Case reports

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Brachmann-de Lange syndrome in sibs

K K NAGUIB, A S TEEBI, S A AL-AWADI, AND M J MARAFIE

Kuwait Medical Genetics Centre, Maternity Hospital, Kuwait.

SUMMARY We report an Arab family of phenotypically normal first cousin parents with two offspring showing variable manifestations of Brachmann-de Lange syndrome. The proband, who had many diagnostic symptoms of the syndrome with apparently normal chromosomes, died at the age of three months. His sister was less severely affected and lived for six years. The genetic basis of Brachmann-de Lange syndrome is discussed and homozygosity for an autosomal recessive allele is suggested as an underlying cause in some cases.

Familial occurrence of Brachmann-de Lange syndrome (BDLS) has been reported frequently and was reviewed recently.¹ Most of the cases reported seem to be the result of an autosomal dominant trait and only a few are not convincingly explained by this form of inheritance. However, consanguinity has been reported in several cases.^{2–8} We report on two sibs with BDLS who have normal first cousin parents.

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Case report

The proband was male and was seen soon after birth. He was the result of the fifth pregnancy of a 32 year old mother and 38 year old father, who are phenotypically normal first cousins from Kuwait. Preconceptional and pregnancy history were unremarkable except for polyhydramnios in the last trimester. Delivery was at term by caesarean section. Birth weight was 2.2 kg, length 42 cm, and head circumference (OFC) 31 cm (all below the 3rd centile). Craniofacial features (fig 1) included, in addition to microcephaly, a narrow, hairy forehead, long eyelashes, synophrys, depressed nasal bridge, anteverted nostrils, long philtrum, a characteristic thin upper lip, and micrognathia. The upper limbs showed bilateral absence of the second to fifth fingers, absent palms, and short forearms. In the lower limbs the toes were small. The external genitalia were hypoplastic with a small penis and underdeveloped scrotum. Chromosomal studies on peripheral blood lymphocytes with trypsin G banding and prometaphase chromosomes showed a normal chromosomal constitution (46,XY).

Study of the pedigree (fig 2) showed that the proband had two normal older sibs, a stillborn male

FIG 1 *The proband.*

FIG 2 Family pedigree.

infant recorded as having no malformations (no photograph available), and a term female sib who died at the age of six years and showed several stigmata of BDLS, namely severe developmental and growth retardation, craniofacial dysmorphism (including microcephaly, synophrys, long eyelashes, thin lips, anteverted nostrils, and micrognathia), hirsutism, and micromelia (fig 3).

The chromosomes of both parents were normal.

Discussion

Brachmann-de Lange syndrome is a fairly common complex malformation syndrome with an incidence of 1/10 000 to 1/50 000 livebirths.¹⁻¹¹ Mildly affected cases of BDLS may not be diagnosed and this could account for the lower incidence in some reports.¹² Patients with BDLS have a characteristic phenotype, but with a wide range of variability.¹³ Because of the broad spectrum of BDLS, Miller¹⁴ listed nine minimal diagnostic criteria to help in the

diagnosis of borderline cases. Mental retardation was reported in most cases, though normal mentality has been recorded in a few.¹⁵⁻¹⁷

Most cases of BDLS are sporadic, but the striking concordance in MZ twins, discordance in DZ twins, and familial occurrence strongly suggest a genetic basis. In some cases, aneuploidy has been found.^{7, 18-20} The rarity and inconsistency of the reported chromosome abnormalities makes them unlikely to be the underlying cause of BDLS, although it may not be possible to rule out the existence of a sub-microscopic deletion or duplication. Autosomal dominant inheritance has also been suggested by other authors.^{21, 22}

On account of occurrence in sibs with generally normal parents and several instances of first cousin (or closer) consanguinity, Opitz,¹ in his review suggested autosomal recessive inheritance in some cases with high prenatal lethality of homozygotes to explain a segregation ratio about one order of magnitude less than expected under the recessive hypothesis.

In this report, two affected sibs with phenotypically normal, consanguineous parents and normal chromosomal constitutions adds further evidence for the autosomal recessive hypothesis in some cases of BDLS and supports the causal heterogeneity in this syndrome.

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FIG 3 Sister of the proband.

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Correspondence and requests for reprints to Dr K K Naguib, Kuwait Medical Genetics Centre, Maternity Hospital, PO Box 4080, 13041 Safat, Kuwait.

A lethal presentation of de novo deletion 7q

LYDIA E McMORROW*†, I R TOTH‡, MURIEL M GLUCKSON§, ALENA LEFF*, AND SANDRA R WOLMAN*

*Department of Pathology, New York University Medical Center, New York, NY 10016; and the Departments of Pathology‡ and Pediatrics§, St Vincent's Hospital and Medical Center, New York, NY, USA.

SUMMARY Deletion of 7q32→qter is a well defined syndrome which usually arises de novo. The proband we report was the result of an uncomplicated 36 week first pregnancy of non-consanguineous Oriental parents. The male infant died shortly after birth. Chromosome studies of peripheral blood and umbilical cord revealed 46,XY,del(7), apparently (q32→qter). The parents' karyotypes were normal. The observed facial structural abnormalities and hydrocephalus rather than microcephaly are in sharp contrast to the clinically described syndrome.^{1,2} The lethal components, absence of suprarenal glands and hydranencephaly, suggest either an unknown con-

founder factor or a more proximal deletion with an alternative interpretation of 7q-(q23.1→q36.1) rather than the apparent breakpoint at 7q32.

Although relatively few cases have been reported, partial monosomy of 7q appears to be a well defined syndrome which usually arises de novo.¹⁻³ Young *et al*⁴ reviewed published reports and added new cases of terminal and interstitial deletions, bringing the total number of reported cases to 38. The clinical features found in more than 50% of the patients with terminal deletions of 7q are mental and growth retardation, microcephaly, low birth weight, eye anomalies, flat, broad nasal bridge, bulbous nasal tip, ear malformations, abnormal palm and sole creases, prominent forehead, and genital anomalies in males. Many of these features are also seen in patients with interstitial deletions of 7q which have been reported less frequently. While the proband

†Present address: Division of Human Genetics, Department of Pediatrics, University of Medicine and Dentistry of New Jersey-School of Osteopathic Medicine, 401 Haddon Avenue, Camden, NJ 08103, USA.
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