The prune belly anomaly

Heterogeneity and superficial X-linkage mimicry

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SUMMARY The genetic, clinical, and necropsy findings of 2 brothers with the prune belly anomaly are presented and the literature reviewed. The combined data emphasise the clinical and genetic heterogeneity of the disorder and show that in at least some instances a heritable component may be the primary insult. The most likely heritable explanation involves a two-step autosomal dominant mutation with sex-limited expression that partially mimics X-linkage.

The triad of deficient abdominal musculature, urinary tract and renal anomalies, and cryptorchidism has been recognised for many years (Parker, 1895; Howard, 1940; Roberts, 1956; Nunn and Stephens, 1961; Bourne and Cerny, 1967; Williams and Burkholder, 1967; Texter and Murphy, 1968; Burke *et al.*, 1969; Burkholder *et al.*, 1970; Afifi *et al.*, 1972; Palmer and Tesluk, 1974; Welch and Kearney, 1974). More than 250 patients with this constellation of features, referred to as the prune belly anomaly (PBA), have been described (Ives, 1974). None the less, pathogenetic mechanisms to account for this pattern of abnormalities have proved difficult to find. Many mechanisms and aetiologies have been suggested (e.g. see Nunn and Stephens, 1961), but no one explanation has accounted for the entire spectrum of features which include non-abdominal anomalies, a wide variation in severity, a distinct preponderance of male patients (more than 95%), greater severity in males, occasional familial occurrences (always males), and concordance in only 2 pairs of liked-sex twins (Sladezyk, 1967; Petersen *et al.*, 1972) but discordance for at least 5 pairs of monozygotic twins (Ives, 1974). In addition, several observers have noted a distinctive 'dimpling' at the lateral aspects of the knees in a number of patients, suggesting to some authors (Garlinger and Ott, 1974; J. Herrmann, 1977, personal communication), possible muscle defects of the limbs.

In the family presented below, 2 affected brothers born to a mother whose father was 42 years old at her conception suggest a new X-linked mutation, with a high recurrence risk. Yet the literature on this subject,

taken *in toto*, does not readily allow for genetic counselling on a straightforward X-linked basis. Genetic heterogeneity (including genocopies and phenocopies) (Childs and Der Kaloustian, 1968) and two-step mutations (Herrmann, 1976) have not yet been given proper consideration in sorting out the recurrence risk possibilities. We will address ourselves to these issues.

Case reports

Cases 1 and 2 are brothers, born 20 months apart in the second and fourth pregnancies to a non-consanguineous couple who were aged 29 (mother) and 35 years at the conception of Case 2. The first pregnancy had resulted in a normal daughter, and the third in a 2-month miscarriage. Both parents were normal. The family history was noteworthy for two reasons: (1) the absence of similar defects among other genetic relatives (including the mother's 5 maternal uncles, and her 3 male first-cousins and 8 male first-cousins once removed through maternal aunts and their daughters, respectively); (2) our patients' mother's father was 42 years old at the time of her conception. In addition, about a year before that he had a transient orchitis. There were no known mutagenic exposures to either parent, and no teratogenic exposures in either pregnancy.

CASE 1

This male infant was born in March 1975 at 7 months gestation from a pregnancy complicated by a second trimester urinary tract infection and the development

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of progressive polyhydramnios which had been apparent by the third month. The onset of labour was spontaneous. Because of failure to progress a caesarean section was performed, and a stillborn male infant was delivered.

At necropsy the length was 39.5 cm and weight 1505 g. The head and scalp were normal, though the face was compressed in a vertical dimension and there was diffuse oedema. The palate was narrow and highly arched. The neck was short. The auricles were normally shaped, but very low set (external auditory meati at the angle of the mandible). The chest and rib cage were unremarkable. The superficial abdominal veins were unusually prominent. The abdomen appeared as a 'collapsed water bag' and a firm mass was palpable in its lower half. The penis was normal. The scrotum was very small; on the right it was soft and flaccid, and on the left indurated. Neither testis was palpable. The anal orifice was unremarkable. The lower extremities were of equal length, but by circumference measurements the right had an absolute decrease in muscle mass, while the left was oedematous and generally enlarged. Both feet were well formed with normal toes and nails, but there was distinct ankle varus deformities (soles in the vertical plane). The upper extremities were symmetrical and normally formed but oedematous.

Internal examination

The anterior abdominal wall was very oedematous, particularly inferiorly; at the xiphoid process thickness was 8 mm, at the symphysis pubis, 17 mm. At the umbilicus there was a small omphalocele. Two umbilical arteries were present. Except as noted, the viscera were unremarkable. The spleen appeared as a bulbous mass. The stomach was elongated and thinned. The intraperitoneal bowel comprised loops of small and large intestine clustered as in a glomerular tuft; a Meckel's diverticulum and a hypoplastic ileum were noted. A distended bladder reached to the umbilicus; its walls were oedematous and its mucosa granular in appearance. No urethral lumen was present beyond the distal aspects of the prostate. There was mild constriction at both uretero-vesicle junctions and both ureters were dilated to diameters as great as 8 mm. Both kidneys were small and flattened: the right was oval and measured $3.5 \times 3.0 \times 0.6$ cm; the left was C-shaped and measured $4.8 \times 1.2 \times 0.8$ cm. The adrenals were normal-sized, flattened structures superior to each kidney. The lungs were collapsed, unaerated structures adherent to the mediastinum. The intracranial contents were normal.

Microscopical examination was normal or merely indicated congestion or autolysis except as noted. *Kidney*: cortical and medullary zones were well

defined. Along their juncture there were frequent abnormal aggregates of blood vessels and immature cells. Residual areas of erythropoiesis were noted. The *bladder wall* was very thick and the muscularis distinctly hypertrophied. The mucosa showed frequent areas of necrosis and ulceration of the transitional epithelium. *Lungs*: the air passages and parenchyma were well formed, with no definitive evidence of aeration. *Liver*: the sinusoids were dilated and contained numerous blood vessels, and areas of erythropoiesis were noted.

CASE 2

This infant was born in November 1976. Though in retrospect the similarity of this pregnancy to that of Case 1 was probably apparent by 3 months' gestation, it was at 6 months that the mother and her physician suspected a recurrence. At that time ultrasound and x-ray examinations indicated both polyhydramnios and fetal anasarca. A caesarean section was performed; the infant survived for one hour.

At necropsy weight was 2110 g and length was 33 cm. Except as noted, findings were normal. The abdomen was very distended, fluctuant, and filled with fluid. The head and face were somewhat flattened on the right side but were otherwise normal. The palate was high. The upper thorax was normal, but the lower ribs were flared outward. The wall of the abdomen was very thin and overlying skin had a diffuse haemorrhagic discoloration. The umbilicus was thin and slightly everted; just below it was the upper edge of a tense midline intra-abdominal mass. The scrotum had a palpable midline defect. Neither testis was palpable. The anal orifice was normal. The lower extremities were normal except for severe ankle varus deformities and flat feet.

Internal examination

After abdominal incision and drainage of peritoneal fluid the body weight dropped to 1790 g. The lower two-thirds of the abdominal cavity was occupied by a distended, thin-walled urinary bladder. After it was drained of 800 ml clear, light yellow urine the body weighed only 990 g. Though the internal urethral meatus and proximal urethra had a diameter of about 1 cm there was no grossly identifiable urethra at the base of the penis. A probe could be passed only 2 to 3 mm into the urethra from the external meatus. The tissue of the ventral abdominal wall and the scrotum was oedematous, almost gelatinous. Testes could not be identified in the scrotum, inguinal canal, or abdomen. The left ureter joined, but did not enter the bladder; it was tortuous, fluid-filled, and dilated up to 2 cm diameter. The right ureter was similarly tortuous and dilated, but it communicated with the bladder through a small ostium. Both kidneys were

small, each measuring about 2 cm in length and showing surface lobulation and superiorly attached adrenals. The liver was flattened against the diaphragm. The lungs were not aerated. The intracranial contents were not examined.

Microscopical examination

The skin of the *abdominal wall* was normal; below it the connective tissue was loose, with numerous dilated, empty vascular spaces. No muscle was disclosed. The *kidneys* were lobulated, with distortion of the corticomedullary junction. The cortex contained numerous glomeruli, many of which showed extensive dysplastic changes. In these the tufts were fused, without discrete capillary loops; the cells had a smudged, confluent epithelial quality. The tubules were sparse and most were dilated. In the outer zone of the cortex there were cysts, which appeared to be dilated tubules. The stroma was loose and prominent. Scattered deposits of calcium were noted in both tubules and interstitial tissue. Medullary connective tissue was quite cellular and almost myxomatous. The calyces were lined by flattened or partially sloughed transitional epithelium. The *bladder* wall was characterised by diffuse oedema and a loose appearance to the musculature. The *urethra* at the neck of the bladder and base of the penis showed no intrinsic abnormalities. Sections of the *lungs* showed an immature organ, with relatively thick-walled alveoli. The *liver* showed pronounced hematopoiesis.

The *mother* of these patients had no symptoms or other indications of urinary tract disease, except for the purported urinary tract infection in the pregnancy noted above. The abdomen was unremarkable; the abdominal muscles were normally present by palpation as determined both at rest and as she performed sit-up exercises with her hips and knees flexed. The knees and legs were normal. An intravenous pyelogram was normal.

Discussion

The two brothers presented here indicate all the classic features of the prune belly anomaly: absence of the abdominal muscles, congenital massive dilatation of the bladder and ureters, urethral obstruction, cryptorchidism, renal dysplasia, and secondary posturing deformities of the lower extremities. Case 1 also showed the occasionally associated features of asymmetric lower limb deformities and anomalous bowel and mesentery. In addition, there is circumstantial evidence that their mother carries a mutated Mendelian gene which is responsible for the disorder: her father was 42 years old at the time of her conception (Jones *et al.*, 1975). Since she is clinically normal

there are several possible genetic mechanisms to explain the situation. The three most likely are as follows. (1) An X-linked recessive mutation, expressed only in hemizygous males; (2) An ordinary autosomal dominant mutation with sex-limited (male) expression. This would be comparable, for example, to the monorchidism trait in German shepherd dogs (V. M. Riccardi, unpublished data); (3) She has a germinal mutation which merely represents the first of two necessary steps, either as a premutation which requires a second mutational event at the same locus (telomutation) (Herrmann, 1976), or as a complete, though merely permissive, mutation which requires a second mutational event at a separate locus. If the locus is not X-linked another mechanism to account for the sex-limited expression must also be introduced. Other genetic explanations, including autosomal recessive and polygenic inheritance, have nothing specifically in their favour. An autosomal recessive mutation could not explain affected cousins (Sladezyk, 1967; Garlinger and Ott, 1974) or discordant monozygous twins (Ives, 1974); in addition, consanguinity has been noted only once (Fletcher, 1928). Argument against a polygenic or multifactorial basis relies more on pathophysiological grounds than on family data: congenital anomalies of that basis are ordinarily limited to a single organ or tissue in terms of primary involvement. Since the multiple organs involved in prune belly anomaly do not reflect a causal sequence we presume that another mechanism, with simultaneous pleiotropic effects involved, i.e. teratogenesis or a Mendelian gene defect. No basis for the former has been found.

Our patient's family history, taken on its own would ordinarily suggest an X-linked recessive trait sufficient to warrant at least discretionary, if not definitive, genetic counselling respecting this inheritance pattern. The many previous published reports and reviews, however, fail to corroborate this simple schema. Though the vast excess of affected males is consistent with this approach, there are several instances of discordant male monozygotic twins (Ives, 1974) and there are two instances of affected male cousins with an interposed normal male (Sladezyk, 1967; Garlinger and Ott, 1974). In an effort to make sense out of the apparently conflicting data we examined two particular elements, genetic heterogeneity and the two-step mutation model.

Heterogeneity is clearly present on two levels. First, there is a distinct variation in the severity among affected individuals, with our two patients at one extreme, and 37-, 60-, and 70-year-old patients (Asplund and Laska, 1975; Housden, 1935) at the other extreme. But these types of differences do not establish genetic heterogeneity, though they are compatible with it. The two brothers with the pruned

belly anomaly and mosaic monosomy 16 (Harley *et al.*, 1972) and the patient with trisomy for a small acrocentric chromosome (or fragment) (Qazi *et al.*, 1973) do indicate genetic heterogeneity, however. All other instances where chromosomes have been analysed have indicated normal karyotypes, except for one instance where a small chromosomal fragment was coincidental (i.e. other, normal family members also carried it) (Halbrecht *et al.*, 1972). Acknowledgement of genetic heterogeneity, entailing both genocopies and phenocopies, allows for separate mechanisms to explain differences in clinical severity between cases, as well as differences in family clustering. For most cases there are no affected relatives, while for 7 (not counting twins) there are affected sibs (Kohn, 1935; Grenet *et al.*, 1972; Harley *et al.*, 1972; Bronzini and Moscatelli, 1973; Garlinger and Ott, 1974; Welling *et al.*, 1975) and for 2, affected cousins (Sladezyk, 1967; Garlinger and Ott, 1974). However, genetic heterogeneity by itself does not account for either the striking male preponderance or the discordant monozygotic twin brothers.

Although a sex preponderance is compatible with a polygenic/multifactorial trait this mechanism is unlikely for reasons noted above. One type of Mendelian gene defect could account for the male preponderance, the one severely affected female (Rogers and Ostrow, 1973), and the small number and pattern of affected family members, including twins: an autosomal dominant two-step mutation with sex-limited expression. If we disregard possible genetic heterogeneity, and we presume that the families with the affected cousins related through a normal male parent (Sladezyk, 1967; Garlinger and Ott, 1974) are not to be distinguished from our family, then an autosomal locus is necessary. From then it is merely a matter of respecting a two-step mutational process and considering whether the telomutation is germinal or somatic. On the other hand, if we respect genetic heterogeneity and presume that an autosomal locus in one family does not discount an X-linked locus in another, then an X-linked mutation is not precluded in our family. However, without a clear basis for documenting genetic heterogeneity in chromosomally normal patients or families we feel that genetic explanations for the prune belly anomaly must consider an autosomal two-step mutation with sex-limited expression as likely and X-linkage merely acknowledged as possible in some instances.

For those individuals with a negative family we cannot surmise the source of the first mutation (premutation), i.e. whether it is unique to the affected person or transmitted from a parent. With a positive family history the premutation is presumably transferred from a parent, with the second mutation (telomutation) occurring in the affected person.

Whether the telomutation is germinal (i.e. zygotic, present in all cells, including germ cells) or somatic (i.e. peculiar to the tissue manifesting the trait) is conjectural at this point. The only way convincingly to show the difference is transmission of the disorder from one affected individual to another, indicating a germinal telomutation. (In fact in the absence of vertical transmission of the disorder one cannot even be certain that the second mutation occurs at the same locus or a closely linked one.) However, discordance in monozygotic twins does suggest a post-zygotic telomutation, potentially somatic. In any case, the schema involving a two-step mutation with sex-limited expression fits all the available data taken as a whole. This in turn engenders a sib recurrence risk maximum as for an X-linked recessive trait: 1 in 4 for each pregnancy, or 1 in 2 for each male conceptus. The actual risk would be somewhat lower because the likelihood of the telomutation presumably would be less than 100%. We feel, none the less, that amniocentesis for prenatal sex determination and available abortion for males would be reasonable for a mother who has already had two affected sons. With a different type of positive family history or only one affected son the situation is still too tenuous to develop general rules. At the least, however, the parents should be told that recurrence is not totally ruled out.

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