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Severe congenital hypoacusia in a patient with mosaic ring chromosome 7.

Clinical Case

José M. Ceballos-Quintal, Doris Pinto-Escalante, Ileana Castillo-Zapata, Jorge Canto-Herrera.

Laboratorio de Genética, Centro de Investigaciones Regionales "Dr. Hideyo Noguchi", Universidad Autónoma de Yucatán. Mérida, Yucatán, México.

SUMMARY.

Introduction. Ring chromosome is a chromosomal aberration which can be found in patients of small stature, minor dismorphies and normal intelligence. Those produced by ring chromosome 7 are rare. The most frequent findings in such cases include small stature, microcephaly and dermatological abnormalities.

Clinical case. In this paper we report a male child with mosaic ring seven chromosome who had unusual hypoacusia and hypochromic dermal spots. Other clinical findings were similar to some previously reported in patients with the same chromosomal abnormality: low height, weight and OFC, mental retardation, dermatological abnormalities and few dysmorphies.

Discussion. Although most manifestations present in this patient have been described before, this is the first report in which severe hypoacusia is found, and the second with hypochromic spots. We propose this skin manifestation could be included in the variability of dermatological expressions of ring

seven. Additionally we recommend further investigation about hearing ability in patients with chromosome 7 abnormalities in subtelomeric regions. (*Rev Biomed 1999; 10:235-239*)

Key words: human chromosomal aberration, mosaic, ring 7, congenital malformations, mental retardation, hypochromic dermatological spots, hypoacusia.

RESUMEN.

Hipoacusia severa congénita en un paciente con mosaico del cromosoma siete en anillo.

Introducción. Los cromosomas en anillo son aberraciones cromosómicas que pueden encontrarse como hallazgo en pacientes con talla baja, dismorfias menores e inteligencia normal. Los anillos del cromosoma 7 son raros. Los hallazgos mas frecuentes en estos casos incluyen: talla baja, microcefalia y alteraciones dermatológicas.

Caso clínico. En este artículo presentamos a un

*Corresponding address: Doris Pinto-Escalante, Centro de Investigaciones Regionales "Dr. Hideyo Noguchi". Universidad Autónoma de Yucatán. Av. Itzáes No 490 x 59, Mérida, Yucatán, México. C.P. 97000 Tel: (99) 24 57 55 Fax: (99) 23 61 20
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JM Ceballos-Quintal, D Pinto-Escalante, I Castillo-Zapata, J Canto-Herrera.

niño con mosaico del cromosoma siete en anillo, quien tuvo hipoacusia y manchas hipocrómicas en la piel. Presentó otras manifestaciones clínicas similares a las descritas previamente en pacientes con la misma aberración cromosómica: talla, peso y perímetro cefálico bajos, retraso mental, anomalías dermatológicas y algunas dismorfias.

Discusión. Aunque la mayoría de las manifestaciones presentes en este paciente se han descrito con anterioridad, este es el primer caso en el que se encuentra hipoacusia, y el segundo con manchas hipocrómicas. Nosotros proponemos que esta manifestación dérmica quede incluida entre la variabilidad de expresiones dermatológicas del cromosoma siete en anillo. Además, recomendamos realizar búsqueda intencionada de alteraciones auditivas en pacientes con anomalías de cromosoma siete que involucren regiones subtelo méricas.

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Palabras clave: aberración de cromosomas humanos, mosaico, anillo del 7, malformaciones congénitas, retraso mental, manchas hipocrómicas en piel, hipoacusia.

INTRODUCTION.

Among chromosomal aberrations, those which occur by ring chromosome 7 are rare (1-11). Most frequent findings in such cases include small stature, microcephaly and dermatological abnormalities: pigmented naevi, *café-au-lait* spots, naevi flammeus, hemangiomas, melanoma and achromic spots in one case (12). Mental retardation has been found in some cases (1, 2, 5, 7, 11), but intelligence can be normal (1, 4, 6, 8-10). In this report we present a patient with mosaic ring chromosome 7 who had severe hypoacusia, a feature not previously described in this chromosomal disorder.

CLINICAL REPORT.

The patient was the third child of healthy non-consanguineous parents. The mother and father

were 38 and 28 years old respectively at the time of patient's birth. The elder children appear normal. An additional pregnancy after the patient's birth ended with *in utero* death of unknown causes at 7 months. The patient's gestation was unremarkable, except for an urinary infection at month two. Delivery occurred spontaneously at 38 weeks of pregnancy. At birth, the patient's weight was 1.3 kg (< 3rd centile), length was 44 cm (< 10th centile) and OFC was 29.5 cm (< 3rd centile). He was referred to us at one month because of failure to thrive and developmental delay. The physical examination at this time showed a small, microcephalic, and hypotonic male baby (fig. 1), with several dysmorphies: capillary hemangioma of 5 cm in size in the forehead, and two small ones in the occiput and the neck, upslanting palpebral fissures, broad nasal base, small nose with anteverted nostrils, ojival palate, short neck, clinodactily of the 5th finger and slight cutaneous syndactily in both hands. A computed tomography scan of the head was carried out and no abnormalities were detected.



Figure 1. The proband at three months old.



Figure 2. Clinical appearance at 8 years old. Note the facial asymmetry.

When we saw the patient again at 8 years old (fig. 2), his weight was 11 kg, length 99 cm and the OFC 36 cm, all below the 3rd centile. His evolution had been with slow psychomotor development, mental retardation, malimplanted teeth and slow thrive. He had developed facial asymmetry caused by hypoplasia of the left side, and bilateral joint limitation to elbow extension. Additional dermatological manifestations were found in different skin regions: *café-au lait* spots in the right clavicular region, on the thorax, abdominal wall, both arms and dorsal hands; dark pigmented naevi on the palm of the right hand and multiple naevi on the back. Multiple hypocromic small spots were found on both legs. Hearing deficiency was identified, potentials evocated and audiometry studies confirmed severe hypoacusia at 5 months old. At 14 months it was recognized as sensori-neural type, with ear shot of about 67-69 dBHL. He had had abdominal surgery at 4 years old for a urinary reflux produced by a uretero-bowel defect.

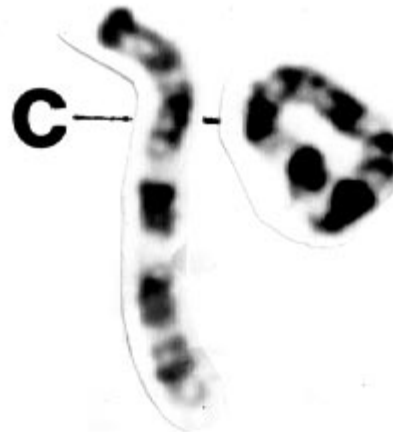


Figure 3. Normal and ring 7 chromosome. Centromere region is referred with C.

CYTOGENETIC ANALYSIS.

A karyotype was realized of the propositus from peripheral blood lymphocytes cultured by conventional methodology. The analysis of 100 metaphases with routine GTG banding revealed a ring chromosome 7 in 83 of the metaphases (fig. 3), two 7 rings in 5, a double ring in 1, monosomic without ring in 2, and normal chromosomal constitution in 9 cells. Break points were identified at p22.2 and q36.3. Chromosome analysis was performed on the parents. Both had normal karyotype in 15 metaphases analyzed from them.

DISCUSSION.

A broad variation in clinical manifestations has been described for ring 7 chromosome. The findings of the previously reported cases have been summarized and discussed before (9,10). All the patients had growth retardation in common and at least one of the following dermatological abnormalities: vascular lesions, dark pigmented naevi,

café-au-lait spots and achromic spots (12). Our patient had severe growth retardation and developed all the dermatological abnormalities described. This is the second case in which hypochromic spots are found, so we think this skin finding could be included in the variable expression of dermal abnormalities found in ring 7 patients. One patient with multiple pigmented skin lesions developed malignant melanoma at 17 years old (13). Because of the possible link between this chromosomal aberration and the presence of melanoma in patients with pigmented naevi, this risk must be evaluated in patients with this dermatological manifestation. Our patient developed pigmented naevi but has not had signs of melanoma to date.

Among other frequent manifestations described in ring seven, microcephaly, low birth weight, and mental retardation are present in our patient. Additionally, several less common findings have been described in some patients: genital abnormalities, respiratory distress, craniosynostosis, cleft lip and palate, congenital heart disease, situs inversus, syndactyly, quadriplegia and convulsions. None of these infrequent manifestations include the hearing defect found in our patient. To our knowledge, this is the first case with ring seven and severe sensorineural hypoacusia. The patient did not have any complication to explain it, and therefore, it suggests the possibility that some genes related to this defect may be assigned to distal segments of 7 chromosome. Further investigation about hearing ability, in patients with chromosomal anomalies found near telomeric regions in chromosome 7 is recommended, in order to identify some specific gene related to this defect.

Chromosome studies from all the cases with ring 7 in which break points are described include the same break points identified in our patient at p22q36 (4-11). Some variation is expected in clinical manifestations among the ring 7 patients with the same break points, the differences could be explained by different break points within the same region, and variability in the amount of chromosomal material lost. Because of the multiple

clinical manifestations in our patient, we think the mechanism for production of this ring 7 occurred by breakage in both arms of the chromosome with loss of DNA and subsequent fusion of both arm ends. Sawyer et al. (1996) found, following FISH procedures, his patient with holoprosencephaly had a subband deletion at 7q36.3 which included the HPE3 gene, and suggested that most patients with ring 7 have more distal deletions that do not include 7q36.3 critical region for holoprosencephaly. The absence of clinical and computed tomography evidence for holoprosencephaly in our patient, suggests the occurrence of breakpoint in the long arm was distal to 7q36.3 critical region for holoprosencephaly.

Patients with ring 7 and minimal clinical expression could be considered part of the ring chromosome formation by telomere to telomere fusion, with minimal or no loss of chromosomal material, and could be included in the "ring chromosome syndrome" (14,15). Patients with ring syndrome may have little phenotype consequences and normal intelligence. In the present patient we found the same breakpoints as in cases previously reported, and manifestations not described previously. However, the presence of multiple defects and mental deficiency suggests the loss of chromosomal material including some segment proximal to telomeric regions. As better identified extension of each deletion in ring 7 becomes available, and correlates with the clinical picture of the patients, it will be possible to correlate the different manifestations with the chromosome region lost.

REFERENCES.

1. Zackai EH, Breg WR. Ring chromosome 7 with variable phenotypic expression. *Cytogenet Cell Genet* 1973; 12:40-8.
2. Nakano S, Miyamoto N. A ring C7 chromosome in a mentally and physically retarded male .with various somatic abnormalities. *Jap J Human Genet* 1977; 22:33-41.
3. Delozier CD, Theintz G, Sizonenko P, Engel E. A fourth