Trisomy 8 Mosaicism Syndrome

Contents

In 1971, de Grouchy et al. (1971) first described trisomy 8 mosaicism which was further delineated by Fryns et al., Sanchez and Yunis, Schinzel, and Riccardi in 1977. This syndrome, also known as Warkany syndrome, is a well-recognized syndrome despite its phenotypic variability.

Synonyms and Related Disorders

Warkany syndrome

Genetics/Basic Defects

1. Trisomy 8 mosaicism: chromosome complement mosaic for chromosome 8 (presence of a chromosomally normal cell line in addition to the trisomic 8 cell line) (Fineman et al. 1975)
    1. A case of trisomy 8 mosaicism detected prenatally in a single clone of amniotic fluid culture, and confirmed on fetal blood and on peripheral lymphocytes after birth.
    2. A follow-up was performed over 3 years, showing a clinically normal female with cognitive, neuropsychological, and linguistic development in a normal range (Camurri and Chiesi 1991).
2. Origin of trisomy 8 mosaicism
    1. Different from the common autosomal trisomies that usually result from maternal meiotic errors.
    2. Trisomy 8 in spontaneous abortions: meiotic origin in the majority of cases.
    3. Postzygotic (mitotic) nondisjunction error in a diploid conceptus: the most likely origin of trisomy 8 in the live-born population.
    4. Postzygotic (mitotic) nondisjunction error in a diploid conceptus, followed by nonrandom distribution of aneuploid cells between the different compartments.
    5. Affected fetuses usually show a pattern of absence, or low levels of trisomy in cytotrophoblast cells (STC villi), high levels in extraembryonic mesoderm (LTC villi), and again low levels of trisomic cells in AF cells and/or fetal blood lymphocytes.
    6. LTC villi are more likely to reflect the true fetal chromosomal constitution than STC villi.
    7. The chromosomal mechanisms accounting for the WS include either literal trisomy 8 (aneuploidy), usually if not always with

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mosaicism, or translocation leading to partial trisomy 8 (8q2). In addition, some patients with mosaic trisomy 8 may not have the Warkany syndrome (Riccardi 1977).

8. A report on a mildly dysmorphic male patient with partial low-level trisomy 8 mosaicism due to a pseudoisodicentric chromosome 8 with normal 6.0 SNP microarray and high resolution chromosome analyses in lymphocytes. The aneuploidy was detected in fibroblasts and confirmed by FISH in lymphocytes. This report elaborates further the clinical variability seen in trisomy 8 mosaicism (Leon et al. 2011).

Clinical Features

1. Wide range of phenotypic variation ranging from normal individual to severe malformation syndrome (Fineman et al. 1975; Kurtyka et al. 1988; Agrawal and Agrawal 2011) and cytogenetic expression (Jordan et al. 1998; Udayakumar and Al-Kindy 2013)
2. Central nervous system (Habecker-Green et al. 1998)
    1. Intelligence: range from normal to mental retardation
    2. Agenesis of the corpus callosum
    3. Arrhinencephaly
3. Craniofacial features
    1. Skull
        1. Asymmetrical skull
        2. Microcephaly
        3. Hydrocephaly
        4. Prominent forehead
        5. Flattened occiput
        6. Low posterior hairline
    2. Eyes
        1. Ocular hypertelorism
        2. Deep-set eyes
        3. Strabismus
        4. Corneal clouding
        5. Cataracts
        6. Amblyopia
    3. Nose
        1. Plump nose with broad base
        2. Prominent nares
    4. Mouth
        1. Micrognathia
        2. Everted lower lip
        3. High palate
        4. Cleft soft palate
    5. Low-set and malformed ears
4. Chest
    1. Pectus excavatum
    2. Widely spaced nipples
5. Heart: congenital heart disease
6. Gastrointestinal tract
    1. Meckel diverticulum
    2. Hirschsprung disease
    3. Anal anomalies
7. Genitourinary tract
    1. Cryptorchidism
    2. Unilateral renal agenesis
    3. Wilms tumor
    4. Ureteral anomalies
    5. Perineal anomalies
    6. Inguinal hernia
    7. Genital hypoplasia in males
8. Skeletal system
    1. Short stature
    2. Abnormal clavicle
    3. Absent or dysplastic patellae
    4. Joint contracture or limitation
    5. Vertebral anomalies
    6. Narrow pelvis
    7. Rib anomalies
    8. Scoliosis
    9. Camptodactyly of second through fifth fingers and toes
9. Skin
    1. Deep palmar skin furrows
    2. Deep plantar skin furrows: a hallmark of the syndrome
10. Neoplasia in individuals with trisomy 8 mosaicism (Habecker-Green et al. 1998)
    1. Leukemia
    2. Wilms tumor
    3. Cystic renal tumors
    4. Gastric Leiomyosarcoma
    5. Gestational trophoblastic disease

11. Fertility: an increased risk of infertility for males and females with trisomy 8 mosaicism (Habecker-Green et al. 1998)
12. Life expectancy: usually normal

Diagnostic Investigations

1. Necessary to perform both karyotyping and FISH to detect low mosaic trisomy 8
2. Traditional cytogenetic diagnosis
    1. Detection of mosaic trisomy 8 from various tissue.
    2. Abnormal cell line tends to decrease from lymphocytes with time (Jordan et al. 1998).
    3. In older patients, aneuploidy can sometimes be demonstrated in fibroblast cultures only.
3. Interphase fluorescent in situ hybridization (FISH) using a chromosome 8 centromere-specific probe
4. Array comparative genomic hybridization (array-CGH)

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: recurrence risk not increased
    2. Patient's offspring
        1. An increased risk of spontaneous abortion for trisomic conceptuses
        2. Fetuses with complete trisomy 8: nonviable
        3. Chromosomally normal pregnancies possible
2. Prenatal diagnosis
    1. Ultrasonography (Gün et al. 2012)
        1. Bilateral renal pyelectasis
        2. Single umbilical artery
        3. Polyhydramnios
        4. Axial view of the head demonstrating the "teardrop sign" in the lateral ventricle (ventriculomegaly)
        5. Agenesis of corpus callosum
        6. 3D surface rendering of the fetal dysmorphic face
            1. Prominent forehead and ears
            2. Hypertelorism
            3. Broad-based nose
            4. Large mouth
            5. Large head
    2. Prenatal cytogenetic diagnosis of mosaicism
        1. Metaphase analysis of cultured cells from either amniotic fluid or chorionic villi (Guichet et al. 1995): currently the standard technique (analysis of 30 colonies needed to exclude 10% mosaicism with a 95% confidence level)
        2. Interphase fluorescent in situ hybridization (FISH) with a centromere-specific probe: to further define the level of mosaicism
        3. The application of interphase FISH to uncultured amniocytes is better than cordocentesis in prenatal confirmation of trisomy 8 mosaicism (Chen et al. 2012).
        4. Array comparative genomic hybridization (array-CGH): enables faster results than standard cell culture and metaphase analysis (capable of detecting mosaicism at levels as low as 7%)
        5. A report of a case of a fetus mosaic for trisomy of the entire long arm (q) of chromosome 8 without additional chromosomal aberrations (Wood et al. 2008).
            1. The diagnosis was made by amniocentesis performed following an 18 week sonogram that showed multiple fetal anomalies.
            2. Mosaicism for trisomy 8q was confirmed by routine karyotyping and fluorescent in situ hybridization (FISH) analysis.
            3. The case proved useful for testing the sensitivity of array comparative genomic hybridization (array-CGH) with respect to segmental trisomy in the presence of chromosomal mosaicism.
3. Problems in genetic counseling (Rodriguez et al. 2013)
    1. Prediction of phenotype difficult since clinical severity is not related to the level of mosaicism

2. Problems in detecting trisomy 8 mosaicism in chorionic villi (Klein et al. 1994)
    1. Do not necessarily reflect a constitutional mosaicism of the fetus
    2. Most likely represent confined placental mosaicism (a chromosomally abnormal cell line limited to the trophoblast tissue and/or extraembryonic mesoderm, with a normal karyotype in the fetus proper)
    3. In large published series of amniotic fluid chromosome analysis, 0.2% of cases are mosaic, and in addition, up to 8% of cases have single or multiple cell pseudomosaicism (Hsu et al. 1992)
    4. Possible false-negative cases of trisomy 8 mosaicism in short-term culture villi, as well as cultured amniotic fluid cells (Schneider et al. 1994; Hanna et al. 1995)
    5. Follow-up investigations in fetal blood cells recommended when trisomy 8 mosaicism is encountered in chorionic villi
    6. Very low-level trisomy 8 mosaicism may be compatible with a normal phenotype
3. Difficulties in the prenatal diagnosis of trisomy 8 mosaicism (van Haelst et al. 2001)
    1. When found in chorionic villi, it mostly represented confined placental mosaicism, while in a case of true fetal trisomy 8 mosaicism, the cytotrophoblast cells showed a normal karyotype. So, the cytotrophoblast compartment of chorionic villi is a poor indicator of the presence or absence of fetal trisomy 8 mosaicism.
    2. Follow-up investigations including amniocentesis and especially fetal blood sampling are required to come to a definite prenatal diagnosis of trisomy 8 mosaicism.
4. Problems in detecting trisomy 8 mosaicism in amniotic fluid
    1. Amniocentesis: not the best way to reveal trisomy 8 mosaicism
    2. Cases of missed trisomy 8 mosaicism reported (Tsai et al. 2014)
3. Management
    1. Mostly supportive.
    2. A report of a patient with constitutional mosaic trisomy 8 syndrome and infantile spasms, who became seizure free after treatment with adrencorticotropic hormone and clonazepam (Datta et al. 2010).
    3. Constitutional trisomy 8 mosaicism (CT8M) in a healthy bone marrow donor: Confirmation of first reported donor origin trisomy 8 (Uddin et al. 2010). The diagnosis of CT8M in the donor was completely serendipitous as it was only identified after the recipient developed donor-derived T8, post-transplant (Frey et al. 2008).
    4. Surgical management may be needed for those individuals with major malformations.
    5. While taking into consideration the natural prognosis, underlying malformations, and surgical benefits and risks, the indications for cardiac surgery in patients with mosaic trisomy 8 should be carefully individualized (Hasegawa et al. 2016).

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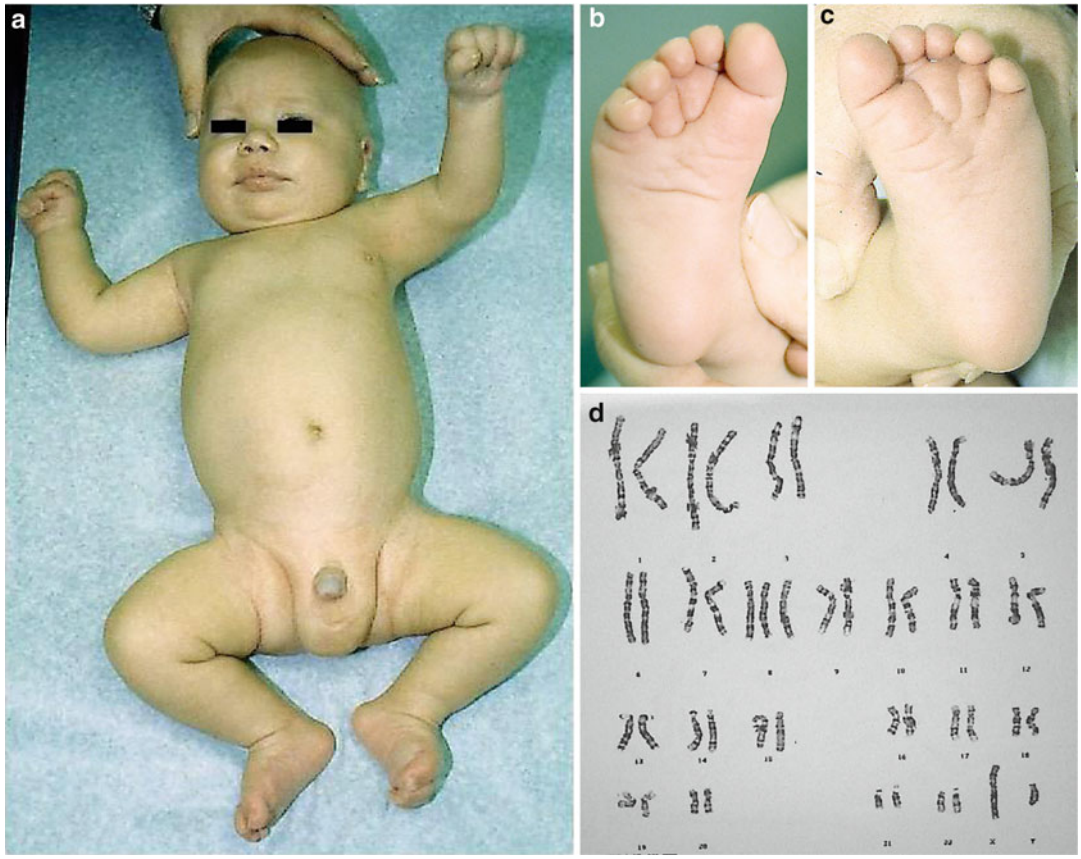

Fig. 1 (**a**–**d**) An infant boy with trisomy 8 mosaicism showing typical craniofacies (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) (**a**) and characteristic deep plantar skin furrows (**b**, **c**). Chromosome analysis showed trisomy 8 mosaicism (only trisomy 8 karyotype is shown here) (**d**)

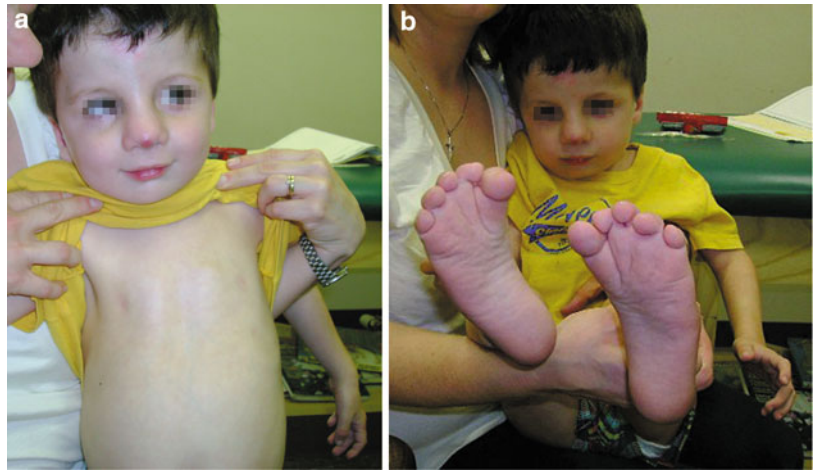

Fig. 2 (**a**, **b**) A 2-year-and-6-month-old boy with trisomy 8 mosaicism showing typical craniofacial features (prominent forehead, ocular hypertelorism, plump nose with broad base, micrognathia) (**a**) and characteristic deep plantar furrows in both feet (**b**)

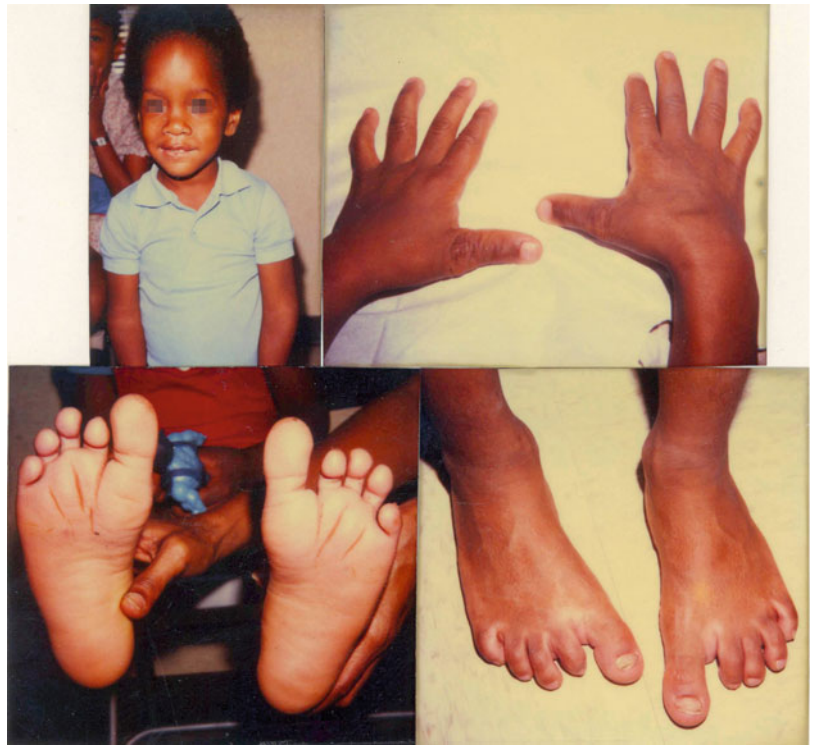

Fig. 3 Another child with trisomy 8 mosaicism with typical phenotype

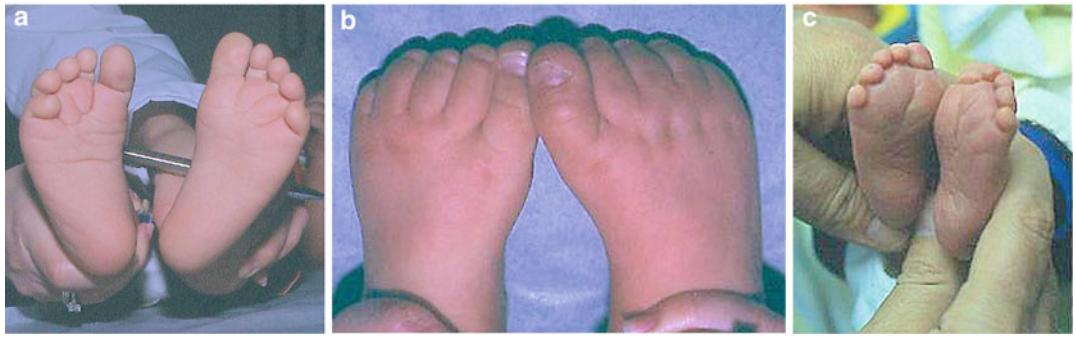

Fig. 4 (**a**–**c**) Two infants (**a**, **b**, **c**) with trisomy 8 mosaicism showing characteristic deep plantar furrows in both feet