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monosomy 13q32.\(^5\)\(^8\) Conversely, deficiency of band 13q33 appears to be associated with a different phenotype without the typical head profile and thumb anomalies.\(^3\) The association of coagulation defects with (probable) loss of 13q34 observed in two unrelated patients\(^5\) was not found in our case 2. Our findings, together with the absence of coagulation disorders in the majority of 13qter monosomy cases, do not support the proposed relationship between monosomy 13q34 and deficiency of factors VII and X.\(^5\) Such a defect may rather be an unspecific and inconsistent finding in some chromosome disorders as it has also been observed in three cases of trisomy 8.\(^9\)

To conclude, the observations reported here contribute to the establishment of the phenotypic mapping of chromosome 13,\(^7\)\(^8\)\(^10\) which nevertheless remains incomplete.

The authors wish to thank A Alcaraz for the art work.

Addendum

Recently, de Grouchy et al (Hum Genet 1984:66: 230–3) have provided additional evidence for the assignment of the structural genes of clotting factors VII and X to 13q34. Whether the coagulation in our cases is indeed abnormal remains uncertain.

References


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Congenital diaphragmatic hernia in half sibs

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SUMMARY Half brothers from the same mother had congenital left sided posterolateral diaphragmatic hernias repaired in the neonatal period. The inheritance of diaphragmatic hernia should probably be based on the multifactorial hypothesis.

There are two types of developmental defects of the diaphragm, posterolateral defects or Bochdalek hernia and retrosternal defects or Morgagni hernia. Other, more extensive, defects can involve most or all of the hemidiaphragm. Evagination of the diaphragm and hiatus hernia will not be considered. The patient usually presents in the first hours or days of life with respiratory distress. The condition is amenable to surgical repair, the first successful cases having been treated in the 1940s. We wish to report left sided posterolateral diaphragmatic hernias in two half brothers from the same mother and review published reports concerning the familial incidence of diaphragmatic hernia.

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The first child, a male, was born at term weighing

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3·2 kg and he developed respiratory distress in the first 12 hours. A left sided diaphragmatic hernia was diagnosed and a posterolateral defect was repaired on the first day of life. The child was subsequently noted to have malrotation of the small bowel and a left undescended testis which was repaired at the age of 2 years. There were no other abnormalities or dysmorphic features. Subsequent physical and developmental progress has been satisfactory. After two further normal male children the mother divorced and remarried. The first child of the subsequent marriage, a male, was born at term weighing 3·6 kg and developed respiratory distress in the first hours after birth. A left sided diaphragmatic hernia was diagnosed and a posterolateral defect repaired on the first day of life. This child had considerable problems with postoperative pulmonary hypertension but eventually made a good recovery. No other abnormalities or dysmorphic features were noted. Based on the operative description there was no difference in the size of the hernia between the two sibs. Repair was affected without grafting and there was ample redundant diaphragmatic muscle. The second affected child also had a left undescended testis. The fathers were unrelated. The mother is adopted and has a normal chest x-ray.

Discussion

In the 31 familial cases of diaphragmatic hernia recorded,1-14 all but three were in sibs. The exceptions were first cousins,11 an uncle and two nephews,2 and a nephew of three affected sibs.13 Two sibs were identical twins.14 There have been no case reports of transmission from parent to child, though Mertins7 noted a high diaphragm in the mother of two affected children. All the cases either had a posterolateral defect or aplasia of one or both hemidiaphragms.

Recurrence of diaphragmatic hernia in a family may be underestimated, as may be the true incidence in a newborn population. In Butler and Claireaux's study15 the lesion was present in 1 in 2200 births (1 in 1100 stillborns and 1 in 4000 live births) and comprised 8% of all major congenital anomalies. It is certain that, at least until recently, neonatal surgical centres received only a proportion of the better risk patients. In an early study 1 in 8000 to 1 in 10 000 live births were referred to a neonatal surgical centre with diaphragmatic hernia.16 A more recent study with full ascertainment of cases from a university hospital has revealed an incidence of 1 in 2644 births.17 Reports of increased incidence are therefore probably due to greater ascertainment.18 Presumably some cases used to be unrecognised, presenting either as a stillbirth or as fatal respiratory distress of the newborn. Wolff1 found two familial cases by checking a 10 year necropsy series. Butler and Claireaux15 found one familial case in their necropsy series, and David and Illingworth19 had four unexplained cases of neonatal mortality among 181 sibs of patients with diaphragmatic hernia.

The causes of diaphragmatic hernia are heterogeneous, being associated with chromosomal trisomies,19 teratogenic agents,2 20 and recognisable patterns of malformation.1 About 50% of all cases have other congenital malformations, in particular related to the central nervous system.19 Excluding persistent ductus arteriosus and malrotation of the bowel (which is embryologically linked), only nine of 66 familial cases had a reported associated malformation, usually related to the cardiovascular system. In addition, a bilateral lesion is up to seven times more likely in the familial cases.15

Passarge et al10 argued that aplasia of the diaphragm may be a distinct entity with autosomal recessive inheritance. His description is insufficient to exclude a large posterolateral defect with a rim of diaphragm.2 Five families have been reported in which there is discordance in the extent of the defect, with one child having a posterolateral lesion and a sib having a large defect or aplasia.2 5 7 8 10 The paucity of consanguineous cases,3 13 and the marked excess of males (40:21) in the familial cases compared to the group as a whole,19 are uncharacteristic of autosomal recessive inheritance. Sex linked or autosomal dominant inheritance with incomplete penetrance have been proposed as modes of inheritance,2 but do not fit all the extended pedigrees. The multifactorial model is the most likely type of inheritance because of the male predominance, the compatibility of all pedigrees, including the cases reported here in half sibs, and the exclusion of other modes of inheritance to account for all familial cases. Occasional consanguinity is compatible with multifactorial inheritance presuming that each side carries some of the polygenic predisposing genes.13 Expected recurrence rate in first degree relatives can be calculated using the formula \( \sqrt{P} \) where P is the frequency in the general population.21 Taking the figure of Butler and Claireaux15 of 1 in 2200, a 1 in 47 or 2% risk can be expected, keeping in mind that a significant proportion may be perinatal deaths. The absence of associated malformations and the presence of a bilateral lesion would increase a recurrence risk. Genetic heterogeneity cannot, however, be excluded and conclusions from the combined data may be inappropriate. No case has yet been reported in parent and child, though this should occur if the multifactorial basis is indeed correct.
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We thank Dr M J Glasson for permission to report the cases.

References

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A case of suspected teratogenic holoprosencephaly

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SUMMARY A case of holoprosencephaly is reported in which the mother was prescribed high doses of oestroprogestins during the first 5 months of the pregnancy. Investigation of the family failed to reveal any sign of physical abnormality. A normal karyotype was detected in the proband. The authors suggest that this case may shed some light on the normal and abnormal way in which embryonic fields develop.

The action of teratogenic factors in the aetiology of holoprosencephaly has been studied experimentally using various animals (amphibia, birds, and mammals) and different agents (surgical removal of the prechordal mesoderm or its destruction by localised X irradiation, vitamin A excess, etc.). The great majority of reports of this condition in man refer to cases with various chromosomal abnormalities, Mendelian aetiology with autosomal dominant transmission in some families and autosomal recessive in others. Only a very few reported cases have well documented teratogenic mechanisms as causative factors. In the other cases Mendelian or chromosomal aetiology cannot be ruled out.

We report a case of alobar holoprosencephaly with a known exposure to a teratogenic agent.

Case report

The proband (fig 1) was a term newborn male (birth weight 3.5 kg, head circumference 40 cm) who died.
Congenital diaphragmatic hernia in half sibs.

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