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CASE REPORTS

Phenotypic Overlap of 22q11.2 Microduplication and Noonan Syndrome in a Fetus with Increased NT, Facial Dysmorphism, and Narrow Pulmonary Trunk

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Abstract 22q11.2 deletion syndrome is a common microdeletion syndrome with a prevalence of 1 in 2000-6000 live births. Clinical features include conotruncal congenital heart defect (CHD), characteristic facial features, neurodevelopmental delay, and immunological abnormalities. Microduplications of 22q11.2 are rare compared to deletions due to ill-defined variable phenotype. A few cases of 22q duplication have been identified in the prenatal period in fetuses with increased nuchal translucency (NT), cardiac anomalies, cleft palate and micrognathia. We report a case of a fetus with increased NT in ultrasound and facial dysmorphism, narrow pulmonary trunk on autopsy evaluation, diagnosed to have microduplication of 22q11.2.

Keywords 22q11.2 · 22q11.2 duplication syndrome · Nuchal translucency · Cardiac anomalies

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Introduction

22q11.2 microduplication is a rare abnormality which presents with a variable phenotype. In published literature both prenatal and postnatal cases have been described. Prenatal cases present with congenital anomalies. Postnatal cases present with hypotonia, facial dysmorphism, CHD, developmental delay and intellectual or learning disability [1, 2]. It is inherited in an autosomal dominant manner or can occur de novo. The severity of the phenotype is not related to the size of the duplication suggesting that in addition to gene dosage, the phenotype is determined by environmental interactions and imprinting mechanism.

Case Report

This is a case report of a non-consanguineous couple who presented at 7 weeks of gestation. They had a history of termination of a previous pregnancy at 20 weeks because of sacral agenesis. This was confirmed following termination with an infantogram. Family history was not significant. There were no maternal comorbidities or exposure to teratogens. Karyotype of the couple, done in view of the previous history of neural tube defect, was normal. The current pregnancy was a spontaneous conception. A nuchal scan at 13 weeks 5 days revealed increased nuchal translucency with bilateral jugular lymph sacs (Fig. 1A). No other structural anomalies were detected. Other sonological markers such as fetal heart rate, tricuspid doppler, and ductus venosus doppler were normal. The couple were counseled. They opted for chorionic villous sampling. DNA isolation and chromosomal microarray were done.

Chromosomal microarray revealed heterozygous pathogenic 2.78 Mb duplication involving chromosome

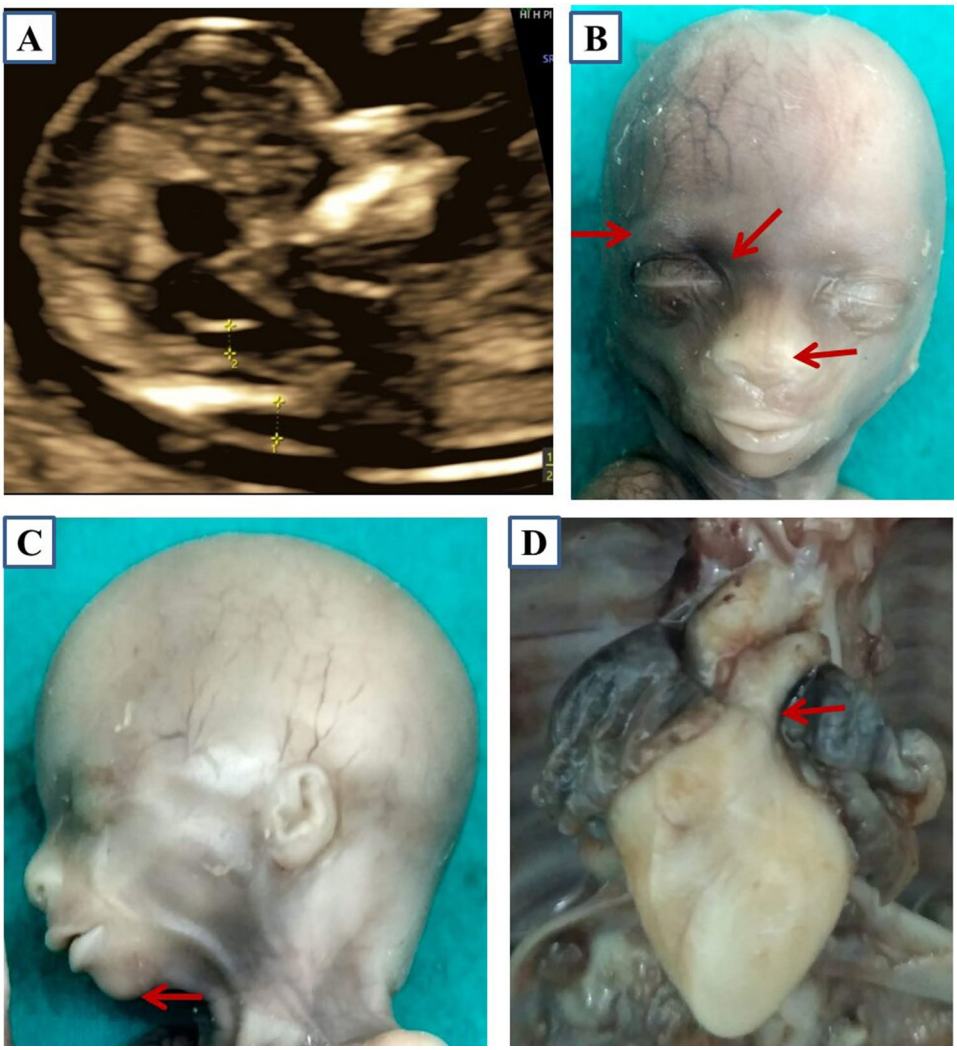

Fig. 1 **A** Ultrasound showing increased nuchal translucency in the fetus. **B**, **C**: Autopsy findings showing facial dysmorphism in the fetus with prominent wrinkled skin over the scalp, prominent supraorbital ridges, bilateral epicanthal folds, broad nasal bridge with hypoplastic anterior nares, midfacial hypoplasia and mild retrognathia. **D** Autopsy finding of the narrow pulmonary trunk in the fetus

22 encompassing the 22q11.21 region. They were counseled regarding the inheritance, variable expressivity of the 22q11.2 microduplication and were advised chromosomal microarray of the couple.

The couple did not wish to continue the pregnancy and opted for termination. The fetus was sent for autopsy. Autopsy showed facial dysmorphism with prominent wrinkled skin over the scalp, prominent supraorbital ridges, bilateral epicanthal folds, broad nasal root, nasal bridge and nasal tip with hypoplastic anterior nares, midfacial hypoplasia, triangular face and mild retrognathia (Fig. 1B, 1C). In addition, nuchal edema and narrow pulmonary trunk (Fig. 1D) were noted. Other internal structures were grossly normal. Though chromosomal microarray has revealed 22q microduplication, in view of the presence of facial dysmorphism and narrow pulmonary trunk there was a likely possibility of Noonan syndrome as well. The couple were counseled and were advised exome sequencing from stored fetal DNA to look for a pathogenic variant in the genes known to cause Noonan syndrome. Exome sequencing from fetal DNA revealed a heterozygous variant of uncertain significance c.881G > A in exon 9 of the *LZTR1* gene which is known to cause Noonan syndrome. Targeted testing of the couple for the *LZTR1* gene revealed the presence of a variant in the asymptomatic husband. The couple were explained that the variant in *LZTR1* gene is a familial benign variant and is not responsible for the phenotype of the fetus. Chromosomal microarray of the couple was normal. The phenotype of the fetus was due to 22q11.2 microduplication. The recurrence risk of less than 1% and the option of prenatal invasive testing in the subsequent conceptions were discussed.

Discussion

The 22q11.2 region is susceptible to both microdeletions and duplications. Unequal crossing over of low-copy repeats (LCRs) leads to nonallelic homologous recombination (NAHR) and results in deletions/duplications of chromosome 22q. LCRs are highly homologous sequences which

constitute approximately 4–5% of the human genome. The association of heterozygous deletion of chromosome 22q11.2 and Di George syndrome was first reported by Driscoll et al. in 1992. The association of duplication syndrome with chromosome 22q11.2 was reported in 1999 by Edelmann et al. Until then 22q11.2 microduplication was described as a variant of cat-eye syndrome, partial tetrasomy of short arm (p) and a small portion of the long arm (q) of chromosome 22.

The size of duplications of 22q ranges from ~3 Mb to ~6 Mb with 3 Mb duplication being most common. The prevalence of 22q11.2 microduplication is low. This could be because of underdiagnosis due to milder phenotypic presentation and at the same time, microduplications are not easily detectable by karyotyping [3].

The phenotypic expressions of 22q11.2 microduplication is highly variable with marked inter- and intrafamilial variability [4, 5]. There is no correlation between the size of the duplication and the severity of the phenotype. The exact cause of phenotypic variability is not known. Based on literature search and previous reports non-penetrance, epigenetic factors, modifier genes, and environmental factors were proposed to be responsible for the variable expressivity [5]. Counseling of the couple regarding the prognosis of the fetus is difficult in such cases.

Prenatal detection of 22q microduplication has been diagnosed in fetuses with increased NT, congenital cardiac anomalies and micrognathia, cleft palate and in one case with tracheoesophageal fistula [6, 7]. VACTERL association was also reported in a case of 22q11.21 microduplication [8]. 22q11.2 microduplication is the common copy number variant in fetuses with isolated fetal growth restriction [9]. Though 22q11.2 microduplication has been reported in cases with congenital cardiac anomalies, it seems to be a common occurrence in 22q11.2 deletion syndrome. Cardiac phenotype in 22q11.2 duplication syndrome is heterogeneous. Both conotruncal and other congenital cardiac anomalies have been reported in cases with 22q11.21 microduplication [10]. Narrow pulmonary trunk or pulmonary stenosis have not been reported previously. Facial dysmorphism in the form of a long narrow face, posteriorly rotated ears, preauricular pits, downslanting palpebral fissures, flattened and wide nasal root, micrognathia were reported in children with 22q microduplication. Delayed developmental milestones, hearing deficit and behavioral abnormalities have also been reported [11]. Children with nested deletions/duplications of 22q11.2 including LCR-A to LCR-B may be at higher risk for autism spectrum disorder [12].

Microduplications of 22q are frequently inherited. The chance of recurrence risk is 50% in the offspring, if one of the asymptomatic parents has 22q microduplication. Thus chromosomal microarray of parents is vital to provide appropriate genetic counseling and definitive prenatal testing though the exact phenotype of the child is difficult to predict. Reassurance of prospective parents is specifically difficult when a detailed ultrasound has no congenital structural anomalies in the fetus.

Conclusion

This case exemplifies that in cases undergoing termination of pregnancy, fetal autopsy evaluation and further genetic evaluation, as required, would help in understanding the phenotype better. In addition, follow up of cases with prenatally diagnosed microduplication of 22q11.2 in a large series further helps us in better understanding of the phenotype. This in turn would assist in reassuring the prospective parents regarding the exact phenotype of the fetus with 22q microduplication in near future.

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