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BRIEF COMMUNICATION

ALG9 Associated Gillessen-Kaesbach–Nishimura Syndrome (GIKANIS): An Uncommon Aetiology of Enlarged Foetal Kidneys

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Abstract There are innumerable causes of enlarged kidneys along with dysmorphism in the foetus. Various chromosomal microdeletion syndromes, ciliopathies, Zellweger syndrome, Perlman syndrome and congenital disorders of glycosylation. CDG are a large group of syndromes which cause disruption of one of the several synthetic pathways of glycan synthesis. Here, we describe an unusual and extremely rare presentation cause of enlarged foetal kidneys due to a novel missense variant causing Gillessen-Kaesbach–Nishimura syndrome. The role of deep phenotyping is emphasised as it is a pre-requisite for making a diagnosis and establishing a given mutation as pathogenic. The genetic and clinic aspects of the previously published data are also reviewed.

Keywords Congenital disorders of glycosylation · ALG9 gene · Enlarged echogenic cystic kidneys · Fetal · Autopsy

Case Report

An apparently healthy non-consanguineous couple presented at 19 weeks with level II ultrasound showing fetal malformations. Their first pregnancy was terminated in view of bilateral echogenic kidneys and bilateral clubfeet detected on the second trimester anomaly scan. In the current pregnancy, prenatal ultrasound again suggested echogenic enlarged cystic kidneys, increased nuchal fold thickness (8 mm), unossified nasal bone and polyhydramnios. Following this, the couple opted for termination and was referred for postnatal evaluation. Fetal autopsy was performed, pictures were taken, and X-rays were done. On gross examination of the fetus, facial dysmorphism was present which included high forehead, large anterior fontanelle, flat facial profile, hypertelorism, large palpebral fissures, depressed nasal bridge, beaked nose, short neck, retrognathia, large mouth and posteriorly rotated ears (Fig. 1). Fetal weight was 180 g, head circumference: 20 cm, CRL-18.5 cm, all corresponding to 19 weeks of gestation. Bilateral kidneys were enlarged (4 × 1 × 1 cm, weighing 14 g, corresponding to 31 weeks) and cystic with no dilatation of ureters or megacystis (Fig. 2). Rest of the examination was unremarkable. Infantogram revealed rounded iliac crests but otherwise normal axial and appendicular skeleton present (Fig. 3). Cardiac dissection revealed no abnormalities. Fetal karyotype was reported to be normal. A TRIO whole exome sequencing was ordered in view of recurrence of fetal malformations and to ascertain a diagnosis.

The whole exome analysis revealed a homozygous missense variation in exon 13 of the ALG9 gene, NM_001077690.1 (ALG9): c.1068T > G, p.Asn356Lys. This variant is not reported in 1000 genomes and ExAC databases and lies in the ALG9-like mannosyltransferase family protein domain. In silico prediction of the variant was damaging by various softwares. Sanger validation of the variant was done and the parents were found to be heterozygous carriers.

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Fig. 1 **a** Lateral facial profile showing flat facies. **b**, **c** Facial profile showing hypertelorism, large palpebral fissure beaked nose, long philtrum & large mouth

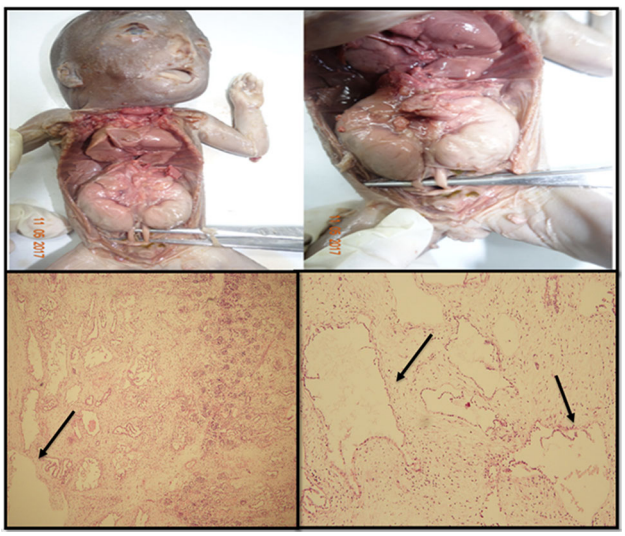

Fig. 2 Top panel-bilateral enlarged kidneys. Bottom panel left-Low power view showing dilated tubules with radial arrangement within the renal medulla (H & E stain 100 x original magnification). Bottom panel right-Cystically dialted renal collecting tubules lined by falttened to low cuboidal epithelium (H & E stain 200 x original magnification)

The reference region is conserved across species. It is likely pathogenic according to the modified ACMG criteria.

Discussion

Whole exome sequencing has brought about a revolution in genetic diagnosis and has increased the yield of diagnosis by about 20–30% over the conventional techniques [1]. But like most newer interventions, it has its limitations. One of the biggest challenges is its use in prenatal diagnosis. As

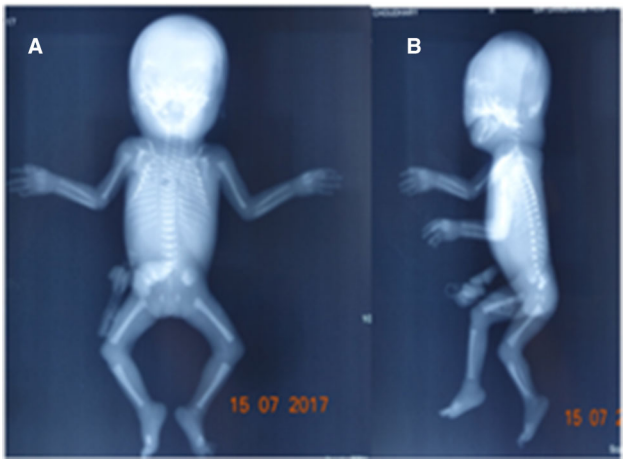

Fig. 3 Infantogram showing rounded iliac crests, normal vertebral bodies, ribs and tubular bones

the phenotype is not completely manifested in the fetal stage, it becomes very difficult to establish a genotype–phenotype correlation.

Single gene disorders causing bilateral enlarged and echogenic kidneys include ciliopathies, Zellweger syndrome, Perlman syndrome and autosomal recessive polycystic kidney disease. Another aetiology is the rare GKNIAS which was first described by Gillessen in foetuses and neonates dysmorphism, skeletal dysplasia and visceral involvement [2, 3]. More recently, GKNIAS is identified as the most severe end of spectrum of *ALG-9* associated congenital disorders of glycosylation which ranges from prenatally lethal disease [2, 4] to live born children with skeletal dysplasia, hypotonia, microcephaly and intellectual disability [5]. CDG are a large family of disorders with variable presentation affecting one or multiple organ systems. CDG-N-linked are caused by the defective synthesis of N-linked oligosaccharides which are attached to proteins and lipids (N-linked glycans link to the amide group of asparagine via an N-acetylglucosamine residue) [6–8]. Forty-nine different genes are known to cause CDG, most of which are inherited in an autosomal recessive manner. *ALG9-CDG* (TYPE 1-L) is known to be caused by mutations in *ALG9* gene which encodes alpha-1,2-mannosyltransferase enzyme that functions in lipid-linked oligosaccharide assembly. Currently, assessment of transferrin isoforms by transferrin isoelectric focusing is the most widely used test to screen for N-glycosylation defects, patients identified to have an abnormal pattern can be further assessed by glycan profiling [9, 10].

In *ALG9*, GKNIAS phenotype foetuses, hypertelorism, beaked nose, hypoplastic alae nasi, micrognathia and retrognathia, low-set posteriorly rotated ears, short

extremities with ulnar deviation of the hands, enlarged kidneys, deformed feet, rounded pelvis, flat vertebral bodies have been reported [4]. The facial dysmorphism was strikingly similar to this foetus as was the presence of enlarged kidneys, however it lacked skeletal involvement except the presence of rounded ilia and thickened skull. The difference in the phenotype may be explained by the pattern of mutations identified. All of the three affected foetuses in the series had a novel homozygous splice site variant NM_024740.2: c.1173 + 2T > A in the *ALG9* [4] which results in skipping of an exon and causing a severe phenotype whereas here, the milder phenotype can be attributed to a missense mutation. A limitation in our case is the lack of confirmation of isoelectric transferrin isoforms as a sample of frozen spleen was not available. However, the presence of a detailed foetal phenotype allowed for an appropriate diagnosis to be established.

Thus, we report a novel missense change causing a rare disorder for a relatively common finding of foetal enlarged cystic kidneys. This case highlights the importance of detailed evaluation and phenotyping in all malformed foetuses by prenatal ultrasounds, postnatal X-rays, ultrasound and autopsy to establish a genotype–phenotype correlation in this genomic era.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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