Case Report:

Trisomy 8 mosaicism syndrome with bilateral undescended testes: A case report and literature review

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Abstract:
Trisomy 8 mosaicism syndrome (Warkany syndrome 2) is a rare chromosomal disorder, with an estimated prevalence ranging from 1:25,000 to 1:50,000. It has a wide spectrum of clinical presentations ranging from un-noted at all or mild to severe. Case description: A newborn male baby with dysmorphic features, congenital anomalies, and hypotonia was admitted to the neonatal intensive care unit of a hospital in Saudi Arabia for further evaluation. The patient's clinical presentations included dysmorphic features, hypotonia, bilateral undescended testes, multiple bilateral choroid plexus cysts, a left cerebral vermis cyst, a small patent foramen ovale, a small patent ductus arteriosus, thrombocytopenia, bilateral grade 2 hydronephrosis, right positional talipus with medially deviated toes, and left fixed talipus. On the basis of these presentations, he was diagnosed with Trisomy 8 mosaicism syndrome (Warkany syndrome 2). Currently, he is 4 years old, with a stable overall clinical condition.: A diagnosis of Warkany syndrome 2 should be considered in patients with multiple congenital abnormalities and choroid plexus cysts with unilateral or bilateral undescended testes. In such cases, further evaluation, especially with karyotyping, is advised.

Keywords:
Trisomy 8 mosaicism syndrome, Warkany syndrome 2, undescended testes, dysmorphic features

Introduction:

Trisomy 8 mosaicism syndrome (also known as Warkany syndrome 2) is a rare chromosomal disorder, with an estimated prevalence ranging from 1:25,000 to 1:50,000. It has a wide spectrum of clinical presentations ranging from none at all or mild to severe [1]. Males are more vulnerable to Warkany syndrome 2 than females (at a sex ratio of 4:1), and the reasons for this male predisposition are unclear [1]. Several case studies on Warkany syndrome 2 have been published [2,3,4-11,12], and the reported cases were reviewed, However, to our knowledge, no cases from Saudi Arabia have been reported. Thus, in this study, we present the case of a newborn male baby who was admitted with dysmorphic features, congenital anomalies, and hypotonia. On the basis of these presentations, the patient was diagnosed with Warkany syndrome 2. In addition, this paper presents a literature review to address this chromosomal abnormality and recommendations for further research .

Case Presentation:

The patient was a newborn male baby from Saudi Arabia. He was born to healthy parents who were first-degree relatives and was the seventh child. Five of his siblings were normal, and one male sibling had a sudden death at 3 years of age despite being completely healthy. The mother was 30 years old when she gave birth to the patient, and the father was 46 years old. The mother did not receive regular antenatal follow-up or prenatal screening. She delivered the baby spontaneous vaginal delivery at 40 weeks' gestation. No complications occurred during pregnancy or delivery. The baby was born vigorous, with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. At delivery, the patient's anthropometric measurements were as follows: weight, 2.7 kg in the 25th percentile; height, 48 cm in the 25th percentile; and head circumference, 34 cm in the 50th percentile. His skin examination was normal. However, he was admitted in the neonatal intensive care unit (NICU) as case of dysmorphic features, congenital anomalies, and hypotonia for further evaluation. A multidisciplinary team that included a pediatric neurologist, ophthalmologist, otolaryngologist, cardiologist, hematologist, and medical geneticist discussed further management plans. After the initial assessment of the patient, he was found to have the following dysmorphic features: including low-set posteriorly rotated ears, right positional talipus with medially deviated toes, and left fixed talipus. No abnormalities were found in the fundoscopic examination and hearing tests.

Investigations:

The initial investigation revealed a normal complete blood count except for

thrombocytopenia (platelet 61,000 mcL), which was corrected. The patient's renal and liver profiles and chest radiograph were normal. A skeletal survey revealed the flexion configuration of the right thumb and index finger. The right foot showed valgus heel and varus forefoot deformities, while the left foot demonstrated varus heel and forefoot deformities. The spine and pelvis showed a T2 vertebral segmentation/fusion anomaly and bilateral shallow acetabulums (Figure 1).

Head ultrasonography revealed multiple bilateral choroid plexus cysts and a left cerebral vermis cyst, a prominent retrocerebellar cerebrospinal fluid space, and a right occipital scalp hematoma. On abdominal ultrasonography, bilateral grade 2 hydronephrosis was found. Brain magnetic resonance imaging (MRI) revealed supratentorial and infratentorial choroid plexus cysts, the largest of which was found at the foramen of Magendie (Figure 2). Echocardiography revealed a small patent foramen ovale and ductus arteriosus. Karyotyping revealed "47,XY,+8 12/46,XY[8]," a male karyotype with an extra free chromosome 8 in 60% of all analyzed cells, consistent with Trisomy 8 mosaicism (Warkany syndrome 2).



Figure 1. the right foot demonstrates valgus deformity along with various deformities of forefoot; the left foot demonstrates various deformities of the heel and forefoot.

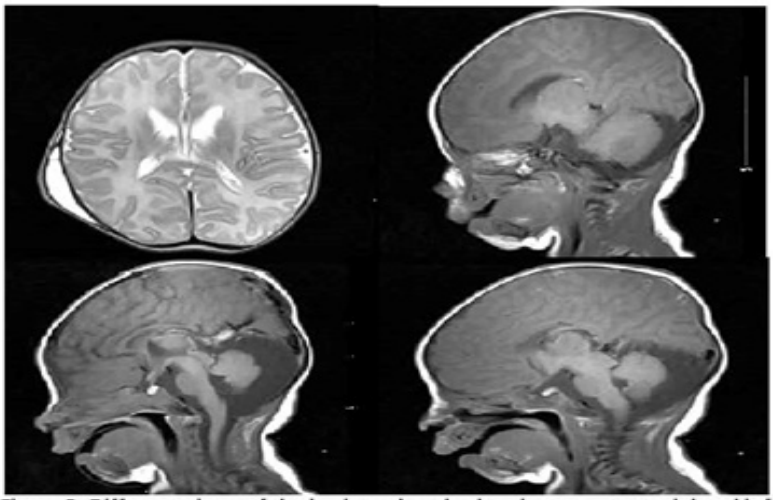


Figure 2. Different views of the brain and neck, showing supratentorial and infratentorial choroid plexus cysts, the largest of which is in the foramen of Magendie.

Management plan and follow-up:

After 25 days, the patient was discharged from the NICU and was scheduled for out-patient follow up in different disciplines. At the patient's last follow-up visit, when he was 4 years old, his cognitive function was normal.

Discussion:

To the best of our knowledge, this is the first reported case of Trisomy 8 mosaicism in Saudi Arabia. The patient's male gender is consistent with previous reported cases [1–10], and statistics have shown that males are more vulnerable to the disorder than females at a ratio of 4:1 [11]. The present case was discovered relatively early by healthcare workers compared with other reported cases in India at 3 and 11 years old [2,3] and Colombia at 4 old years [1]. Thus, early admission of patients with Warkany syndrome 2 in the first months of life is not a good sign of health, especially when associated with complications [1]. Other reported clinical presentations include cholestatic jaundice [3], pigmentation anomalies [6], recurrent respiratory infections [8], and corneal abnormalities [10]. Reporting such clinical presentations is crucial to establishing a database for Warkany syndrome 2. The association between Warkany syndrome2 and various reported presentations is attributed to developmental stages and the time of cell division. Therefore, further research is needed to identify certain triggering factors that contribute to chromosomal disjunction at the development stages of systems, including the genital system. Awareness of the triggering factor might reduce the risk of abortion attributed to full Trisomy 8. For example, Kneidl et al. [12] proposed the use of ACI rat models instead of humans in studying the correlation between Trisomy 8 and urogenital abnormalities.

Minor abnormalities were reported in the present case, such as hydronephrosis, which is similar to those reported in previous studies. Renal and urinary tract abnormalities, including hydronephrosis, are the abnormalities commonly reported in Warkany syndrome 2 (75% of cases) [13]. However, the present case had one remarkable abnormal feature: bilateral undescended testes. This finding is consistent with the case reported by Balasar and Oltulua in which a man from Turkey who was diagnosed with Warkany syndrome 2 at 36 years of age had undergone surgery for right cryptorchidism when he was 10 years old [6]. In another case of Warkany syndrome, bya 6-year-old patient showed a normal health status at birth except for bilateral testis ectopia and hypospadias [8]. Hence, patients with Warkany syndrome 2 can show no apparent abnormalities. Thus, karyotyping is preferable for children with undescended testes, especially in the pres-

ence of other congenital anomalies.

Although the present case did not show abnormal ophthalmological findings, a previously reported case showed corneal abnormalities [10]. Recently, the management of Warkany syndrome 2 has advanced. For example, virtual reality (VR) technology has been added to traditional neurorehabilitation[14]. Settimo et al. suggested that further studies are needed to elucidate the role of Virtual Reality (VR) training in the cognitive rehabilitation of patients with Warkany syndrome 2 and agenesis of the corpus callosum, as the technique had shown promising outcomes in gaining cognitive and motor function [14]. Counseling is key in the management of patients with Warkany syndrome 2, especially because they are vulnerable to certain cancers such as hematologic malignancies in late life [1]. Therefore, close monitoring and evaluation are crucial for these patients.

Currently, Warkany syndrome 2 can be detected at the prenatal stage via either amniotic fluid or chorionic villi sampling[15], however prenatal cytogenetic negative studies cannot rule out its presence 4. Cho et al. attributed the normal karyotype in prenatal testing to an extremely low level of mosaicism in amniotic fluid or to the selective growth disadvantage of the Trisomy 8 cell line in culture. Chen et al. observed a cytogenetic discrepancy between cultured and uncultured amniocytes in Trisomy 8 mosaicism at amniocentesis and addressed the usefulness of interphase fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH) analysis of uncultured amniocytes in confirming Trisomy 8 mosaicism at amniocentesis[9].

In addition to karyotyping, FISH and aCGH could potentially detect this low-level mosaic clone to confirm the diagnosis in patients with such variable clinical presentations [5]. Moreover, cytogenetic technologies have undergone recent advances, particularly in chromosomal analysis [16]. Prenatal diagnosis of such chromosomal abnormalities is crucial to provide appropriate counseling to family members regarding Warkany syndrome 2 and to discuss with them in advance all possible outcomes and how to overcome them. However, one problem with genetic counseling regarding Warkany syndrome 2 is the difficulty of predicting the phenotype, as clinical severity is not related to the level of mosaicism [17].

Although many genetic diseases are associated with consanguineous marriages, this was not the case regarding Warkany syndrome, except for the cases reported in the Arab region that were similar to our case. For example, in the reported case of Warkany syndrome 2 in Oman, the patient was born to consanguineous parents 5.

Conclusions:

A diagnosis of Warkany syndrome 2 should be considered in patients with multiple congenital abnormalities and unilateral or bilateral undescended testes. Karyotyping is preferable for infants with unilateral or bilateral undescended testes and dysmorphic features.

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AA Conceptualization, data curation, writing—original draft, writing—review and editing.

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Institutional Review Board Statement:

Ethical review and approval of this study were not required by the Institutional Review Board. The patient's information has been de-identified.

Informed Consent Statement:

The parents signed written informed consent to publish their child case.

Data Availability Statement:

The data supporting the current study's findings will be available upon rational request from the author.

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Conflicts of Interest:

The author declares no conflicts of interest.

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