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CASE REPORT

Atypical down syndrome features with an atypical chromosomal rearrangement: a case report

Hiba Abu Khalil[1], Mohammed Almannai[1], Mohammed Albalwi[2,3,4], Wafaa Eyaid[1*]

ABSTRACT

Background: 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, and congenital heart defects, among others.

Case Presentation: 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 (DS). Chromosomal analysis revealed an isodicentric chromosome 21 (46, XX idic(21)(q22.3). Array comparative genomic hybridization revealed 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).

Conclusion: Our study highlights a unique etiology of Down syndrome that is associated with a milder phenotype. However, its limitations include the rarity of the case, which restricts the availability of comparative data, and potential influencing factors like prematurity and low birth weight.

Keywords: Down syndrome, trisomy 21, isodicentric chromosome 21.

Introduction

Down syndrome (DS) 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]. DS is one of the 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 the maternal age, the higher the chance of delivering a baby with DS [2]. Common features present in all individuals with DS encompass learning disabilities, characteristic craniofacial abnormalities, and hypotonia early in life [2]. Some individuals with DS exhibit additional variations, such as atrioventricular septal defects (AVSDs), leukemia, Alzheimer's disease, and Huntington's disease [3,4]. Physical attributes commonly seen in individuals with DS consist of upslanting palpebral fissures, a small chin, reduced muscle tone, a flat nasal bridge, a single crease on the palm, and an enlarged tongue resulting in a protruding mouth [2]. Most cases of DS result from the presence of an extra chromosome 21 due to a non-disjunction event, representing around 95% of all cases. Isodicentric

Correspondence to: Wafaa Eyaid
* Genetics & Precision Medicine Department (GPM), King Abdullah Specialist Children's Hospital (KASCH), King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia.
Email: eyaidw@mngha.med.sa
Full list of author information is available at the end of the article.
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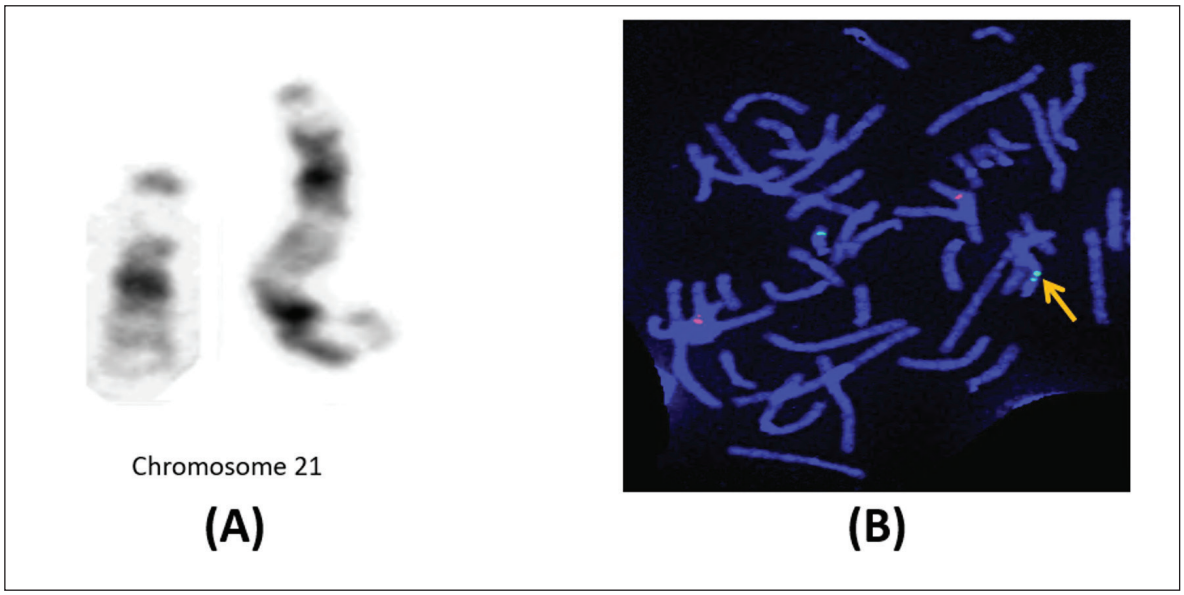

Figure 1. *(A) G-Banding that reveals a female with 46 XX, idic(21)(q22.3). (B) Metaphase FISH probed with Ch.21 (AML1 gene, Green) and Ch.8 (ETO gene, Red) orange arrow indicates presence of idic (21)(q22).*

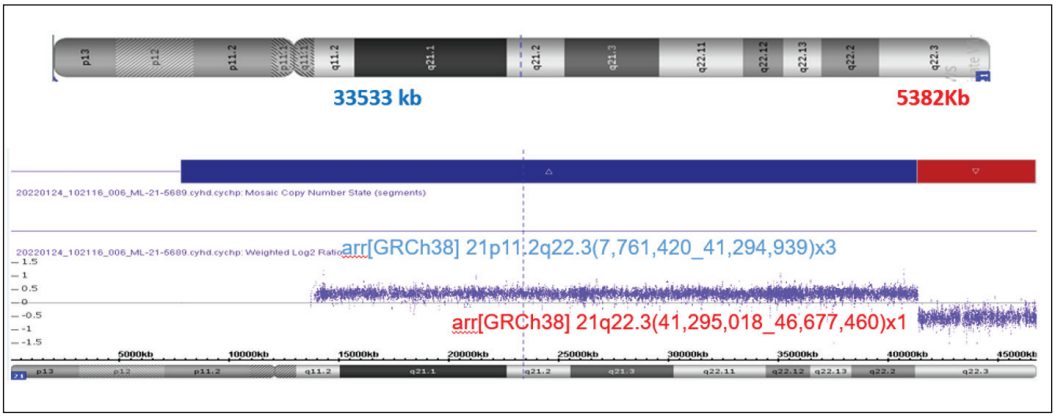

Figure 2. *Array CGH revealed a female with one gain copy number (one duplication involving 2p11.2q22.3 region and loss in the terminal (21q22.3qter) region of chromosome 21. This result confirmed idic(21) (q22.3).*

chromosome 21 is a very rare form of chromosomal rearrangement reported in a few cases in the literature. It is mainly composed of two copies of chromosome 21 fused together at the distal long arm [5]. Potential processes leading to the development of an inverted isochromosome encompass a fusion occurring at the telomeres, a reciprocal translocation involving the long arms of homologous chromosomes (or sister chromatids) during meiosis, or a translocation event occurring early in post-zygotic development involving two chromosomes 21 [5].

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 DS. The baby experienced a prolonged stay in the neonatal intensive care unit due to complications associated with prematurity, such as respiratory distress syndrome that required oxygen therapy. Additionally, she was diagnosed with laryngomalacia, which caused feeding difficulties. A head ultrasound did not show any abnormalities. Genetic testing, including chromosomal analysis and fluorescence in situ hybridization (FISH), was performed, and the results indicated the presence of an isodicentric chromosome 21 (46, XX, idic(21)(q22.3) (Figure 1A and B). Array comparative genomic hybridization (CGH) further revealed a concurrent duplication of most of

chromosome 21 [21p11.2q22.3(7761419_41294939)] and a 4.5 Mb deletion of the long arm of chromosome 21 [21p11.2q22.3(7761419_41294939)] (Figure 2). Chromosomal analysis was also conducted for both parents, and their results were normal.

Discussion

DS is a chromosomal disorder characterized by one of the most frequently occurring chromosomal abnormalities, with an estimated incidence ranging between 1 in 310 and 1 in 1,000 live births. The occurrence of DS 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 DS typically exhibit variable learning disabilities, hypotonia early in life, and distinct dysmorphic features such as upslanting palpebral fissures, small chin, flat nasal bridge, reduced muscle tone, a single palmar crease on the palms, and an enlarged tongue [2]. Cardiac defects, such as AVSDs may also be present [2]. 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 are attached together by the centromere [5]. In this report, we present the case of a premature baby with atypical features of DS 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 DS, along with hypotonia and developmental delay [5,3]. 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 DS facial features, may be attributed to the larger size of the deletion in the 21.q22.3 region compared to previously reported cases, in which the deletion involving the terminal long arm of chromosome 21 was relatively smaller [5].

In previous reports, conventional karyotyping alone was utilized, resulting in an inability to accurately determine the precise size of the deletion in chromosome 21. However, in subsequent studies, molecular techniques were employed to investigate the correlation between phenotype and genotype. The introduction of chromosomal microarray analysis has significantly enhanced the ability to ascertain the precise breakpoint and deletion region with greater precision when compared to earlier reports [5].

Conclusion

In conclusion, further examination of the genes in the deleted region found in our case may provide valuable insights into the pathogenesis of DS features. While our study aimed to highlight a distinct cause for DS, it is important to acknowledge the limitations that may have influenced our findings. First, the rarity of the case. It limited our ability to gather data from the literature with similar findings for comparison purposes. Additionally, prematurity and low birth weight, as potential confounding factors, may have influenced some of the typical physical features associated with DS.

Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication

Informed consent was obtained and all reasonable efforts were made to maintain patient confidentiality

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Hiba Abu Khalil[1], Mohammed Almannai[1], Mohammed Albalwi[2,3,4], Wafaa Eyaid[1]

1. Genetics & Precision Medicine Department (GPM), King Abdullah Specialist Children's Hospital (KASCH), King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia
2. Pathology and Laboratory Medicine Department, King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia
3. Medical Genomics Research Department, King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia
4. College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia

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