Thrombocytopenia in a Filipino Child with Mosaic Monosomy 21/ Ring Chromosome 21

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ABSTRACT

We present a two year old female with mosaic monosomy 21 and ring chromosome 21 on chromosomal analysis. Pertinent features include delayed developmental milestones, intrauterine growth retardation (IUGR), seizures, microcephaly, down slanting palpebral fissures, broad nasal tip, cleft lip, overfolded ears and persistent thrombocytopenia since birth.

Key Words: monosomy 21, ring chromosome 21

Introduction

Monosomy 21 and ring chromosome 21 are two cytogenetic abnormalities well described in literature. Monosomy 21, which may involve a deletion of the whole chromosome or just a portion of the q arm, has been described as having variable phenotypic features including IUGR, psychomotor retardation, hypertonia, anti-mongoloid slant, prominent nasal bridge, low set ears, micrognathia, arthrogryposis-like symptoms, heart defects and mental retardation.[1-4] Other reports on partial deletions have described patients with thrombocytopenia, immunologic problems such as leukocyte adhesion deficiency, and holoprosencephaly.[3,5,6,7,8] A mouse model with 21q- reported by Besson showed modulation of inflammatory and airway responses.[9]

Likewise, ring chromosome 21 presents with variable features because telomeric deletions can occur, but larger rings can have duplications that involve the Down Syndrome Critical Region (DSCR).[10] Semilobar holoprosencephaly with dysmorphic features, epilepsy with mental retardation, cleft palate and hypogammaglobulinemia are just some of the case reports on ring chromosome 21 presenting with monosomy 21 features due to deletions.[11,12]

We present here a Filipino child with mosaic monosomy 21 and ring chromosome 21.

Case Report

Our patient was a 1 year 5 month old female, the only child of a non-consanguineous Filipino couple. She was born to a 24 year old primigravid, with pregnancy complicated by prenatal ultrasound findings of intrauterine growth retardation at 5 months age of gestation (AOG) and oligohydramnios at 8 months AOG. She was delivered at 36-37 weeks by caesarian section due to fetal distress. Birth weight was 1.2 kg and pediatric aging was at 36-37 weeks. A unilateral cleft lip was noted at birth which led to feeding problems. Baseline CBC showed thrombocytopenia but the patient had no signs of bleeding. She was given platelet transfusions. After discharge from the nursery, regular monitoring of her persistent thrombocytopenia was done but since there was no bleeding, no further transfusions were given. The patient later developed frequent eye discharges due to lacrimal duct obstruction. Developmental milestones were delayed. At 1 year of life, she developed seizures. Her EEG was abnormal and the magnetic resonance spectroscopy (MRS) showed a possible focal cortical dysplasia on the left frontal lobe. She was started on oxycarbazepine which provided good control of the seizures.

Review of the family history revealed that one maternal grandmother has cleft lip and palate but did not have any of the other features in our patient. She had normal intelligence.

On physical examination at 1 ½ years of age, the patient's weight, height and head circumference were all below the 5th percentile for age. Aside from the surgically corrected unilateral (right) cleft lip, she had downslanted palpebral fissures with eye discharges, median epicanthic folds, ptosis of the left eye, deeply set right eye, wide nasal bridge, a broad nasal tip, small ears that were low set with prominent antihelices and overfolded helices, malocclusion of the teeth, proximal thumb insertion, low arched feet, hypoplastic toe nails and dorsiflexed big toes (Figure 1). No murmur was appreciated.

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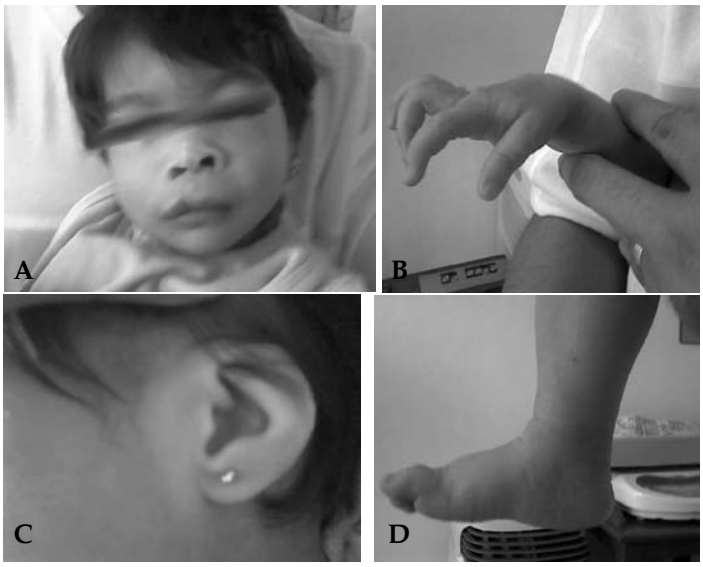
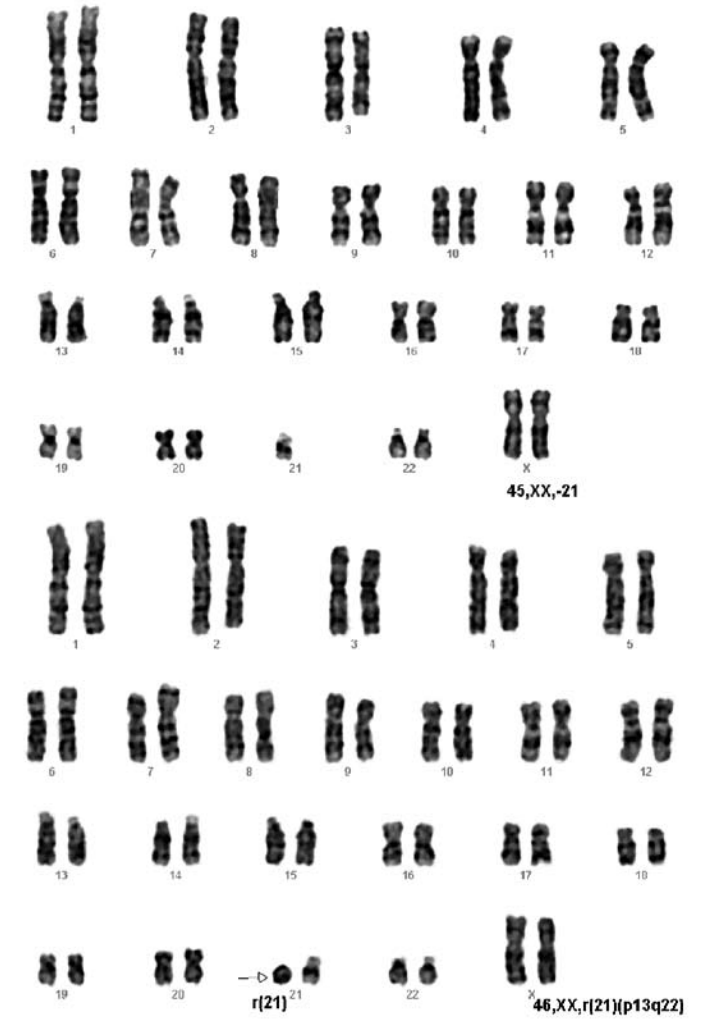


Figure 1. A) Broad nasal tip and the surgically corrected cleft lip; B) Proximal thumb insertion; C) Small lowset ear with overfolded helix and prominent antihelix; D) Slightly dorsiflexed toe.



45, XX,-21/ 46, XX, r(21)(p13q22).

Figure 2. Karyotype of the patient. (Source: Cytogenetics Laboratory, Institute of Human Genetics)

Platelet count has remained low (51,000/uL). Her chromosomal analysis showed: 45, XX,-21/ 46, XX, r(21)(p13q22) (Figure 2). Out of 15 cells, 40% were monosomic for chromosome 21 while the rest had the ring chromosome 21. Imaging studies of the spine revealed a spina bifida occulta.

She has been referred for early intervention services (developmental assessment, physical and occupational therapy) and parents have been advised regarding anticipatory care for all her medical problems.

Discussion

The phenotypic features of our patient are consistent with monosomy 21, including intrauterine and postnatal growth retardation, microcephaly, delayed milestones, deep set eyes, low set ears with overfolded helices, and broad nasal tip. Many of our patient's features are typical of full monosomy 21, as described by Chettouh.[2] Lacrimal duct system anomalies, cortical dysplasia, cleft lip, spina bifida, and dorsiflexed toe are less commonly reported, as is thrombocytopenia.[6] Studies have looked at candidate genes on chromosome 21 that may explain the phenotypic and physiologic features. They have included the genes for SIM2, minibrain (MNB), and CD18 gene.[5] Theories have been put forth that there may be holoprosencephaly genes, and genes for megakaryocytic differentiation in chromosome 21 too.[6] In our patient, there has been no formal assessment yet for immunodeficiency, a problem which has been described in some patients.[3,5,6]

Autosomal ring chromosomes usually arise sporadically but approximately 1% of these are inherited.[13] The patient's parents then are possible asymptomatic carriers of the chromosome 21-structural abnormality. Parental karyotypes were recommended to the family during counseling. Sasagawa's case is a mosaic karyotype, like our patient, with monosomy 21 and ring chromosome 21.[12] However, 87% of the cells had the ring chromosome, while our patient had 60% ring chromosome 21. Features of monosomy 21 and ring 21 do overlap since both involve similar regions of the chromosome. Chettouh et al. attempted to map the features associated with partial monosomy 21.[2] One of the regions she identified was on 21q22.2 (between markers DS21S11 and DS21S55) and the features associated with a deletion of that region overlap with our patient's findings (intrauterine growth retardation, post natal growth retardation, microcephaly, low set ears, and cleft palate). However, no further detailed study of our patient's breakpoints using other methods like fluorescence-in-situ hybridization was done. Management plans for this patient include control of seizures, physical and occupational therapy, and close monitoring of her platelet count. There is no specific prognosis reported for monosomy 21/ring 21. However, ring syndromes which result to larger genetic imbalance have been known to result to more severe growth retardation and impaired pathways of organ development.[13] This may hold true for our patient

since she was also monosomic for chromosome 21 in some cells.

Conclusion

We presented a Filipino child with a mosaic karyotype (monosomy 21/ ring chromosome 21) who had the typical features of monosomy 21/ring 21. Parental karyotypes would help determine if the parents are carriers of the ring chromosome. Management of the associated medical issues remains to be a multidisciplinary team approach.

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