Miller-Dieker syndrome with ring chromosome 17

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Abstract
A girl presented at 6 weeks of age with failure to thrive and arching of the back. She had various dysmorphic features, hepatospleno-megaly, and developmental delay. The electroencephalogram and cranial ultrasound were abnormal, and a computed tomogram showed lissencephaly and apparent agenesis of the corpus callosum. Because of frequent aspiration she became oxygen dependent. She later developed intractable convulsions and died at the age of 9 months.

Miller described two and Dieker et al described four infants all of whom had microcephaly, developmental delay, hypotonia, opisthotonos, micrognathia, ear anomalies, and lissencephaly. Other non-consistent features included seizures, bitemporal grooving of a high forehead, antverted nares, cardiac defects, and undescended testes. The eponym Miller-Dieker syndrome was proposed by Jones et al. Dobyns et al described three patients and reviewed five additional patients from the literature, all of whom had Miller-Dieker syndrome and an abnormality of 17p. They proposed that monosomy of distal 17p may be the cause of Miller-Dieker syndrome in some patients. Ono et al were the first to describe a child with a ring chromosome 17. Four further cases with ring chromosome 17 have since been reported, and two of them had features in common with Miller-Dieker syndrome including lissencephaly.

We describe another infant who had features of both Miller-Dieker syndrome and ring chromosome 17 phenotype.

Case report
A girl, the second child of healthy unrelated parents, was born at full term at home by normal vaginal delivery. She had been found to be small for dates on ultrasound scan at 17 weeks and this was confirmed on a further scan at 39 weeks. Her birth weight was 2270 g. There were no neonatal problems and she was totally breast fed.

At 6 weeks of age she was referred to hospital because of failure to gain weight and attacks of arching her back and screaming, mostly during feeds. Examination showed a dysmorphic child (fig 1) whose weight, length, and head circumference were below the 3rd centile for age. Her eyes were widely set and the palpebral fissures slanted downwards. Her ears were rotated posteriorly, the nasal bridge was low, the nose was small with anteverted nostrils, and the jaw was also small. She had clinodactyly and abnormal palmar creases but her dermatoglyphics were normal. Her spleen was 2.5 cm below the costal margin and her liver was palpable 2 cm below the costal margin. She was generally hypotonic, she arched her back periodically, and she did not seem to follow light or objects although her corneas were clear.

Cranial ultrasonography showed bilateral dilatation of the posterior horns of the lateral ventricles. A computed tomogram showed lissencephaly and apparent agenesis of the corpus callosum (fig 2). An electroencephalogram showed pronounced abnormalities with runs of large amplitude rhythmic slow and intermediate slow activities, particularly in the anterior regions. There were no clear focal signs or paroxysmal features. Contrast radiographic examination with propylene showed gross nasal escape and aspiration on swallowing, indicating pharyngeal incoordination. She continued to feed well by bottle, albeit with frequent attacks of aspiration, until she was 16 weeks old and then required nasogastric feeding. She had difficulty in swallowing her saliva and required frequent suction of her oropharynx. Secondary to frequent aspiration she developed chronic lung disease and was oxygen dependent from the age of 25 weeks. She continued to gain weight and at 8 months of
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The karyotypes of both parents were normal.

Discussion

Stratton et al reviewed the cytogenetics of the 11 reports of Miller-Dieker syndrome: nine showed monosomy for the terminal region of 17p down to band p13.3 No deletion was present in one (case 2 reported by Dobyns et al4), and in another family (Norman et al5) where parental chromosomes were normal, the affected subjects did not have the typical Miller-Dieker syndrome facies.9 To the above nine cases can be added the 12 year old boy with typical facies and terminal 17p deletion reported recently by Selypes and Laszlo.11 In this case lissencephaly was also shown on the computed tomogram. Stratton et al concluded from the extent of the various deletions for 17p that the critical region for Miller-Dieker syndrome is the sub band p13-3.3 More recently, application of DNA probes has provided substantial evidence to support this. Schwartz et al, and Van Tuinen et al, have shown that there are submicroscopic deletions of this sub band in patients with Miller-Dieker syndrome who were previously thought to have had normal chromosomes.12 13

There are to our knowledge five previous reports of liveborn patients with non-mosaic ring chromosome 17.4 8 The 20 week fetus with r(17) described by Weinberg et al and the 4 year old girl with mental retardation and growth failure found to be a mosaic 46XX/46XX, r(17) by Petit and Koulischer are excluded from this discussion.14 15 In addition, the report by Burdea et al (who described a father and son with apparent ring chromosome 17, the son being microcephalic and with mental retardation) will not be considered here as the identity of the chromosome was not confirmed by banding.16

These five patients had enough clinical abnormalities in common for a 'ring 17 chromo-

Figure 2 Computed tomogram showing a smooth cortex with absence of normal gyral pattern (lissencephaly). The lateral ventricles are totally separated with the third ventricle reaching up between them suggesting agenesis or hypoplasia of the corpus callosum.
some syndrome to be proposed by Carpenter et al.7 The most common features are mental and motor retardation, growth retardation, microcephaly, flattened nasal bridge, antverted nostrils, epicanthus, clinodactyly, hypotonia, seizures, cafe au lait spots, and a transverse palmar crease. The patients of Dobyns et al and Chudley et al with ring 17 reinforced this impression with further evidence that loss of material from chromosome 17 was the cause of this clinical appearance. 8-10 Two of the cases also had lissencephaly, but only one had a defective corpus callosum. 9, 10 The break points in their ring chromosomes must therefore render them monosomic for the critical region distal to 17p12. The patients of Ono et al, Qazi et al, and Chudley et al had neither lissencephaly nor a typical Miller-Dieker syndrome phenotype suggesting that the short arm region including 17p13 was almost entirely preserved in them.5, 6, 8 A comparison of the clinical features of ring 17 phenotype and Miller-Dieker syndrome is shown in table 1, together with the clinical details of the present case.

Our patient exhibited features of both ring chromosome 17 (psychomotor and growth retardation, microcephaly, flat nasal bridge, antverted nares, fits and cafe au lait patches), and of Miller-Dieker syndrome (lissencephaly, antenatal and postnatal growth retardation, bitemporal hollowing, antverted nares, long philtrum, thin upper lip, micrognathia, fits, and developmental delay). Chromosome analysis confirmed the presence of r(17) with breakpoints indicating that she was monosomic for the Miller-Dieker syndrome critical region 17p13-3. She also had hypoplasia of the corpus callosum similar to cases 1 and 3 reported by Dobyns et al.4 The agenesis of the corpus callosum has been reported in a girl with partial deletion of distal 17q.17 Our patient and case 1 of Dobyns et al were also monosomic for distal 17q but case 3 of Dobyns et al with r(7;17) translocation was not, as the q arm was not affected.10 It is unlikely therefore that monosomy 17q is the only determining factor for this congenital malformation of the brain. Our patient had nodular heterotopia within the white matter and bilateral olivary heterotopia of the medulla, as previously reported.1, 4, 10

In conclusion, we have presented a case in which the features of Miller-Dieker syndrome and r(17) were present. As far as we know it is the first case reported from the United Kingdom.

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