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SHORT NOTE

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Prune Belly Syndrome and Heart Defect in One of Monozygotic Twins, Following Exposure to Tigan and Bendectin

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Abstract. One of twins was born with prune belly syndrome and congenital heart defect following exposure to Bendectin and Tigan. Red cell antigens and HLA typing were compatible with monozygosity. The possible associations of the prune belly syndrome to monozygotic twinning or to teratogenic agents is considered in light of this patient and review of the literature.

Key words: Prune belly, Heart defect, Discordant monozygotic twins, Tigan, Bendectin

INTRODUCTION

The association of absent abdominal muscles, urinary tract abnormalities, and cryptorchidism, "Prune Belly Syndrome", occurs in approximately 1 in 30,000 to 40,000 live births [3,9]. Associated malformations of the skeleton (talipes, dislocated hips, absence deformities, etc) have been described in up to 50% of patients [7,17]. Other visceral anomalies including gastrointestinal and cardiac malformations have been reported [1,11]. Most of the patients described are males and the relatively few affected females have had less severe abnormalities [7]. Affected family members, including siblings [2,7,8,20,22] and twin pairs both concordant [18,22] and discordant [1,9,13] for prune belly, have been described. Various possibilities which have been considered in the explanation of the association include single gene defects, chromosomal abnormalities, a primary mesodermal disorder, and consequences of obstructive urinary tract malformations [1,2,4,6-12,15,17,18,20,22,24]. We present a patient, one of MZ twins, in whom prune belly syndrome and a congenital heart defect were found following exposure to Tigan and Bendectin.

CASE REPORT

CH was born one of twins at 35 weeks gestation by cesarean section to a 30-year-old primigravida and 32-year-old father, both apparently healthy and nonconsanguineous. Pregnancy was complicated by severe nausea and vomiting initially treated at 6 to 7 weeks gestation with Bendectin 40 mg daily for ten days, then with Tigan, 400 mg daily for three days, then 600 mg daily for three days. At 9 weeks gestation Mrs. H was hospitalized and treated for four days with intravenous fluids. Following discharge, treatment was continued with Bendectin, 100 mg daily. At 17 weeks gestation, ultrasound revealed twin gestation with two sacs, with one twin showing evidence of an abnormality of the urinary tract. Bendectin was discontinued by the mother following this observation.

At birth, KH, the healthy twin, weighed 1900 g while CH weighed 2980 g. Physical examination revealed markedly enlarged wrinkled abdomen with ascites. Following drainage of the ascites fluid, CH weighed 2500 g (50th percentile for his estimated gestational age of 35 weeks). His length was 45.5 cm (50th percentile) and head circumference 34.25 cm (90th percentile). Urologic evaluation revealed a bladder of normal size and configuration with massive bilateral hydronephrosis and hydroureters. Voiding cystourethrogram showed failure of bladder emptying and vesicostomy was performed at age 6 days. Renal function, as documented by hippuran renal scan, has gradually improved over time. At age 9 months BUN was 10 mg% and creatinine 0.4 mg %. Congenital heart disease was diagnosed at birth, and cardiac catheterization at 9 months showed severe infundibular and valvular pulmonic stenosis with a small ASD. At 9 months resection of the infundibular hypertrophy and valvulotomy was performed with closure of a large patent foramen ovale.

Clinical evaluation at the age of 18 months revealed normal developmental milestones. CH's first words were at 7 months, two months before his twin; he crawled at 9 months and walked at 17 months, two months after his twin. On physical examination height was 78.5 cm, weight 10.65 kg, and head circumference 47.5 cm (all within the 10th to 50th percentile). There was mild brachycephaly and relatively hypoplastic midface with horizontal palpebral fissures. Ears were asymmetric with the right ear smaller than the left, and the left ear simple and cupped (very similar to the father's ears). Deficiency of the abdominal muscles and bilateral cryptorchidism were apparent. No significant heart murmur was heard. There was an overriding second toe on the right. Physical examination of the unaffected twin, KG, revealed similar relative hypoplasia of the midface with horizontal palpebral fissures and overriding second toe, whereas his abdominal muscles were normal and both testes were descended.

On family history of three generations, no other individuals with a congenital heart defect, renal disease, weak abdominal muscles or the prune belly syndrome were described. There was no family history of twinning.

EVALUATION OF ZYGOSITY

Blood was obtained from both twins and typed for the following red cell antigens: ABO (A, A1, B), Rh (C, c, D, E, e), Kell (K), MNS (M, N, S, s), P (P1), Fy (a, b), Xg (a), Jk (a), Lu (a) and Le (a, b). HLA typing (HLA-A, HLA-B, HLA-C) was also done. The twins were concordant for all systems.

The ratio of the likelihood that the twins are concordant given the twins are DZ to the likelihood given the twins are MZ is 0.035 for the ten red cell antigen systems. If prior probabilities for DZ to MZ twins in the population (0.7:0.3) and of like sexed twins (0.5) are used, then the posterior probability of monozygosity is 96.05% [19,23,25].

The method of determining the posterior probability of monozygosity assumes that the marker systems are independent. Since the three HLA loci are tightly linked and do not segregate independently, two approaches may be used to include HLA markers in the determination of the posterior probability of monozygosity. In the first, only one of the three loci is used. Then, the posterior probability of monozygosity for the ten red cell antigen systems plus one of the three HLA loci is 98.80%, 98.88% and 98.71% for the HLA-A, HLA-B and HLA-C loci respectively. Alternatively, a haplotype approach is used. In this case, frequency data were readily available for only the HLA-A and HLA-B haplotypes. If the probability of crossingover is ignored, then the posterior probability of monozygosity for the ten red cell antigen systems plus the HLA-AB haplotype is then 98.97%.

DISCUSSION

In the present report discordance in identical twins suggests that simple mendelian inheritance cannot be the etiology of all instances of the prune belly syndrome. The exposure of our patient to a potential teratogen illustrates the possibility that environmental factors may be involved in the etiology of prune belly syndrome.

In reviewing the literature on prune belly syndrome we found 15 reported sets of like-sex twins [1,9,11,13,18,22] and 2 sets of unlike-sex twins [1,9]. Both concordant and discordant twins have been reported. The 2 unlike-sex twin pairs were both discordant; the male twin was affected in one [1] and the female twin in the other [9]. In one set of discordant MZ female twins, the abdominal wall in the affected twin was typical of prune belly but there were no genitourinary anomalies and the defect was ascribed to effects of fetal ascites due to twin-twin transfusion [13]. In a pair of discordant male twins of unknown zygosity the unaffected twin died at birth with "hydramnios" [11] while for another set of male twins of unknown zygosity the health of the second twin was not reported [1]. In another set of male twins of unknown zygosity that were concordant for prune belly syndrome, one twin had the classic findings of the syndrome while the other had omphalocele and absence of one kidney and ureter [18]. Another set of concordant male twins of unknown zygosity had an affected maternal male cousin [22]. Of the remaining 10 reports of like-sex twins, 6 were MZ discordant twin pairs [1,9] and 4 were discordant with unknown zygosity [1,9].

Ives [9] pointed out an association of twinning and prune belly syndrome, especially with MZ twins. She raised the possibility that in twins with prune belly, and perhaps in some singletons, the etiology of the prune belly syndrome may relate to MZ twinning, as has been suggested for other birth defects by Nance [16].

Other proposed etiologies of the prune belly syndrome include virtually all known modes of inheritance and mechanisms of developmental defects. Prune belly has been reported with chromosomal abnormalities [7,8,12], and in family aggregations suggestive of either X-linked [7,22] or autosomal dominant [7,20] inheritance. The abdominal wall muscle defect has been proposed as the primary defect [8,9] or reported as secondary to ascites [13,15] or to dilation of the genitourinary tract with either mechanical or functional obstruction [4,6,8,10,17,24]. We considered the possibility that in our patient exposure to Bendectin (doxylamine succinate) and to Tigan (trimethobenzamide HCl) may have been associated with the prune belly syndrome. While neither Tigan nor Bendectin has been proven to cause birth defects, reports in the literature continue to raise the issue of possible teratogenicity of both [5,14]. At least one study [14] did raise the possibility of a statistically significant increase in the risk of congenital anomalies following exposure to Tigan. Exposure to doxylamine succinate-containing compounds [21] was found in five babies born with agenesis of the cloacal membrane leading, in four of them, to markedly distended abdomen due to dilation of obstructed urinary tract. These findings somewhat resemble those of the prune belly syndrome. While our patient does not have any evidence of such a cloacal abnormality, we do feel that the association of prune belly syndrome with drug exposure in utero should raise the possibility that specific drugs or other teratogenic environmental effects may be important in the etiology of the prune belly syndrome.

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