either.Echocardiography was normal. There were no ocular abnormalities and fundus examination revealed no significant abnormalities. Based upon the morphologic findings, various differential diagnoses of Pierre Robin Sequence, Nager Syndrome, Miller syndrome and Stickler syndrome were considered and Whole Exome Sequencing (WES) was performed after obtaining consent from parents. A heterozygous

frameshift variant c.956dupT in Exon 5 of the *SF3B4* gene that results in the amino acid substitution p.Leu319fs*108 was identified, confirming a diagnosis of Nager syndrome with autosomal dominant inheritance.Anotherheterozygous missense variant c.4307C>T in Exon 58 of the *COL11A1* gene that results in the amino acid substitution p.Pro1436Leu was also identified, which is associated with Stickler Syndrome type II. Feeding was established after placement of orogastric tube with airway protective measures. After proper counselling regarding the prognosis and what the future holds for the baby, he was discharged and parents were advised to consult a plastic surgeon for reconstructive surgery of the child such as pollicization of index finger.

Discussion

Nager syndrome is the prototype of a group of very rare disorders collectively known as Acrofacial Dysostosis (AFD), characterized by malformations of craniofacial skeleton and limbs. It is a rare congenital malformation syndrome resulting from abnormal development of first and second branchial arches and limb buds [4]. First reported by Slingenberg in 1908 and recognized by Nager and de Reynier in 1948, the exact cause of this abnormal development is still incompletely understood [5]. Although majority of the cases are sporadic, the mode of inheritance can be either Autosomal Dominant or Autosomal Recessive and multiple families showing highly variable expressivity of the disease have been reported [4,6].

Appropriate genetic expression in eukaryotic cells relies upon pre-mRNA splicing, an important step in which precise removal of introns from pre-mRNA gives rise to mature mRNA. This splicing takes place in Spliceosomes, large RNA-protein complexes, that consist of a set of snRNPs, including U1, U2, U4/U6 and U5 complexes. SF3B4, the only gene associated with Nager acrofacial dysostosis, is a gene encoding a core subunit of the metazoan SF3b complex, which is part of U2-type spliceosome [7].It is also an important gene related to Bone Morphogenic Protein (BMP) signaling pathway [8]. Haploinsufficiency of SF3B4 is found in greater than 50% of cases of Nager syndrome [6]. Extensive genetic heterogeneity is suggested by identification of deletions encompassing SF3B4 in some cases, which has been helpful in prenatal diagnosis of fetuses as early as 12 weeks of gestation by virtue of chromosomal microarray [9].

Distinguished from Mandibulofacial dysostosis, Nager syndrome affects the muscles and nerves associated with mastication, lower jaw, bones of middle ear and the muscles of facial expression [4]. The major clinical features of this disorder include down-slanting palpebral fissures, micrognathia, malar hypoplasia, pre-axial limb abnormalities such as small or absent thumbs, triphalangeal thumbs, arachnodactyly, radial aplasia or hypoplasia and radio-ulnar synostosis [6,10]. Although congenital cardiac defects like septal defects and tetralogy of Fallot have been reported, they are extremely uncommon [2].

The major problem faced by parents in the neonatal period and infancy is feeding issues courtesy of cleft palate and retrognathia, often necessitating placement of a feeding tube into stomach. Trismus and glossoptosis as a consequence of mandibular abnormalities can lead to life threatening respiratory distress in infancy, entailing placement of tracheostomy tube [10,11]. Later on, Conductive Hearing Loss (CHL) and speech delay further complicate the development of the children affected with this syndrome [12].Patients surviving into adulthood are typically riddled with history of multiple interventions such as

repair of cleft palate, chin implant, bone-anchored hearing aid implantation, spinal fusion and extremely difficult intubation when required [11]. If untreated, cases have been reported where CHL has gradually progressed to Sensorineural Hearing Loss (SNHL) culminating in mixed hearing loss, not amenable to surgical interventions [12].

Conclusion

A multidisciplinary team consisting of neonatologists, otorhinolaryngologists, anesthesiologists, obstetricians, audiologists, plastic surgeons, and geneticists is best suited to care for babies afflicted with this rare and challenging disorder, for which a high index of suspicion and availability of genetic tests like whole exome sequencing or chromosomal microarray analysis can prove helpful in prenatal or early neonatal diagnosis. Pediatric intensivists need to be extremely skillful in managing conditions with difficult airway such as this and must always be prepared for emergency and elective tracheostomy. Availability of equipment like pediatric video laryngoscope and fiber optic bronchoscope can aid in the management of patients with Nager syndrome.

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