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CASE reports

Ring chromosome 5 with dental anomalies

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Abstract

Although ring chromosomes are observed in almost all autosomal groups in man, they are rare. We describe a male patient exhibiting cri du chat syndrome in which cytogenetic studies demonstrate the presense of a ring chromosome 5. Deletion of the ring chromosome 5 is found between the p15 and q35 bands. Dental, medical and cytogenetic findings are compared to other ring chromosome 5 cases described in literature.

Introduction

Cri du chat syndrome, first described in 1963,[1] is characterized by a shrill high cry similar to that of a young cat. The cry is attributed to a hypotonic, dysmorphic larynx noted in some patients.[2] The cry may not be pathognomonic of the syndrome since it is absent in some patients and is reported in other chromosomal abnormalities.[3]

The following traits may be found during infancy:[4,5,6] microcephaly, round facies, apparent ocular hypertelorism, downward slant of palpebral fissures, epicanthal folds, low-set posteriorly angulated ears, preauricular tags, micrognathia/retrognathia, prominent nasal bridge, muscular hypotonia, congenital defects of heart and genitourinary tract, abnormal dermatoglyphic findings, short metacarpals or metatarsals, and "dysmorphic" hips. Various characteristics change with age. The faces becomes thin and asymmetric.[3,7] Hypotonia disappears[7,8] and hyperactive reflexes develop.[9] The cry usually disappears or changes character.[10,11] Hypertelorism and micrognathia are not as apparent. Older patients may exhibit premature greying, optic atrophy, strabismus, scoliosis, small wings of the ilia, large frontal sinuses, and awkward, shuffling gaits.[7] Almost all cases exhibit severe mental, growth, and motor retardation.[8,9] Breg et al.[7] report dental malocclusions in adults consisting of micrognathia, flaring of anterior teeth, overbite, openbite and local malalignments. Analysis of patients' pictures indicates Breg probably used the term overbite to describe marked overjet. The presence of high arched palate is variable.[7] Premature eruption of second permanent molars is reported in one case.[10]

Although some patients survive to adulthood,[3,7] most patients die in infancy due to severe respiratory and feeding problems.[4]

Diagnosis is based on clinical features, abnormal crying during infancy, chromosomal studies, and dermatoglyphic features. Diagnosis based soley on clinical features is difficult in some cases due to phenotypic variability and to characteristics changing with age. Clinical features are used, however, as indications for confirmatory chromosomal studies.[11]

Cri du chat syndrome is usually attributed to a partial deletion, either terminal or interstitial, of the short arm of chromosome 5[7] in the area of p14 to p15 band.[12] The most commonly reported cause is de novo deletion occurring in approximately 85 percent of the cases.[13,14] There are eight reported cases of ring chromosome 5.[11,15-20]

Ring chromosomes result when deletions occur at the proximal and distal ends of the chromosome and the two broken ends fuse.[15] Rings may not be present in all cells of affected individuals, may break into smaller pieces (ring products), or may contain more than one centromere.[21] Rings that look alike may not be alike due to different amounts of chromosomal deletions.[22]

Phenotype may be affected by the presence and stability of a ring,[22,23] the translocation of chromosome 5 segments to other chromosomes,[14,24] the translocation of other chromosomes onto chromosome 5,[25-27] or by varying amounts of deletion of chromosome 5. Patients with ring chromosome 13, for example, appear to fall into three clinical syndromes with some overlapping features depending on how much of the ring is lost in the major cell line.[21] There is, however, little information about ring chromosome 5. Clinical characteristics of patients with ring chromosome 5 are compared in this paper for better understanding of the influence of a chromosomal ring information on cri du chat.

Case Report

Medical History

A 2310 gm white male was born to a 20-year-old mother and 24-year-old father. Following a normal pregnancy, delivery took place several weeks later than the expected date of birth. A weak high-pitched cry was noted shortly after birth.

The head circumference was 30 cm; fontanels and sutures, including a metopic suture, were open. Body length was 45 cm. The nasal bridge protruded significantly (Figure 1). Other dysmorphic facial features included: large, low-set ears, widened external ear canals, retrognathia, downward slant of palpebral fissures, and ocular hypertelorism. Skeletal abnormalities included a widened anterior-posterior chest diameter, short sternum, short fingers, and slight lumbar kyphosis. A sixth supernumerary lumbar vertebra was noted on x-ray. A small ventricular septal defect, noted at birth, spontaneously closed by three years of age. Rectus diastus was present. The genitalia were normal. Extremities were proportional with considerable muscular hypertonia and hyperactive reflexes. Both palms showed a single upper transverse Palmer crease. The toenails were small and concave.

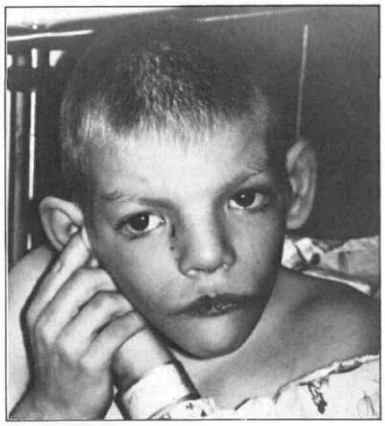

Figure 1. Patient with ring 5 chromosome disorder.

Subsequent studies over seven years revealed severe developmental delay. The child sat at two years of age and walked unsupported at five years of age. There was no language development although the patient did make sounds. There was marked growth failure at seven years of age (height and weight below fifth percentile). The child had a history of pneumonia and failure to thrive.

Cytogenetic Findings

Chromosome analysis was done on lymphocytes and skin fibroblast cells using Giemsa and Quinacrine banding procedures. One hundred metaphase cells from the peripheral blood lymphocytes were analyzed over a seven-year span (Table 1). Eighty percent of the cells had 46 chromosomes with a ring 5 (45,+r), 11 percent with 45 chromosomes with ring (44,+r) and 7 percent without ring product (46,-r,+ring products). The presence of two double rings was noted in ten cells. Nearly 70 percent of the skin fibroblasts showed a ring chromosome 5.

It appears that a small amount of chromosomal material was lost from the clearly banded ring chromosome (Figure 2) at break points, 5p15 and 5q35 (long arm), as reported in other studies.[18,20] Thus, the karyotype was designated as 46,XY,r(5)(p15q35). Both parents had normal karyotypes.

Dental Findings

At the age of seven years and two months, the patient was first seen in the dental clinic at the University Hospital School of the University of Iowa with a history of dental pain.

The patient was extremely uncooperative. Examination revealed micrognathia (Figure 3), an ulcerated lesion on the maxillary lip, gingivitis, and poor oral hygiene. Occlusal examination indicated an openbite of approximately 2 mm, an overjet of approximately 15 mm with flaring anterior teeth, and a Class II molar relationship. Multiple carious lesions of the posterior teeth with radiographic evidence of internal root resorption were found. Class I incisal fractures were present on the maxillary central incisors. Radiographically, there was an apparent lack of alveolar bone around both maxillary centrals. Fusion of the mandibular left primary canine and lateral was noted, as was the absence of the left permanent lateral. The mandibular right primary molar was markedly smaller than the left, although no measurements were taken. The patient's dental age as determined by calcification was 7.5 years. Eruption was within normal limits for a seven-year-old male. Hypomineralization was present on the maxillary primary canines and mandibular permanent left lateral incisor. The maxillary left first permanent molar was hypoplastic.

Due to the lack of patient cooperation, distance the parent traveled for treatment and, at that time, an uncertain medical condition, the patient was hospitalized. Oral rehabilitation utilizing nitrous oxide, oxygen, and halothane anesthesia with nasoendotracheal intubation consisted of: examination, nine radiographs, oral prophylaxis, topical fluoride, three stainless crowns, six amalgam restorations, one occlusal sealant and two extractions.

Although the parent was instructed in positioning brushing, flossing, and the use of daily topical fluo-

Table 1. Chromosome data on blood and skin fibroblast cells.

Tissue	45,r	44,+r	45,+r	46,-r, + ring products	Number of cells analyzed
Blood	2	11	80	7	100
Skin	27	5	89	14	135

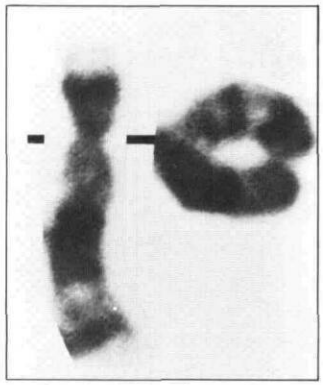

Figure 2. Ring chromosome 5 with homologous chromosome. **r [5]** (See cover photo)

ride, both before and after oral rehabilitation, the patient exhibited poor oral hygiene with severe gingivitis at the postoperative appointment. A white 0.5 x 0.5 cm lesion was found on the soft palate but the ulcerated lip lesion had healed.

Two months later, the patient was referred from the pediatric clinic with complaints of failure to thrive, bruxing and biting. The father asked that all teeth be extracted because he could not stand the noise caused by the patient grinding his teeth.

An examination revealed poor oral hygiene, generalized severe gingivitis, mobility of the maxillary and mandibular centrals, radiographic evidence of widened periodontal ligaments around the mandibular right central (Figure 4) and lack of bony support around the maxillary centrals (Figure 5). The pulp canals of the maxillary centrals were open whereas the root formation of the mandibular centrals was complete. Our impression was that the mobility and widened periodontal ligaments of the anteriors and the status of the anterior root canals were probably due to a combination of developmental status of the root canal, lack of bony support around the maxillary anteriors, and possible trauma from either falling or from a noted habit of chewing his bed or other hard substances. The father could not remember the patient retraumatizing his teeth since the oral rehabilitation. The white lesion noted at the postoperative appointment was not present. Since there was no evidence of pain or oral lesions, the parent was informed of our findings and again instructed in oral hygiene. The patient was referred back to the pediatric clinic for examination for other contributing factors. If none were found, extraction of the maxillary incisors would be considered. Otherwise, observation was indicated.

The patient was hospitalized for further examination. His clinical notes indicated he ate and slept well. No oral or medical problems were noted. The physician recommended that the patient receive institutional care.

Discussion

The reported cases of ring chromosome 5 show similar craniofacial features (Table 2). Microcephaly

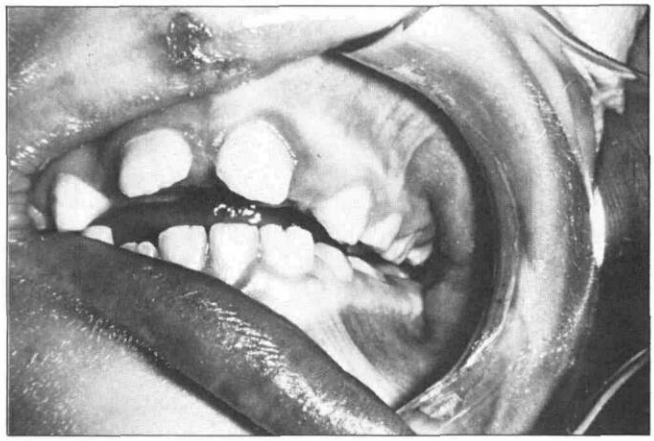

Figure 3. Oral findings include rerognathia, flaring incisors, fusion, fractured maxillary central incisors, gingivitis, and ulceration.

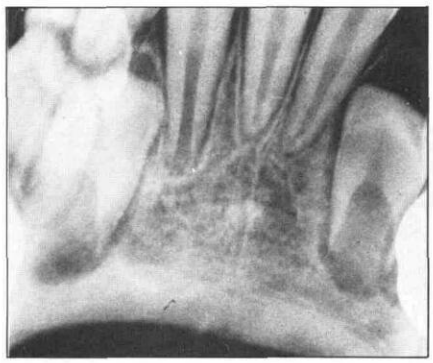

Figure 4. Mandibular periapical radiograph taken at postoperative appointment.

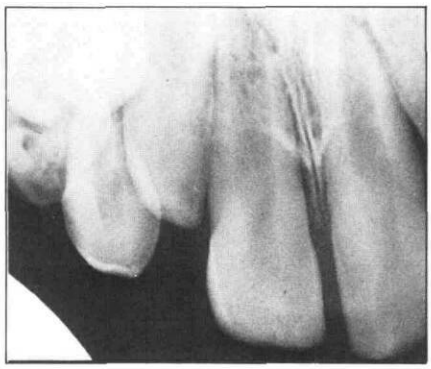

Figure 5. Maxillary periapical radiograph taken at postoperative appointment.

and epicanthic folds are common to all patients. Hypertelorism, dysmorphic ears, retrognathia, and antimongoloid slant are present in over half the patients. The presence of prominent nasal bridge and high arched palate is variable as reported in cri du chat patients.

An abnormal cry is reported in all but two cases. Mental retardation is a consistent finding. Abnormal dermatoglyphics is reported in six of the nine cases, with no mention in the other three cases. Other abnormalities are grouped under organ systems due to lack of specificity. Abnormalities of organ systems include: cardiac abnormalities (grade 3-4 systolic murmur, VSD, enlarged heart), three cases; urogenital abnormalities (undescended testes, atrophied testes), two cases; skeletal abnormalities other than cranial (dys-

Table 2. Clinical findings in patients with ring 5 chromosome.

	Rohde & Tomkins (1965)	Steele et al. (1966)	Cousin et al. (1972)	Nakagome et al. (1972)	Chuang et al. (1976)	Bailon et al. (1977)	Suerinck et al. (1978) Case 1	Suerinck et al. (1978) Case 2	Present Case	
Age	Newborn	18 mons	4 yrs	4 mons	17 mons	15 yrs	1 mo	6 yrs	7 yrs	Total
Craniofacial features										
Microcephaly	+	+	+	+	+	+	+	+	+	9/9
Hypertelorism	+	+	+	+	+	?	+	+	+	8/9
Epicanthic folds	+	+	+	+	+	+	+	+	+	9/9
Prominent nasal bridge	+	-	+	?	?	?	+	-	+	4/9
Dysmorphic ears	+	-	-	?	+	?	+	+	+	5/9
High-arched palate	-	+	?	?	+	?	-	+	-	3/9
Retrognathia	+	+	?	+	+	?	+	+	+	7/9
Antimongoloid slant	+	+	?	+	+	+	?	+	+	7/9
Abnormal cry	+	+	?	+	+	-	+	+	+	7/9
Abnormal dermatoglyphics	+	+	+	?	?	?	+	+	+	6/9
Mental retardation	+	+	+	+	+	+	+	+	+	9/9
Cardiac abnormalities	+	-	-	?	+	?	?	?	+	3/9
Genital abnormalities	?	-	-	?	+	?	?	+	-	2/9
Skeletal abnormalities	+	?	-	+	?	+	?	?	+	4/9
Syndactyly	+	-	?	?	+	?	+	?	-	3/9

+ - reported as present, - - reported as missing, ? - no mention.

plastic fingers, scoliosis, extra vertebra, dysplastic hips, short sternum), four cases; and syndactyly, three cases. Thus, the most constant findings in ring chromosome 5 patients are craniofacial abnormalities, cry, mental retardation, and dermatoglyphics.

As a group, ring chromosome 5 patients cannot be differentiated into a separate syndrome from cri du chat patients. However, comparison of clinical findings (Table 2) and interpretation of the influence of ring structure are complicated. Authors may have deleted mention of various characteristics either because the characteristics were not present, were not considered important, or were not observed although present. As previously discussed, various characteristics are modified with age. Therefore, the paucity of reported phenotypic characteristics in the case of the fifteen-year-old male may be due to craniofacial growth. The phenotype may also be influenced by the amount of chromosomal deletion within a band.[23]

The influence of the ring chromosome on dental characteristics is difficult to determine. Dental observations of ring chromosome 5 patients are scant. Chuang et al.[19] report delayed dentition in a 17-month-old. Steele et al.[17] report the presence of ten teeth in a one-year-old patient. Dental age is normal in this case. Therefore, of interest in our case, is the presence of fusion, a missing permanent lateral incisor, discrepancy in size of mandibular first primary molars, mineralization, and lack of bone around the maxillary incisors. Fusion may be inherited as autosomal dominant with reduced penetrance,[28] although it has not been associated with a particular chromosome. Paternal and maternal dental histories are unknown in this case. Stewart and Prescott[28] assume that identical genetic control determines the size of contralateral teeth and that asymmetry is attributed to environmental influences. Thus, one can do no more than speculate that contralateral tooth size asymmetry in this patient is due to genotypic variation. This patient exhibits retrognathia and overjet as previously reported in cri du chat patients.[7] The incisal fractures are related to trauma either from a chewing habit or the decreased motor ability of the patient. The handicapped condition of the child and reduced parental interest contribute to poor oral health of the patient. Additional studies are needed to understand the influence of the chromosomal ring structure on dental phenotype.

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Quotable Quote

In a message of solace to consumers and industry alike, the Food and Drug Administration (FDA) has concluded that most common food additives are harmless. A review of 415 natural and artificial additives generally regarded as safe turned up few surprises. Only salt was targeted for restriction or possible removal from the food supply, because of its potential for increasing hypertension.

The review, conducted by the Federation of American Societies for Experimental Biology, suggests that additional study be made of more than a dozen additives, including caffeine, on which there was considerable disagreement. Additional information on BHA and BHT, two widely used preservatives, was also sought, as were data on the long-term effects of vitamin additives such as iron, zinc, vitamin A and vitamin D — each consumed in ever-larger quantities.

From: Smith, R. J. Most additives are harmless. Science, 211:260, January 1981.