Caudal regression syndrome and sirenomelia in only one twin in two diabetic pregnancies

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Summary

Many authors consider sirenomelia to be an extreme form of caudal regression syndrome (CRS), while others argue that they are two distinct entities. Maternal diabetes mellitus is considered to be an important predisposing factor for both CRS and sirenomelia. Two rare cases of diabetic, dizygotic twin pregnancies, each with one normal and one affected fetus are presented. In case 1 the affected fetus had CRS. In case 2 the affected fetus had sirenomelia. The present cases suggest that the pathogenesis of CRS and sirenomelia is more complex than previously thought, that maternal diabetes is not the only underlying pathogenetic mechanism and that genetic or epigenetic factors probably contribute to the formation of these conditions.

Key words: Caudal Regression Syndrome; Sirenomelia; Diabetes; Dizygotic pregnancy.

Introduction

Sirenomelia has been traditionally described as an extreme form of caudal regression syndrome (CRS) [1]. In recent years however, some authors have argued that they are two distinct entities [2, 3]. Incidence estimates of each condition are difficult, since both are not always reported separately [3]. The pathogenesis of both anomalies is not exactly known. A vascular steal phenomenon has been proposed for sirenomelia: An aberrant vessel arises from the high abdominal aorta and "steals" blood from structures distal to its origin, namely the caudal fetus [3]. For CRS, an association with maternal diabetes mellitus has been reported [1, 4, 5], while familial cases of CRS also implicate a genetic cause [3]. In addition, unlike CRS, sirenomelia has been associated with twinning, most often monozygotic [6-8].

We present herein two rare cases of diabetic, dizygotic twin pregnancies, each with one normal fetus and one affected either with CRS or sirenomelia, suggesting a complex pathogenesis in both conditions.

Case Report

Case 1

A 27-year-old white female, gravida 3, para 2 presented at 23 weeks' gestation for ultrasound screening for fetal anomalies (18-23 week scan). Gestational diabetes was diagnosed in the current pregnancy, and the patient was under insulin treatment. The previous obstetrical and medical history was otherwise unremarkable. A dichorionic, dizygotic pregnancy was diagnosed. Twin A had normal anatomy and fetal biometry. On the other hand, the femur length (FL) of twin B was below the 5th percentile, there was evident hypoplasia of both lower limbs and an abrupt termination of the fetal spine below the midthoracic level, suggesting the presence of CRS (Figure 1). At 33 weeks the patient under-

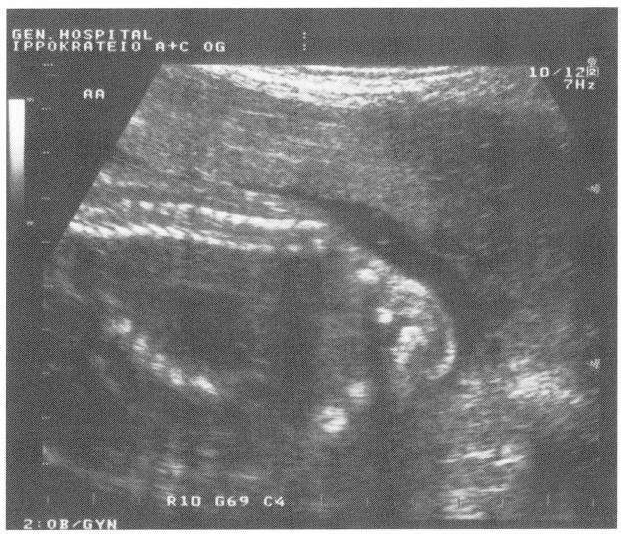

Figure 1. — Prenatal ultrasonographic view of twin B in case 1; abrupt termination of the spine below the midthoracic level can be seen.

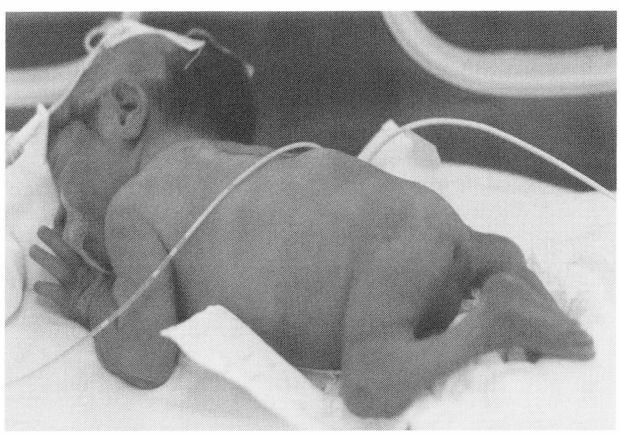

Figure 2. — The affected twin (twin B) in case 1; limb hypoplasia is evident.

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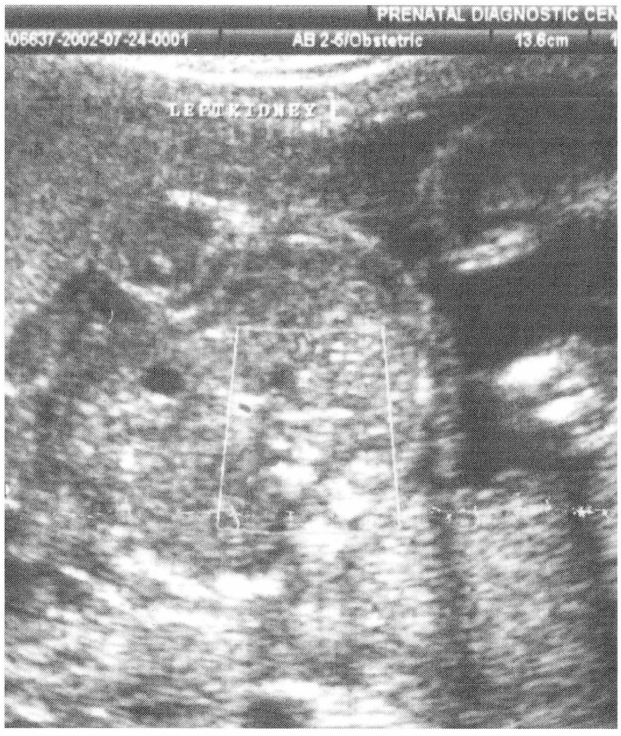

Figure 3. — Prenatal ultrasonographic view of the two fetuses in case 2; oligohydramnios is evident in the affected twin (twin B).

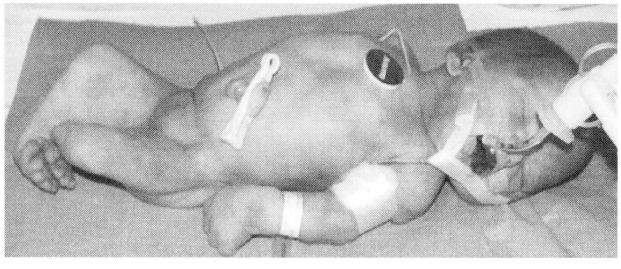

Figure 4. — The affected twin (twin B) in case 2; fusion of the lower extremities is evident.

went cesarean section due to deteriorating preeclampsia. Two live male infants were delivered: Twin A was normal and had a birth weight of 2,010 g, while twin B was, as prenatally diagnosed, affected by CRS and weighed 1,390 g at birth (Figure 2).

Case 2

A 37-year-old white female, gravida 2, para 1, presented at 11 weeks' gestation for a routine 1st trimester ultrasound examination (11-14 week scan), after IVF and transfer of three embryos. A twin dichorionic, dizygotic pregnancy was diagnosed, with no abnormal findings on ultrasound. The woman was re-examined at 19 weeks. Twin A had normal anatomy and fetal biometry, but evaluation of twin B was difficult due to oligohydramnios. Renal agenesis was suspected, even though two large vessels (the adrenal arteries) could be easily seen at the level of the renal arteries on colour Doppler (Figure 3). Diagnosis of renal agenesis was established with administration of furosemide to the mother, which was not followed by urine production from the fetus. At 28 weeks' gestation, previously undetected gestational diabetes was diagnosed and delivery with cesarean section at 32 weeks followed. Diagnosis of sirenomelia, with fusion of the lower extremities (Figure 4), total absence of the anus, and two umbilical vessels, was established postnatally. Despite immediate incubation, the affected infant died three hours after delivery. On autopsy, renal agenesis was confirmed together with complete absence of the ureters and the urinary bladder. The abdominal aorta was hypoplastic with a single umbilical artery.

Discussion

CRS is a rare fetal malformation, characterized by symmetrical sacrococcygeal or lumbosacrococcygeal agenesis of variable extent, most often accompanied by multiple musculoskeletal abnormalities of the pelvis and legs. The main difference between CRS and sirenomelia is that there are two distinct but hypoplastic lower limbs in the former, while the lower limbs are fused or there is only a single extremity in the latter. Other differences include: a) non-lethal renal anomalies versus lethal renal agenesis or dysgenesis, b) normal or imperforate anus versus absence of the anus, c) two versus a single, aberrant umbilical artery, and d) normal or increased versus reduced amniotic fluid [2]. All these characteristics were evident in the affected fetuses of the two cases described here.

The teratogenic mechanism of CRS and sirenomelia is not known. Several theories have been proposed, but firm evidence is lacking due to the rarity of these conditions. In earlier reports, both anomalies have been associated with maternal diabetes mellitus, but this does not seem to be accurate if the two are classified separately. With this distinction, CRS appears to be more often associated with maternal diabetes than sirenomelia [2, 4]. Recently, a case of CRS diagnosed postnatally in one of two twins in a diabetic, monozygotic twin pregnancy has been reported [8], suggesting that the etiology of the syndrome cannot be explained by environmental influence only and that genetic factors are also involved. Case 1, in the present report, supports this theory, since the twins living in the same diabetic intrauterine environment were not genetically identical. Furthermore, case 2 suggests that the same theory can also be applied for sirenomelia.

In diabetic pregnancies several metabolic changes [8-10] could alter one or more processes of normal embryogenesis leading to CRS or sirenomelia [8]. Moreover, data from animal studies support the view that maternal diabetes could alter homebox gene expression or expression of genes with similar function [8, 11]. Homebox (Hox) genes play a key-role in the development of the skeleton and various organs, and such genes have been also described in humans. In particular, a homebox gene (HLXB9) has been identified as a major causative gene in patients with autosomal dominant sacral agenesis [12]. Furthermore, genes playing a crucial role in nephrogenesis [13] could possibly be involved in the pathogenesis of sirenomelia, given its association with renal agenesis.

In conclusion, the pathogenesis of CRS and sirenomelia remains obscure. Maternal diabetes mellitus appears to be a contributing factor, possibly through epigenetic or genetic alterations during early embryogenesis, while other, yet unidentified, environmental factors could also lead to such changes, even in the absence of diabetes.

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