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Atypical Down Syndrome Features with an Atypical Chromosomal Rearrangement: A Case Report

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Abstract

Down Syndrome is one of the most common chromosomal abnormalities occurring in approximately 1 in 700 live births. The majority of cases are attributed to the presence of an additional copy of chromosome 21, resulting in a total chromosome count of 47, as opposed to the typical 46. Distinctive facial characteristics commonly associated with this condition include, but are not limited to, upslanting palpebral fissures, epicanthal folds, protruding tongue, and brachycephaly. Other clinical manifestations encompass hypotonia, intellectual disability, congenital heart defects, among others. In this article, we present the case of a premature neonate delivered at 32 weeks of gestation via emergency cesarean section due to absent diastolic flow. The patient's prenatal history was significant for intrauterine growth restriction. Following birth, the patient displayed very subtle dysmorphic features, notably upslanting palpebral fissures, without additional features suggestive of Down syndrome. Chromosomal analysis was subsequently requested, revealing an isodicentric chromosome 21 (46, XX idic(21)(q22.3). Array Comparative Genomic Hybridization (CGH) was also performed, revealing a concurrent duplication of the majority of chromosome 21 [21p11.2q22.3(7761419_41294939)] and a 4.5 Mb deletion of the long arm of chromosome 21, specifically 21q22.3 (41295017_46677460).

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Introduction

Down Syndrome was first discovered back in 1866 by John Langdon Down, an English physician. However, its association with a chromosomal abnormality was not established until approximately 100 years later when Doctor Jerome Lejeune in Paris made this discovery [1]. Down syndrome is one of most common chromosomal disorders with an estimated incidence ranging between 1 in 310 and 1 in 1,000 live births depending on maternal age. The older maternal age, the higher the chance of delivering a baby with Down syndrome [2]. Most cases of Down syndrome result from the presence of an extra chromosome 21 due to a non-disjunction event, representing around 95% of all cases. Isodicentric chromosome 21 is a very rare form of chromosomal rearrangement reported in few cases in the literature. It is mainly composed of two copies of chromosome 21 fused together at the distal long arm [3].

Case Presentation

A 1-day-old baby girl was born prematurely at 32 weeks of gestation *via* emergency cesarean section due to absent diastolic flow. Prenatal history was remarkable only for intrauterine growth restriction. The mother, who was 37 years old, had a history of transverse myelitis but was otherwise healthy and received regular prenatal care during her pregnancy. The baby was born with a birth weight of 1.1 kg and a length of 40 cm. Initial assessment revealed a large ostium secundum atrial septal defect and mild mitral valve insufficiency. Upon examination, she has some subtle dysmorphic features including upslanting palpebral fissures, but there were no other features suggestive of Down syndrome. The baby experienced a prolonged stay in the Neonatal Intensive Care Unit (NICU) due to complications associated with prematurity, such as respiratory distress syndrome that required oxygen therapy. Additionally, she was diagnosed with laryngomalacia,

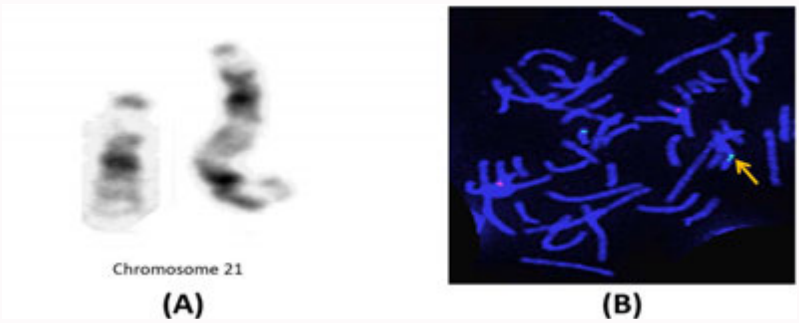

Figure 1: A) G-banding that reveals a female with 46, XX, idic(21)(q22.3). B) Metaphase FISH probed with Ch.21 (AML1 gene, Green) and Ch.8 (ETO gene, Red). Orange arrow indicates presence of idic(21)(q22).

Figure 2: Array CGH revealed a female with one gain copy number (one duplication) involving 21p11.2q22.3 region and a loss in the terminal (21q22.3-qter) region of chromosome 21. This result confirmed idic(21)(q22.3).

which caused feeding difficulties. A head ultrasound did not show any abnormalities. Genetic testing, including chromosomal analysis, was performed, and the results indicated the presence of an isodicentric chromosome 21 (46, XX, idic(21)(q22.3). Array CGH further revealed a concurrent duplication of most of chromosome 21 [21p1 1.2q22.3(7761419_41294939)] and a 4.5 Mb deletion of the long arm of chromosome 21, 21q22.3 (41295017_46677460). Chromosomal analysis was also conducted for both parents, and their results were normal (Figure 1, 2).

Discussion

Down syndrome is a chromosomal disorder characterized by one of most frequently occurring chromosomal abnormalities, with an estimated incidence ranging between 1 in 310 and 1 in 1,000 live births. The occurrence of Down syndrome is inversely related to maternal age. The majority of cases are caused by an extra copy of chromosome 21, resulting in a total chromosome number of 47 instead of 46 [2]. Individuals with Down syndrome typically exhibit distinct dysmorphic features and may experience organ involvement, such as the heart and brain. They are also at an increased risk of developing leukemia and Alzheimer's disease later in life [4,5].

Isodicentric chromosome 21 [46, XX, idic(21)(q22.3)] is a rare structural chromosomal abnormality in which the total number of chromosomes remains the same, but two long arms of chromosome 21 attached together by the centromere [3].

In this report, we present the case of a premature baby with atypical features of Down syndrome due to isodicentric chromosome 21 with a concurrent deletion of a portion of the long arm. The only notable feature observed was upslanting palpebral fissures.

A few cases have been reported in the literature, most of which exhibited the typical facial features of Down syndrome, along with hypotonia and developmental delay [3,4]. However, it was not noted that these cases had any additional features despite having a partial deletion of the terminal region of chromosome 21. In one of the cases, prenatal anomalies were detected, including a ventricular septal defect and non-visualization of the fetal stomach, accompanied by polyhydramnios [1]. Overall, cardiac anomalies are detected in approximately 15.9% of trisomy 21 fetuses [6]. The distinct phenotype observed in our patient, lacking the typical Down syndrome facial features, may be attributed to the larger size of the deletion in the 21.q22.3 region compared to previously reported cases.

In conclusion, further examination of the genes in this region may provide valuable insights into the pathogenesis of Down syndrome features. However, it is important to consider that the preterm birth and significantly low birth weight of the patient may mask some of the typical Down syndrome facial features and other phenotypes associated to trisomy 21.

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