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"A PATIENT WITH TRISOMY 13 MOSAICISM WITH AN UNUSUAL SKIN PIGMENTARY PATTERN AND PROLONGED SURVIVAL"

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PRESENTA

Dr. Alejandro Gaviño Vergara

TUTOR

Dra. Ariadna González del Ángel

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“A PATIENT WITH TRISOMY 13 MOSAICISM WITH AN UNUSUAL SKIN PIGMENTARY PATTERN AND PROLONGED SURVIVAL”

DRA. ROSAURA ROSAS VARGAS
DIRECTORA DE ENSEÑANZA

DR. LUIS MARTIN GARRIDO GARCIA
JEFE DEL DEPARTAMENTO DE PRE Y POSGRADO

DRA. VICTORIA DEL CASTILLO RUIZ
PROFESOR TITULAR DEL CURSO DE GENÉTICA MÉDICA

DRA. ARIADNA GONZÁLEZ DEL ÁNGEL
TUTOR TESIS

DRA. BERNARDETTE ESTANDIA ORTEGA
COTUTOR TESIS

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ABSTRACT: Trisomy 13, or Patau syndrome, is a chromosomal disorder that can occur in complete, partial, or mosaic forms. Mosaicism is observed in 6% of individuals with trisomy 13 and, in contrast to the complete form, has wide phenotypic variability, longer survival, and in some patients an unusual skin pigmentary pattern similar to phylloid hypomelanosis. We describe here a 12-year-old girl with trisomy 13 mosaicism (mos 47,XX,+13[9]/46,XX[16]) who had three major malformations, an unusual skin pigmentary pattern, and prolonged survival.

Trisomy 13, or Patau syndrome, is the third most common trisomy in autosomes, following trisomy 21 and trisomy 18. Its prevalence ranges from 1 in 5,000 to 1 in 12,000 total births (1). Etiologically, approximately 80% of cases of trisomy 13 result from a nondisjunction (complete trisomy 13), with smaller percentages of cases caused by an unbalanced translocation of chromosome 13 with another chromosome (~13.5%) or mosaicism (6%) (2).

The survival of patients with complete trisomy 13 is typically short, with 85% surviving less than 1 year and the majority dying before 6 months (2). In contrast, survival tends to be longer in trisomy 13 mosaicism, with some patients reaching 40 years of age (3).

Complete trisomy 13 is characterized by severe to profound mental retardation and multiple congenital anomalies, including orofacial clefts, microphthalmia or anophthalmia, and postaxial polydactyly (1). Although the phenotype of trisomy 13 mosaicism has not been as well described, the observed clinical features range from normal growth and development with few dysmorphias to major malformations and early death (4). No single clinical manifestation has been reported in more than 50% of the cases described in the literature (3).

Cutaneous manifestations are rare in patients with complete trisomy 13, whereas some individuals with trisomy 13 mosaicism have abnormal skin pigmentation (3). Four major

types of pigmentary patterns associated with human mosaicism have been described. Type 1 is distinguished by the presence of the lines of Blaschko and can be further subclassified as types 1a and 1b, with narrow and broad bands, respectively. Type 3, called a phylloid pattern, is characterized by an arrangement of pigmentary alterations with oval patches, lesions similar to asymmetric begonia leaves, and extensive pyriform areas or oblong macules reminiscent of floral ornaments with dorsal and ventral midline separations (5). This last type of pigmentation has been observed in patients with trisomy 13 mosaicism (3,6).

We describe here a girl with trisomy 13 mosaicism characterized by three major malformations, an unusual skin pigmentary pattern, and longer survival than other patients with trisomy 13 mosaicism.

CASE REPORT

We present a 12-year-old girl with trisomy 13 mosaicism born to healthy, young, nonconsanguineous parents. The patient was born at full term by normal vaginal delivery and weighed 3 kg (50th percentile). During the perinatal period she experienced cardiorespiratory arrest, hypoglycemia, and hyperbilirubinemia so she remained hospitalized for 1 month after birth. Peripheral blood karyotyping showed mos 47, XX,+13[6]/46,XX[50].

At age 17 months the patient was referred to the Instituto Nacional de Pediatria (INP). On initial physical examination she was found to be in the 90th percentile for weight, 75th for height, and less than 3rd for head circumference. She had an extended forehead, bilateral epicanthal folds, convergent strabismus, depressed nasal bridge, bulbous nose, thin superior lip (Fig. 1), oral cavity with incomplete submucosal cleft palate, small ears, normal thorax, no abdominal visceromegaly, normal female external genitalia, thoracic and pelvic limbs without abnormalities, and clinodactyly of the fifth toe of both feet.

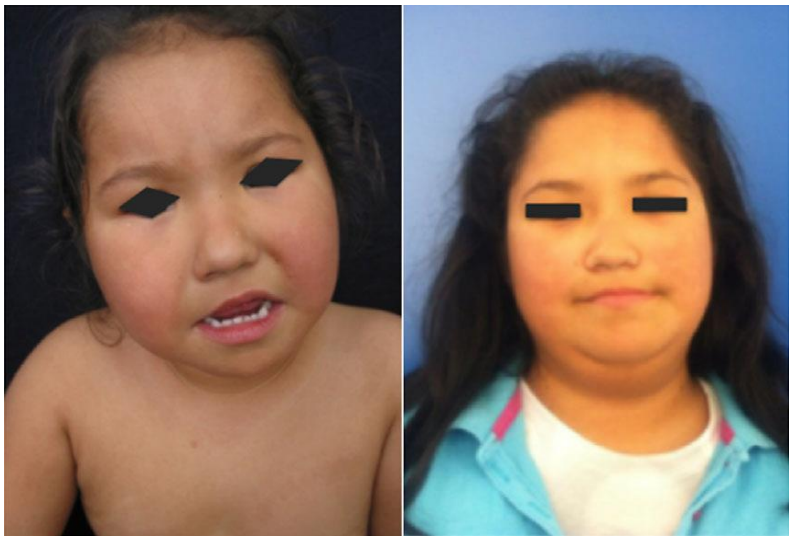

Figure 1. Facial dysmorphism in our patient at age (A) 2 years and (B) 11 years. Features include a round face, extended forehead, oblique upward palpebral fissures, bilateral epicanthal folds, depressed nasal bridge, broad nose, prominent cheeks, and thin lips.

Dermatologic examination at that time revealed hyperpigmented macules, some following Blaschko lines, with a predominance on the left. Most of the macules had a narrowband pattern, although there was an oblong macule on the right side of the trunk (Fig. 2).

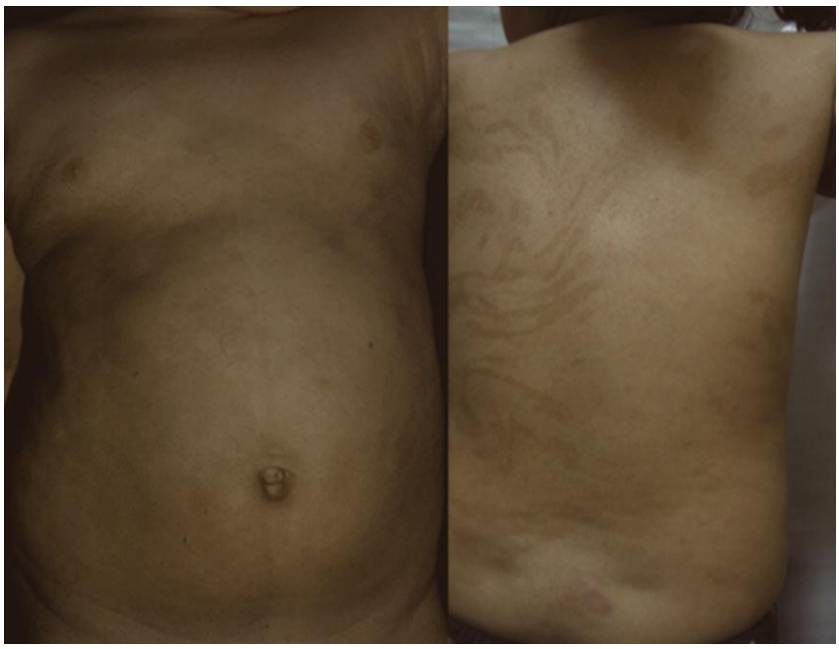

Figure 2. Photographs of our patient at 2 years of age, showing hyperpigmented macules with a narrow Blaschko-linear pattern on the trunk, more evident on the left side, and an oblong macule on the right side.

A hemangioma was observed in the lumbar region and a melanotic nevus on her right leg. The hyperpigmented macules have become less evident.

At age 18 months, we again karyotyped her peripheral blood lymphocytes and the results corroborated the previous finding (mos 47,XX,+13[9]/46,XX [16]). Because of the presence of the abnormal skin pigmentary pattern, we also karyotyped her fibroblasts, finding mos 47,XX,+13[7]/46,XX[78] in light skin samples and mos 47,XX,+13[23]/46,XX[2] in dark skin samples.

The patient had a patent foramen ovale that has now closed and bicornuate uterus observed using pelvic ultrasound. No central nervous system, renal, or gastrointestinal anomalies were identified.

At 10 years of age the patient experienced menarche and has regular menstrual cycles. She has been diagnosed with metabolic syndrome and hidradenitis suppurativa. She has severely delayed speech, normal hearing, and severe global neurologic delay. At 11 years of age her intelligence quotient (IQ) was evaluated using the Wechsler Intelligence Scale for Children—Revised, which showed a verbal IQ of 45, an executive IQ of 55, and a global IQ of 44, corresponding to profound mental retardation. She has self-care skills, goes to primary school with special support, performs arithmetic operations, and recognizes numbers, geometric figures, and letters, but she does not read or write.

DISCUSSION

Trisomy 13 is a severe disorder with a low incidence. Of the fetuses conceived, Parker et al (7) observed that only 18% are live-born, 7% are stillborn, and 7% are eliminated by spontaneous miscarriage. Only 6% of patients with trisomy 13 present with mosaicism (2).

Individuals with complete trisomy 13 rarely survive beyond the first year of life, although those with mosaicism can survive longer, including some, such as our patient, who survive

until adolescence, and others who survive to adulthood (8,9). In contrast to complete trisomy 13, in which most patients have certain characteristics, the development and clinical features of patients with trisomy 13 mosaicism vary greatly. Moreover, the characteristic features in patients with complete trisomy 13 are rarely present in patients with trisomy 13 mosaicism (3). In our patient, for example, the only identified anomalies were microcephaly, incomplete submucosal cleft palate, and bicornuate uterus, with the presence of any other structural anomaly excluded using imaging modalities.

The correlations between the percentage of trisomic cells and the clinical manifestations in patients with trisomy 13 mosaicism are low. Some patients with low mosaicism (<10%) have multiple malformations, whereas other patients with high mosaicism (77%) show intrauterine growth delay but no other associated malformations (4). In our patient, the percentages of trisomic cells were 36% in peripheral blood, 8.2% in light skin, and 92% in dark skin. These differences may explain why our patient had mental retardation, microcephaly, incomplete submucosal cleft palate, and bicornuate uterus but no other major malformations.

Most patients with trisomy 13 mosaicism are karyotyped by analyzing peripheral blood (87.7%), with fewer karyotyped by analyzing skin fibroblasts (40.8%) or other tissues (22.4%). Only 38.7% of reports looked for mosaicism in peripheral blood and skin fibroblasts, as performed in our patient, suggesting that karyotyping of at least two tissues may be necessary for adequate phenotype–genotype correlations (3).

The presence of an abnormal skin pigmentary pattern, irrespective of the type of pattern, suggests the likelihood of chromosomal mosaicism. Because mosaicism is not always evident in peripheral blood, fibroblasts obtained from light and dark skin should be karyotyped (10).

Ten previously described patients with trisomy 13 mosaicism had skin pigmentary abnormalities: eight in a phylloid pattern accompanied by hypopigmentation or hyperpigmentation (5,11,12) and two with hypomelanosis of Ito (13,14). Although hypomelanosis of Ito has been observed in patients mosaic for different chromosomal

anomalies, mosaicisms involving chromosome 13 rather than other chromosomal abnormalities seem to cause phylloid hypomelanosis (6). The abnormal skin pigmentary patterns associated with trisomy 13 mosaicism may be due to the differential expression of pigmentary genes encoded on chromosome 13 (ATP7B, EDNRB, DCT, EFNB2) (15), but this remains unclear.

A Happle type 1a pattern has been observed in incontinentia pigmenti and in most cases of hypomelanosis of Ito, which is the cutaneous manifestation of many different phenotypes that have as a common factor the presence of two genetically different cell lines (5). In contrast to the 10 previous patients with trisomy 13 mosaicism and abnormal skin pigmentation patterns, our patient has a partial phylloid pattern on the right back and a Happle type 1a pattern on the left side, which has not been previously described.

We have described the first reported case of a patient with trisomy 13 mosaicism with prolonged survival and an unusual pattern of skin pigmentation in comparison with the pattern usually reported in patients with this type of aneuploidy.

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