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CASE REPORT

Unique Occurrence of Brachmann-de Lange Syndrome in a Fetus whose Mother Presented with a Diffuse Large B-Cell Lymphoma

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Brachmann-De Lange Syndrome (BDLS, MIM 122470) is a rare multiple congenital anomaly/mental retardation syndrome characterized by a variable phenotype including intrauterine fetal growth retardation, limb reduction and distinctive facial and skull features (low frontal hairline, synophrys, anteverted nostrils, long philtrum, downturned corners of the mouth, micro- and retrognathia, low-set ears and micro-/brachycephaly), as well as a significant psychological developmental delay. A proposed classification system for BDLS include a classic type with characteristic facial and skull changes, a mild type where similar changes may develop with time or may be partially expressed, and a third type including phenocopies, where phenotypic changes are casually related to chromosomal aneuploidies or teratogenic exposures. We report on a 22-week gestation fetus with BDLS, showing intrauterine fetal growth retardation, brachycephaly, micro-/retrognathia and monolateral single bone of the forearm, in a woman harboring diffuse large B-cell lymphoma. Meticulous family history was negative for malformations, syndromes, congenital anomalies or psychiatric disorders. There are very few reports of BDLS at early gestation, but to the best of our knowledge, this is the first case occurring simultaneously with a hematological neoplastic disease of the mother. (Pathology Oncology Research Vol 13, No 3, 255–259)

Key words: Fetal growth retardation, upper limb defect, neoplasia

Introduction

Brachmann-De Lange Syndrome (BDLS, MIM 122470) is a rare multiple congenital anomaly/mental retardation (MCA/MR) syndrome characterized by intrauterine fetal growth retardation, a variable phenotype and mutations in the gene NIPBL (NIPPED-B-like).[7,16] The major criteria for BDLS are (I) the phenotype, including low frontal hairline and synophrys with high arched eyebrows, thin lips with protrusion of the upper lip, long and prominent philtrum, downturned corners of the mouth, small nose with anteverted nostrils, long eyelashes, low-set ears and micro- and retrognathia; (II) pre- and postnatal growth deficiency; (III) internal anomalies of mainly the musculoskeletal system, ranging from tetraphocomelia or peromelia, bilateral monodactyly and ulnar agenesis to variable finger joint contractures and clubfeet and almost normal limbs; (IV) feeding dysfunction, and (V) psychomotor delay with a distinctive behavioral profile.[18] Structural and functional disorders of the inner organs include congenital heart defects, diaphragmatic defects, hearing impairment and gastro-esophageal reflux.[4,10]

The incidence of BDLS is estimated at around 1 in 40,000 births[7,16] with a recurrence risk of less than one percent.[5] Despite this low recurrence, risk apprehension of the parents for subsequent pregnancies is usually high. Recurrences in siblings have been reported, but it is also sporadic. The classification of the phenotypes by Van Allen et al[18] is widely accepted (see abstract).

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Here, we report on a 22-week gestation fetus with BDLS, showing intrauterine fetal growth retardation, brachycephaly, micro-/retrognathia and monolateral single bone of the forearm, in a woman harboring diffuse large B-cell lymphoma.

Case report

A 27-year-old woman of 22 weeks gestation underwent a routine ultrasound examination. The fetus showed growth retardation and an abnormal facial profile with a severe micro-/retrognathia and a protruding upper lip (*Fig. 1a*). There was also an upper limb deficiency with agenesis of the right ulna bone and right monodactyly. The combination of intrauterine growth retardation, limb reduction and abnormal facial profile prompted a rapid genetic counseling and the possibility of poor prognosis was explained to the parents. In the meantime, the mother developed enlargement of multiple lymph nodes. Histological examination of a lymph node showed a diffuse large B-cell lymphoma. The parents decided to terminate the pregnancy and the mother received chemotherapy.

At autopsy, the male fetus was hypotrophic showing severe retrognathia, short nose with depressed nasal bridge and anteverted nostrils, protruding upper lip with a long philtrum, small tongue and dysplastic ears (*Figs. 1b-e*). Postmortem examination of the brain and internal organs did not show any abnormal findings. Fetal fibroblast karyotype was numerically and structurally normal (46, XY). The placenta weighed 120 g and measured 12 x 10 x 2 cm. The assessment of fetal growth was performed using standardized measurements. Lengths of biparietal diameter (BPD) and occipito-frontal diameter (OFD) were measured using a transverse axial plane of the fetal head showing a central midline echo broken in the anterior third by the cavum septi pellucidi and demonstrating the anterior and posterior horns of the lateral ventricles. BPD and OFD were obtained from the measurement of the outer borders of the skull. Head circumference (HC) was calculated by the formula π x (BPD+OFD)/2. The femur length (FL) was measured from the greater trochanter to the lateral condyle. To obtain the calculation of the abdominal circumference (AC), a transverse section of the fetal abdomen was taken at the level of the stomach and the bifurcation of the main portal vein into its right and left branches. Both anteroposterior (AD1) and transverse (AD2) diameters were measured and AC was calculated (π x (AD1+AD2)/2). HC/AC and HC/FL ratios were also calculated. Cephalic index (CI) was determined by the formula: BPD/OFD x 100. The skull is defined dolicocephalic if CI is equal or less than 75%, while it is defined brachycephalic if equal or more than 85%. Pilu and Nicolaides' standard values with linear, quadratic and cubic models were used for data analysis.[12] Our case showed the

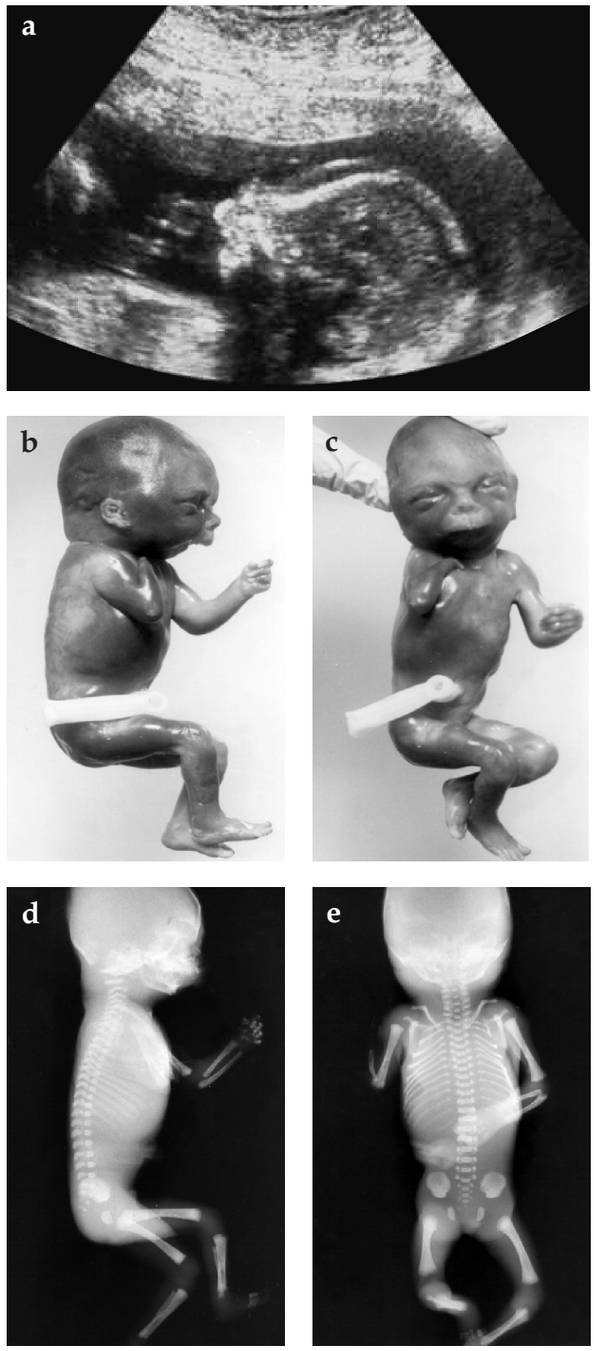

Figure 1. *Ultrasound examination* ***(a),*** *total body view* ***(b, c)*** *and baby X-ray* ***(d, e)*** *of the propositus.* ***(a)*** *Ultrasound examination showing protruding upper lip with a long philtrum (nasolabial distance) and severe micro-/retrognathia.* ***(b, c)*** *Total body view showing the characteristic somatic changes, including anteverted nostrils, protruding upper lip with a long philtrum, downturned corners of the mouth, dysplastic ears, micro- and retrognathia as well as limb reduction defect on the right side.* ***(d, e)*** *Baby roentgenogram showing upper limb deficiency with agenesis of the right ulna bone and right monodactyly*

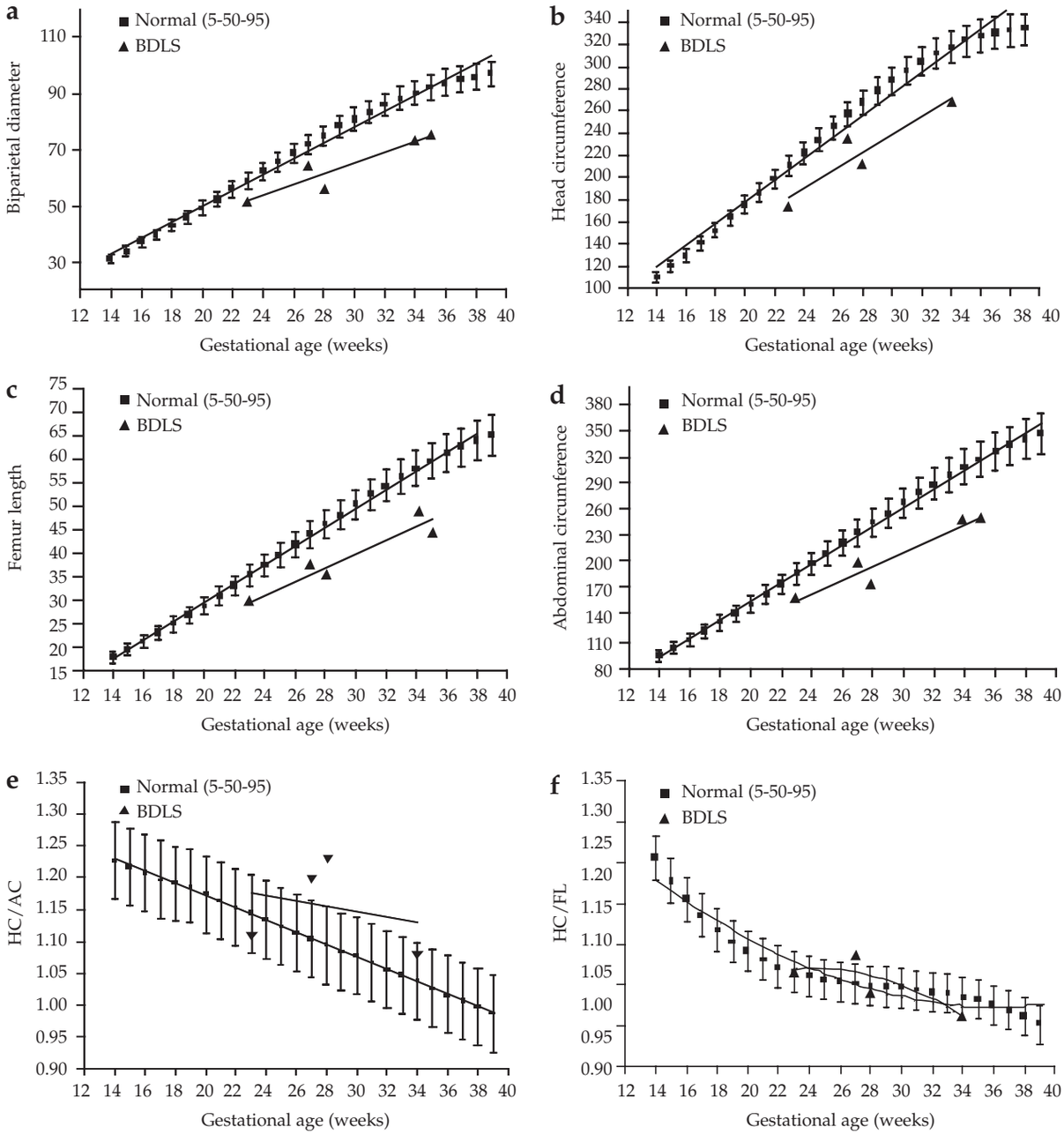

Figure 2. *Biometry of fetuses with intrauterine diagnosis of Brachmann-de Lange syndrome (5 cases: Ranzini et al, 1 case;[13] Sekimoto et al,1 case;[14] Nowaczyk and Mohide, 2 cases;[10] our propositus) compared with normal fetuses without congenital anomalies or intrauterine growth retardation.[12]* ***(a)*** *Biparietal diameter during gestation,* ***(b)*** *head circumference during gestation,* ***(c)*** *femur length during gestation,* ***(d)*** *abdominal circumference during gestation,* ***(e)*** *head circumference to abdominal circumference ratio,* ***(f)*** *head circumference to femur length ratio*

following data at 22-week gestation: BPD, 50.8 mm; OFD, 60 mm; FL, 33.7 mm; AD1 and AD2 were 48.6 mm and 51.7 mm, respectively. Craniometrical analysis showed micro-brachycephaly: HC, 173.9; AC, 157.5; HC/AC, 1.104; HC/FL, 5.16 and CI, 85.

Literature data analysis

To compare our case with similar cases from the medical literature we performed a systematic review using PubMed, Current Contents and ISI databases. The search

was limited to articles published in English during the period 1993–2004. Both articles and abstracts of scientific meetings were evaluated. The analysis entailed a series of comparisons across articles, focusing on both ultrasound diagnosis and complete fetal biometry data. We reviewed in detail four full well-described fetuses with data available in the electronic medical literature (case 1 in our propositus).

Case 2: Intrauterine growth retardation, depressed nasal bridge, short upturned nose, micrognathia, long philtrum, long eyelashes, low posterior hairline, shortening of the radius and ulna on the right, cleft hands with oligodactyly, Dandy Walker variant and enlarged 4th ventricle of the brain;[13]

Case 3: Hirsutism, low posterior hairline, synophrys, long eyelashes, broad depressed nasal bridge, anteverted nostrils, prominent philtrum, downturned angles of mouth, thin lips, low-set ears, micrognathia, lack of forearms and bilateral oligodactyly;[14]

Case 4: Intrauterine growth retardation, micrognathia, persistent curved finger;[10]

Case 5: Micrognathia, midline cleft palate, prominent eyes, single eyebrow, complete encroachment of the anterior hairline on to the forehead, long philtrum, ectrodactyly of the right hand, oligodactyly of the left hand and prominent heels.[10]

Data analysis from linear and non-linear regression studies revealed homogeneous values for BPD, HC, FL, AC and HC to AC ratio using a linear regression model, and homogenous values for HC to FL ratio using a non-linear 3rd polynomial regression model (*Fig. 2*). Although only five BDLS cases were investigated, we found a regression equation with a good r^2 parameter tending to 1 for BPD (r^2: 0.88), FL (r^2: 0.89), and AC (r^2: 0.91).

NIPBL gene study

DNA was extracted from formalin-fixed and paraffin-embedded tissue and PCR amplification of the exons 7, 8, 9, 11, 12, 13, 14, 15, 16, 17 and 21 was set up, but an amplicon was found exclusively for exons 8 and 9. DNA sequencing of both exons showed no mutation. To overcome the difficulty of highly degraded DNA we also carried out a degenerated gradient gel electrophoresis for the exons 8, 11, 21, 30 and 40, but an amplicon was found for exon 40 only. DNA sequencing of this exon also showed no mutation.

Discussion

Upper limb defects, usually asymmetrical and often unilateral with intrauterine growth retardation, support the diagnosis of BDLS.[5] However, upper limb reduction defects are only present in 27 to 58% and an abnormal profile is found in 40% of the cases, making a straightforward prenatal diagnosis difficult in most cases.[1,5,11,17] In addition, the measurement of pregnancy-associated plasma protein A may fail to be found. In this way, a fetal biometric profile could be considered characteristic in the presence of minor abnormalities.[3,4] In this study, we support the thesis that biometric profile does really help in the diagnosis of BDLS. A characteristic facial profile may be rare, whereas a micro-brachycephalic skull profile is more frequent. Craniometrical analysis has a long tradition for syndromes with psychic developmental delay.[9] Micro-brachycephaly or nearby is confirmed to be a relevant finding in BDLS. This aspect has also been suggested by Kliewer et al.,[6] but these authors studied four measurements (BPD, HC, FL, AC) only and their cases occurred in the third trimester. Thus, growth retardation with micro-/brachycephaly may be useful in the diagnosis of BDLS.

Children with BDLS have significant psychological developmental delay with low scores on the Vineland Social Maturity Scale and are unable to live without community support, showing severe limitations in communication, a delay in the acquirement of verbal skills and worse prognosis for cognitive development even in children with mild phenotypic features of BDLS.[18] However, very few cases with BDLS underwent a detailed post mortem examination. We review evidences that a phenotype including characteristic fetal biometry data and some external features, even in the absence of a cardio-diaphragmatic defect, is distinctive for the prenatal diagnosis of BDLS.

With regard to the phenocopies of BDLS, a variety of chromosomal aneuploidies have been reported in patients with BDLS, focusing for example on the 3q26.3 region.[2,8] Teratogenic exposure, including alcohol, valproic acid administration and dilantin use, have also been associated with phenocopies of BDLS.[18] This is the first case of BDLS occurring in a mother harboring a hematological neoplastic disease, which was characterized as diffuse large B-cell lymphoma. The diagnosis of phenocopy remains hypothetical. However, it is not the first case of BDLS linked to neoplasia. It is noteworthy that BDLS has been associated with suprasellar germinoma.[15]

In summary, we reported biometric profile lines and curves that are characteristic of BDLS and present a unique case of BDLS in a fetus whose mother presented with a diffuse large B-cell lymphoma. Prenatal identification of BDLS provides an opportunity for a coordinated multi-task parental counseling. An interdisciplinary intervention is a compulsory choice in the rare cases of women with cancer.

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