High incidence of Meckel's syndrome in Gujarati Indians

I D YOUNG*, A B RICKETT*, AND M CLARKE†

From the Departments of Child Health and Community Health†, University of Leicester, Leicester.*

SUMMARY Five probable cases of Meckel's syndrome have been ascertained retrospectively through the Leicestershire Perinatal Mortality Survey for the years 1976 to 1982. All of these babies were born to Hindu parents originating from the Gujarat State in India, suggesting that Meckel's syndrome is particularly common among this ethnic group, with a gene frequency of approximately 0.028.

Meckel's syndrome, also known as dysencephalia splanchnocystica or the Meckel-Gruber syndrome, is a lethal disorder characterised by the classical triad of occipital encephalocele, polycystic kidneys, and postaxial polydactyly. It takes its name from Johann Friedrich Meckel who described affected sibs in 1822.¹ This condition was established as a distinct entity in contemporary publications in 1969² and subsequently shown to be autosomal recessive in inheritance.^{3,4}

Associated abnormalities include facial clefting, microphthalmia, congenital heart defects, ambiguous or hypoplastic genitalia, and talipes.³ Conventionally, the diagnosis is based on the presence of normal chromosomes and at least two of the three cardinal abnormalities, although it has been suggested following review of affected sibs of probands that diagnostic criteria should include cystic renal dysplasia plus at least two other defects.⁵

In this paper the authors present evidence which indicates that the gene frequency of Meckel's syndrome is particularly high in the Leicestershire Asian Hindu community originating from the Gujarat State in western India.

Case reports

The following cases were ascertained through the records of the Leicestershire Perinatal Mortality Survey for the years 1976 to 1982 inclusive. This continuing survey, details of which have been published elsewhere,⁶ records information about all babies dying in the perinatal period in Leicestershire. The survey is organised through the Depart-

ment of Community Health in collaboration with the Department of Obstetrics and Gynaecology.

In total, five probable cases of Meckel's syndrome, all occurring in non-Caucasian babies, were ascertained. There was only one possible case among Caucasian births.

CASE 1

This female infant was born in 1976. She was delivered by Caesarean section following antepartum haemorrhage at 42 weeks. Birth weight was 3.60 kg and the placenta weighed 660 g. The infant is recorded as having gasped a few times with no measurable Apgar score. Documented abnormalities included anencephaly, cleft lip and palate, polydactyly involving the left hand and both feet, and an 'imperforate vulva'. Chromosome and necropsy studies were not performed. This child was the product of the second pregnancy of healthy unrelated Hindu parents originating from different villages in the Surat district in the southern part of the Gujarat State. The first pregnancy resulted in a healthy male infant and the third pregnancy constitutes case 2.

CASE 2

This female infant was born in 1981. She was delivered at 32 weeks with birth weight 1.63 kg and lived only a few minutes. External abnormalities included microcephaly, an encephalocele, bilateral cleft lip and palate, abdominal distension, bilateral talipes, hexadactyly of the right hand and both feet, and septadactyly of the left hand. Chromosomes showed a normal female karyotype.

Additional abnormalities noted at necropsy were aniridia of the right eye, left microphthalmia, incomplete fusion of the tip of the mandible, a

distended choledocal cyst, a small accessory spleen, large polycystic kidneys with ureteric insertions on the anterior surface of the kidneys, and a small paraovarian cyst. A midline cleft was noted in the occipital bone and the cerebral sulci and gyri were poorly developed.

CASE 3

This female infant was born in 1977. She was delivered by Caesarian section because of fetal distress following induction of labour with a breech presentation at term. Birth weight was 3.08 kg and the placenta weighed 580 g. The baby lived for five minutes. Abnormalities included an occipital encephalocele, cleft palate, and postaxial polydactyly of all four limbs. At necropsy the liver was described as 'cystic' and the kidneys were noted to be large. Chromosome studies were not performed. This baby was the product of the first pregnancy of healthy unrelated Hindu parents originating from the city of Jamnagar in West Gujarat. The second pregnancy resulted in a spontaneous first trimester miscarriage and the third in a normal male infant.

CASE 4

This male infant was born in 1980. He was delivered by Caesarian section following an antepartum haemorrhage at 33 weeks. Birth weight was 1.74 kg and the placenta weighed 460 g. There were only two vessels in the umbilical cord. The baby lived for two hours. Abnormalities noted at birth included microcephaly, a ruptured occipital encephalocele, arthrogryptic limbs with polydactyly of both hands and the right foot, bilateral talipes equinovarus, and abdominal distension. Chromosome studies showed a normal male karyotype. At necropsy the kidneys were enlarged and polycystic, each weighing 380 g. The brain was noted to be small. This baby was the

FIGURE Post mortem view of case 5.

product of the second pregnancy of healthy unrelated Hindu parents originating from large towns approximately 70 miles apart in West Gujarat. The previous pregnancy had resulted in a normal male infant.

CASE 5

This male infant was born in 1982. He was born at term and lived 20 minutes. Birth weight was 2.72 kg and the placenta weighed 460 g. Abnormalities noted at birth included (figure) a ruptured occipital encephalocele, microcephaly, micrognathia, a widely separated sagittal suture, posterior central cleft palate, arthrogryptic limbs with postaxial hexadactyly of both feet and the left hand, and postaxial

TABLE Documented abnormalities in the five cases.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	F	F	F	M	M
Gestation (wk)	42	32	40	33	40
Birth weight (kg)	3.60	1.63	3.08	1.74	2.72
Survival	<5 min	<5 min	5 min	2 h	20 min
Occipital encephalocele		+	+	+	+
Anencephaly	+				
Ocular abnormalities		+			
Cleft lip/palate	+	+	+		+
Polydactyly					++
R hand		+	+	+	+
L hand	+	++	+	+	+
R foot	+	+	+	+	+
L foot	+	+	+		+
Polycystic kidneys		+	±	+	±
Abnormal genitalia	+				+
Chromosomes	?	N	?	N	N
(N=normal)					

septadactyly of the right hand. Enlarged kidneys could be easily palpated through a lax abdominal wall. The genitalia were ambiguous with absent phallus and empty scrotal sac. Chromosome studies revealed a normal male karyotype. Permission for necropsy was refused. This baby was the second child of healthy unrelated Hindu parents originating from the city of Jamnagar in West Gujarat. The first pregnancy resulted in a healthy male infant.

Three of these four families are of different caste and there is no known interrelationship. All of these mothers have different maiden names. Three of the families came to the United Kingdom via East Africa, two from Uganda and one from Kenya.

The relevant clinical and pathological findings in the five cases are summarised in the table.

Incidence of Meckel's syndrome

During the years 1976 to 1982 inclusive, there was a total of 80 210 live and stillbirths with gestation greater than 28 weeks in Leicestershire. Of these, 9588 were to mothers of Asian origin. It is not known how many of these mothers originated from Gujarat, but it is known that 68% of all Leicester Asians are Gujarati* and there is no reason to believe that the number of Gujarati births will have differed significantly from 68% of 9588 that is, 6520. Thus the incidence of Meckel's syndrome among Gujarati births during that period was approximately 1 in 1304.

Given that this disorder is autosomal recessive and assuming that Hardy-Weinberg equilibrium has been achieved, the gene frequency q equals approximately 0.0277 or 1 in 36. Therefore the frequency of heterozygotes equals approximately 1 in 18.

The standard error of this estimate of q equals

$$\sqrt{\frac{(1-q^2)}{4N}}$$

where N equals the total number of Gujarati births.⁷ Thus the standard error of q equals 0.0062 so that the 95% confidence limits for q equal 0.0277 $\pm$ 0.0122.

Discussion

Of the five cases described in this paper the diagnosis of Meckel's syndrome can be firmly accepted by any criteria in cases 2 and 4. The diagnosis in case 1 can be regarded as highly probable since this baby was a sib of case 2 and

anencephaly has been well documented in this disorder.⁵ In case 5 the withholding of permission for necropsy prevented confirmation that the enlarged palpable kidneys were indeed polycystic, but the clinical features and photographic evidence all indicate that this baby had Meckel's syndrome. The diagnosis in case 3 is less well established with no definite record of polycystic kidneys and no chromosome studies. However, the kidneys were noted to be large and the liver was 'cystic' so that Meckel's syndrome clearly features prominently in the differential diagnosis. Although survival beyond the perinatal period has been recorded in Meckel's syndrome⁸ this is very unusual, so that it is unlikely that any cases have been missed in the population under study.

Information on the incidence of Meckel's syndrome in other populations is scanty but several authors have suggested that the disorder is likely to be much more common than is generally realised. In Finland 28 cases were ascertained 'without active search' and the authors claimed to have knowledge of many other probable cases,⁹ although in retrospect some of these may have had the hydrolethrus syndrome, which is relatively common in Finland.¹⁰ The incidence among Jews in Israel is deemed to be at least 1 in 50 000.¹¹ In Boston eight cases, at least five of which were Caucasian, were identified among 106 000 newborns, giving an incidence of 1 in 13 250,¹² and in Belgium three cases, all Caucasian, were observed among 10 224 births, an incidence of 1 in 3408.¹³ Meckel's syndrome has also been recorded in patients of Pakistani origin¹⁴ and in Arabian¹⁵ and Indian¹⁶ reports.

It is difficult to explain the high incidence of Meckel's syndrome observed in the Leicestershire Asian community. It is very unlikely that a founder effect or inbreeding or both can be implicated, as in the Hutterites,¹⁷ since the families originate from different parts of the Gujarat State, the mothers have different maiden names, consanguinity is denied, and Hindu custom firmly discourages inbreeding. Alternative explanations include a high mutation rate (equal to the incidence of the disorder since the fitness equals zero), heterozygote advantage (equal to approximately 2.85%), or heterogeneity. It is well recognised that there is considerable phenotypic overlap between Meckel's syndrome and other conditions, such as the hydrolethrus and Smith-Lemli-Opitz syndromes,¹⁸ and possible genetic heterogeneity within Meckel's syndrome itself has been considered.¹⁹

The authors would welcome correspondence with regard to whether Meckel's syndrome has been observed in Asian communities in other parts of Britain and elsewhere. In the meantime the import-

*Distribution of Ethnic Minorities in Leicester. Report of the Leicester Council for Community Relations 1978.

ance of recognising this disorder is stressed in view of its associated 25% recurrence risk and the availability of antenatal diagnosis through ultrasonography and alphafetoprotein assay.¹³⁻²⁰

Addendum

Since submitting this paper, the proceedings of the first Meckel Symposium have been published. Evidence presented at this Symposium suggested that the frequency of the Meckel syndrome gene is relatively high among the Tartar population in the Soviet Union,²¹ and that when studied prospectively the incidence of Meckel's syndrome in Finland was approximately 1 in 8500.²² No information was presented concerning the incidence of Meckel's syndrome in the Indian subcontinent.

The authors wish to thank Mrs G Ahmed, Mrs S Kenney, and Miss E Mason for their help with this study. The Leicestershire Perinatal Survey is funded by the Leicestershire Health Authority.

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Correspondence and requests for reprints to Dr I D Young, Department of Child Health, Clinical Sciences Building, PO Box 65, Leicester Royal Infirmary, Leicester LE2 7LX.