Seventeen of the 36 category 1 families (47%) had received formal genetic counselling. Of these, four probands had conditions that can be diagnosed prenatally by established techniques. In two of these families, however, failure to store DNA or a fibroblast cell line made this impossible. The disorders in these two cases were Lowe's syndrome (oculocerebrorenal syndrome) and Hurler's syndrome (mucopolysaccharidosis type 1).

Discussion

The incidence of genetic disease in this study (5.7%) is within the range 3.5–7.1% reported in other studies of paediatric inpatients.^{1,2} Half of the deaths in category 1 were of recessive conditions (two X linked, two autosomal) with risks of recurrence of 25%. The single gene and chromosomal disorders also had a higher readmission rate and longer stay in the intensive care unit. Their prevention thus assumes importance for both affected families and health care planners.

Storage of DNA or cell lines, or both, is recommended for any single gene defect, mapped or unmapped, so that the diagnosis may be confirmed at a molecular level, and to facilitate carrier detection or prenatal diagnostic tests.³ As the importance of storing such samples is easily overlooked during resuscitation and stabilisation of a critically ill child it is vital that within any paediatric intensive care unit there is a protocol for appropriate use of genetic diagnostic services. The clinical geneticist is

best placed to provide the staff with advice about conditions that can be diagnosed and confirmed by genetic testing, and about sampling techniques and appropriate storage.

Although our study showed that single gene disorders accounted for a small but important proportion of the intensive care unit caseload, it is probably an underestimate. For example, in a recent survey of cases of Reye's syndrome, it was found that in 36% the diagnosis was revised to 'inborn errors of metabolism'.⁴ Thus there are almost certainly genetic disorders awaiting delineation that will account for some cases in diagnostic categories such as sudden or 'near-miss' infant death.⁵ In the light of this we recommend that all children and infants with unexplained life threatening illnesses that require intensive care should have urine, serum, and whole blood (EDTA) stored at -70°C . Careful consideration should also be given to obtaining a skin biopsy specimen for fibroblast culture, and storing samples of other tissues (such as muscle and liver) at -70°C .

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Teratogenic effect of carbamazepine

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Abstract

A girl was born to a mother who had undergone treatment for epilepsy with carbamazepine during pregnancy. The infant had dysmorphic features and was physically and mentally retarded. We consider that the malformations were the result of the maternal treatment with carbamazepine.

Antiepileptic drugs taken during pregnancy increase the risk of malformations in the offspring, but the teratogenicity is lower if the mothers are on one drug alone rather than a combination.¹ Carbamazepine is generally considered not to be teratogenic, but recently a pattern of malformations among the offspring of mothers treated with carbamazepine alone has been reported.²

Case report

The mother was 19 years old, para 1, and had

been taking carbamazepine alone for more than two years. She had had no epileptic symptoms for the two years before delivery. The serum carbamazepine concentrations were monitored regularly during the pregnancy and were all in the range 3–8 mg/l (therapeutic range 6–11 mg/l). The daily dose of carbamazepine was increased during the pregnancy from 500 to 1700 mg.

A caesarean section was done during week 38, and a dysmature girl was delivered. The birth weight was 2280 g, length 44 cm, and head circumference 34 cm. The Apgar scores were 8 at 1 minute and 10 at five minutes.

The forehead was prominent, and the ears were large but not malformed. The palpebral fissures slanted downwards. The nasal bridge was flat and the nostrils were anteverted. The philtrum was normal. The palate was arched and the tongue protruded. There was no hypoplasia of finger or toenails, and the hair was normal. Chromosome analysis was normal.

Total skeletal radiography was done when the

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Accepted 27 December 1991
(*Arch Dis Child* 1991;66:641–2)

Figure 1 Frontal view of the girl aged 12 months. The forehead is broad, the nostrils are anteverted, and the nasal bridge is broad. The palpebral fissures slant downwards.

Figure 2 Lateral view of the girl aged 12 months. The forehead is prominent and the ears are set low, but not deformed. The hair is sparse, but otherwise normal.

girl was 1 week old, and no skeletal abnormalities were seen. At 14 months of age a radiograph of the hand was normal, but the bone age was only about 3 months. At 15 months, a computed tomogram of the cerebrum showed a dilated ventricular system.

At follow up at 18 months of age the girl's height and weight were below the 3rd centile, and there was generalised hypotonia and retarded psychomotor development. The dysmorphic facial appearance was still evident (figs 1 and 2). The head circumference was normal. There was no family history of malformations.

Discussion

Until now only a few children with malformations born to mothers being treated with carbamazepine alone have been reported, and descriptions of the malformations are scanty.¹⁻⁶ In a study published in 1981 the head circumferences of 20 offspring of mothers taking carbamazepine alone were on average smaller than those of a control group.³ Among eight other infants of mothers taking carbamazepine alone a few were reported to have reduced head circumference or slight facial dysmorphism, but they were not followed up.⁴

In a multicentre investigation malformations were described in four infants born to mothers taking carbamazepine alone. These malformations were spina bifida, congenital heart disease, diaphragmatic hernia, and digital hypoplasia and hydronephrosis.⁵ In another multicentre investigation a single case with a low birth weight and reduced head circumference was reported, but no details were given.⁶

In 1989 Jones *et al* reported intrauterine weight reduction and craniofacial abnormalities in a retrospective study.² In a prospective investigation of 35 infants of mothers taking carbamazepine alone they found that some of the children had growth retardation, facial abnormalities, developmental delay, or hypoplastic fingernails. In contrast to those of Jones *et al*² and Bertollini *et al*⁵ our case did not have hypoplastic finger nails. In four of 35 cases Jones *et al* found palpebral fissures that slanted upwards. In contrast, our case had palpebral fissures that slanted downwards.

Carbamazepine seems to be associated with different patterns of defects.² In our case we found intrauterine growth retardation and a dysmorphic facial appearance. At follow up at 18 months of age growth retardation and mental retardation was evident. In the study by Jones *et al* developmental delay was found in 20% of the children who underwent formal neurobehavioural assessments.² Until now only a few reports have been published describing malformations in children born to mothers taking carbamazepine alone. This may be because carbamazepine is only slightly teratogenic, or because the problem is unrecognised. The published reports together with our case seem to indicate that carbamazepine alone may have a teratogenic effect, but a possible phenotype of carbamazepine teratogenicity has not yet been identified.

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