Familial caudal regression anomaly and maternal diabetes

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SUMMARY A family is reported in which a diabetic woman gave birth to two children with the caudal regression anomaly (CRA). There were no obvious genetic factors. This is the first reported familial case of CRA with maternal diabetes.

The caudal regression anomaly (CRA) is usually a sporadic abnormality and one which is frequently associated with maternal diabetes (Passarge and Lenz, 1966). Several familial cases have been reported, but there is no clear cut pattern of inheritance. We report here the first case of two sibs with CRA born to a diabetic mother (Fig. 1).

Case reports

III. 1
This case was noted at birth to have abnormalities of both lower extremities and spine. The short, hypoplastic legs were held in a frog-leg position and both hips were dislocated. Popliteal skin webbing and aberrant musculature prevented the legs from being extended beyond 45 degrees and there was no spontaneous movement of either leg. Both feet were plantar flexed. Her back showed a raised protuberance at the T12 level and a dural sinus tract. She had constant urinary dribbling and no response to pain except a reaching movement of the ipsilateral hand in response to pin prick to the sole. The genitalia were poorly developed with an ill-defined clitoris, hypoplastic labia majora, and aplastic labia minora. The nipples were widely spaced and the neck appeared short. X-rays of the spine showed a complete absence of vertebræ below T12 and malformation of the pelvis (Fig. 2). An excretory urogram showed displacement of the lower pole of the right kidney towards the midline, and a horseshoe kidney was questioned but never confirmed. Ureteral reflux was also present.

The non-communicating sinus tract was excised at 2 months. Because of multiple urinary tract infections and to facilitate walking using a bucket prosthesis, an ileal conduit and bilateral high femur amputations were performed at age 4 years. Intelligence is normal.

The mother was a 24-year-old obese woman, gravida 1, para 0, with a 5-year diabetic history at the
time of birth. There had been no prenatal care and she denied knowledge of the pregnancy until delivery. Thirty units of NPH insulin had been used daily without testing the urine, but no other prenatal illnesses were reported. Delivery, complicated by mild pre-eclampsia, was estimated to be at 34 weeks, with a birthweight of 3060 g.

The pedigree (Fig. 1) shows multiple maternal family members with adult onset diabetes, but no other history of obvious congenital malformations. Genetic counselling at this time gave the parents a minimum 1% recurrence risk.

III. 2
This case was transferred to Colorado General Hospital at 5 days of age because of several anomalies noted at birth. He had a right sided cleft lip and a cleft of the alveolar ridge and anterior palate. There was constant leakage of urine and, according to the birth record, a question of an imperforate anus. At the time of the transfer there was definite anal patency which appeared as a longitudinal tear, presumably secondary to a rectal examination performed before transfer. There was poor sphincter tone but the legs were normal and all reflexes, with the exception of the anal wink, were present and equal bilaterally. Movement was both spontaneous and symmetrical and touch appeared intact at all points on the lower extremities. The testes were undescended. His head circumference was at the 10th centile, height and weight were between the 50th and 75th. The palpebral fissures appeared small. An excretory urogram showed complete agenesis of the sacrum below L5 (Fig. 3), and suggested absence of the right kidney which was confirmed by renal scan. G-bandung with trypsin showed a normal male karyotype (46,XY).

At the time of his conception the mother was taking 40 units of NPH insulin after some attempts at dietary control of her diabetes in the interim between pregnancies. Adjustments in the second month included dietary restriction and a change to 34 units of NPH and 14 units of regular insulin. She took ampicillin for 10 days during the second month for a urinary tract infection. A caesarean section was performed at 34 weeks' gestation because of prolonged rupture of the membranes. Birthweight was 2131 g.

After the birth of the second child, spine x-rays of both parents were taken and were normal with all elements of the sacrum and coccyx present.

Discussion
The caudal regression anomaly has been described with a variety of other malformations, including cleft palate, congenital heart disease, and imperforate anus (Passarge and Lenz, 1966; Warkeny, 1971), indicating an early embryological error. Passarge and Lenz (1966) have reported that 16% of all CRA is associated with maternal diabetes, suggesting this to be one environmental contributing factor. The recent

Fig. 2 III. 1. (a) Lateral x-ray of spine showing vertebral agenesis below T12. (b) X-ray showing pelvis and fixed positioning of the legs.
Collaborative Perinatal Project (Chung and Myrianthopoulos, 1975) concluded that insulin played no role in the production of congenital anomalies, but confirmed the reports of the increased incidence of CRA in offspring of diabetic mothers.

On the other hand, the familial cases would indicate a strong and perhaps exclusively genetic influence in some instances. There appears to be a syndrome of partial or complete absence of the sacrum associated with anal stenosis and presacral masses of various types, including teratomas and anterior meningoceles. This has been recently reviewed by Ashcraft et al. (1975). Some of these patients had a neurogenic bladder or other neurological abnormalities, but many are asymptomatic. One affected female had adult onset diabetes. This is inherited in a dominant manner, though there may be some sex limitation as there is a high female: male ratio.

There have been four other familial reports of the more typical CRA not associated with maternal diabetes. Robert et al. (1974) described two families. In the first, two sisters had sacrococcygeal agenesis with secondary limb and neurological abnormalities, as well as microcephaly and severe mental retardation. One of them delivered a normal male infant.

There was in addition a normal sister, and a sister with spina bifida occulta of L5 and enuresis until the age of 15 years. Though the father of this sibship also had prolonged enuresis, spine x-rays were normal. Later, the sister with spina bifida occulta delivered a female with a syndrome identical to her two maternal aunts, and autosomal dominant inheritance with variable expressivity was suggested. The second family of Robert et al. included three sibs with sacral abnormalities; one boy was asymptomatic but his brother and sister both had neurological abnormalities. The parents refused to be x-rayed.

Say and Coldwell (1975) described a woman with partial absence of the sacrum who, by her third husband, had two girls with CRA, as well as a normal male and a stillborn male with cebicocephaly. By her previous two marriages, she had had six normal children (one stillborn) and a child with trisomy 21, cleft lip and palate, and an imperforate anus. The most recent report is by Finer et al. (1978) who described two brothers with CRA, anal atresia, and congenital heart disease. Both parents had normal spine x-rays and the mother had a normal glucose tolerance test. These authors felt that polygenic inheritance was most likely in the majority of cases of CRA in which diabetes was not apparent. In our family, a diabetic mother gave birth to two children with CRA. Both parents were radiographically normal and there were no other obvious genetic factors. To the best of our knowledge, this is the first report of two such children born to a diabetic woman.

Conclusions

While CRA is an uncommon abnormality, the associated disabilities can be severe and genetic counselling may be sought. There may be a history of maternal diabetes with an otherwise negative family history and normal parental x-rays. In these cases, the most important precipitating factor is probably the diabetes. This environment persists in future pregnancies and our family may indicate that there is an increased risk of recurrence. There may also be unknown genetic factors which contribute to a particular diabetic woman producing one or even two offspring with CRA.

The majority of cases of CRA with no family history and no evidence of maternal diabetes may indeed be polygenic, but there are no good recurrence risk figures available at present. The absence of this information for CRA shows the need for a prospective study in which careful family evaluations are done, including pedigrees, parental x-rays, and maternal glucose tolerance tests.
References


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