Miller-Dieker syndrome resulting from rearrangement of a familial chromosome 17 inversion detected by fluorescence in situ hybridisation

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Abstract
We report a case of Miller-Dieker syndrome (MDS) owing to an unbalanced rearrangement of a familial pericentric inversion of chromosome 17 (inv(17)(p13.3q25.1)). In addition to lissencephaly and the facial features of MDS, the affected child had other congenital malformations consistent with distal 17q duplication. Initial cytogenetic analysis failed to show any abnormality and fluorescence in situ hybridisation (FISH) studies confirmed the 17p deletion in the proband and identified the chromosome 17 inversion in his mother. FISH studies were performed in other relatives and enabled first trimester prenatal diagnosis by chorionic villus sampling in a subsequent pregnancy of the proband’s mother. These findings underline the value of FISH in the investigation of MDS families.

Key words: Miller-Dieker syndrome; fluorescence in situ hybridisation; chromosome 17 inversion.

Lissencephaly is a severe brain malformation characterised by a smooth cerebral surface (agyria-pachygyria) and abnormal neuronal migration resulting in profound mental retardation, seizures, and other neurological abnormalities.1 Classical type I lissencephaly may occur as an isolated abnormality or in association with dysmorphic features in Miller-Dieker syndrome (MDS).2 3 The characteristic craniofacial appearance in MDS consists of bitemporal hollowing, prominent forehead and furrowed brow, short nose with anteverted nares, prominent upper lip, and small jaw.4 5 Cardiac defects and other malformations may also be present. Deletions of chromosome 17p13.3 can be shown in the majority of MDS patients. About 50% of cases have a visible deletion detected by high resolution cytogenetic analysis.6 The remainder can be detected by molecular methods such as RFLP analysis or somatic cell hybrid analysis7 8 and more recently by fluorescence in situ hybridisation (FISH).9 10 A gene containing G protein β subunit-like repeats designated lissencephaly-1 (LIS-1) has been identified in this region, and non-overlapping deletions affecting either the 5' or 3' end of the gene found in two patients with MDS identify LIS-1 as a candidate for the disease gene.11 Deletions including LIS-1 have been reported in 92% of Miller-Dieker probands and 38% of classical ILS cases.12 Homology between the sequence of the 45K subunit of platelet activating factor (PAF) acetylhydrolase present in bovine cerebral cortex and the protein encoded by the LIS-1 gene has been reported.13

Many cases of MDS are sporadic, but familial cases are well documented, including the families originally described by Miller2 and Dieker et al.1 Dysmorphic features of multiple rhizomelic shortening of the limbs, short digits, proximally placed thumbs, partial syndactyly of the toes bilaterally, cleft of the soft palate, glandular hypoplasias, bilateralelated defects, and sacral tail. Dysmorphic craniofacial features included prominent forehead, large anterior fontanelle, three hair whorls on the crown, a short neck with a low posterior hairline and redundant skin, short and unusually shaped palpebral fissures, small ears, and small jaw (fig 2). Postnatally the proband developed laryngeal stridor and growth parameters for length, weight, and OFC followed the 3rd, 3rd, and 10th centiles respectively. Convulsions started at the age of 6 months, at which time the EEG showed clusters of raised voltage high frequency rhythms, raising the possibility of lissencephaly. Very high amplitude activity increasing in frequency from theta through alpha to beta activity has been described in lissencephaly.14

Case report (fig 1)
The proband IV-2 was born at term following a pregnancy complicated by intrauterine growth retardation and polyhydramnios from 20 weeks’ gestation. Prenatal ultrasonography indicated short limbs and a cystic mass in the right hypochondrium, thought to be a dilated gall bladder. Chromosome analysis of cultured amniocytes showed an apparently normal male karyotype.

At delivery the birth weight was 2300 g and multiple congenital anomalies were detected consisting of rhizomelic shortening of the limbs, short digits, proximally placed thumbs, partial syndactyly of the toes bilaterally, cleft of the soft palate, glandular hypoplasias, bilateral undescended testes, and sacral tail. Dysmorphologic craniofacial features included prominent forehead, large anterior fontanelle, three hair whorls on the crown, a short neck with a low posterior hairline and redundant skin, short and unusually shaped palpebral fissures, small ears, and small jaw (fig 2). Postnatally the proband developed laryngeal stridor and growth parameters for length, weight, and OFC followed the 3rd, 3rd, and 10th centiles respectively. Convulsions started at the age of 6 months, at which time the EEG showed clusters of raised voltage high frequency rhythms, raising the possibility of lissencephaly. Very high amplitude activity increasing in frequency from theta through alpha to beta activity has been described in lissencephaly.15

CT brain scan
Figure 1 Pedigree of the family indicating several cases of fetal death in utero (FDIU), stillbirth (SB), and neonatal death (NND). For further details see family report.

Figure 2 The proband aged 4 months.

respective an infant death owing to hydrocephalus and a neonatal death of unknown cause. No further information was available for these four latter cases.

Family history
There were several cases of intrauterine death, stillbirth, or neonatal death in the extended family. The first pregnancy of the proband's mother (II-1) had resulted in a fetal death in utero at 22 weeks’ gestation. No obvious external abnormalities were documented in the macerated male fetus. The proband’s grandmother (II-1) had an unexplained male stillbirth and a fetal death in utero in late pregnancy. Two other maternal relatives had

The proband's karyotype can thus be designated 46,XX,inv(17)(p13.3q25.1)mat. FISH studies performed in six other relatives identified the presence of the pericentric inversion only in the proband's grandmother. It is possible that II-2 also carried the mutation and III-5 who declined testing remains at risk.

First trimester chorionic villus sampling was performed during the third pregnancy of the proband’s mother. Chromosome analysis showed an apparently normal 46,XX karyotype, but FISH analysis on both direct and cultured villus preparations identified the presence of a balanced pericentric inversion of chromosome 17. Second trimester ultrasoundography showed no fetal abnormalities and a healthy female infant has subsequently been born. Presence of the balanced pericentric inversion was confirmed postnatally by FISH analysis.
Miller-Dieker syndrome

Discussion

Structural chromosome abnormalities resulting in Miller-Dieker syndrome include sporadic terminal deletions and ring chromosome 17,\(^1\) as well as a variety of unbalanced products of reciprocal translocations.\(^2\) Variation in phenotype in the latter group may be attributed to the presence of different duplicated segments in addition to the 17p monosomy. One other family with Miller-Dieker syndrome owing to rearrangement of a pericentric inversion of chromosome 17 has been reported,\(^3\) although this involved a larger unbalanced segment that could be identified by chromosome banding analysis. Additional features representing distal 17q duplication\(^4\) were present in the affected offspring. In our case additional features consisted of frontal bossing, broad midface, narrow palpebral fissures, cleft palate, multiple abnormal hair whorls, short neck, short proximal limbs, short digits, 2–3 syndactyly of the toes, sacral tail, hypoplasia, and bilateral undescended testes. There was no polyactyly, congenital heart disease, or evidence of renal anomalies. The rudimentary tail present in our case and those of Greenberg et al.\(^\text{5,6}\) has also been observed in another MDS patient,\(^\text{21}\) but not in cases with duplication of 17q. Caine et al.\(^\text{7}\) described calcified gallstones as a previously unreported feature of 17q duplication and it is interesting that our case had a cystic mass in the right hypochondrium detected by prenatal ultrasonography thought to represent a dilated gall bladder.

FISH analysis is a valuable tool in the clarification of subtle reciprocal rearrangements\(^\text{22,23}\) and has been used to identify cryptic and half cryptic translocations in several cases of Miller-Dieker syndrome.\(^\text{9,24}\) The study of Kuwano et al.\(^\text{25}\) included a half cryptic 3q;17p and a full cryptic 8q;17p translocation. The case of Alvarado et al.\(^\text{26}\) represented a full cryptic 17p;19q translocation, while those of Kohler et al.\(^\text{27}\) and Breevic et al.\(^\text{28}\) both represented half cryptic 9p;17p translocations. In our case initial conventional cytogenetic analysis did not identify any chromosome 17 abnormality in the proband or his mother, even though the family history was highly suggestive of a familial chromosome rearrangement and the presence of an abnormality was suspected. Definitive diagnosis of Miller-Dieker syndrome was made by FISH analysis which showed a 17p deletion in the proband. A pericentric inversion of chromosome 17 was detected in the proband’s mother and grandmother. FISH analysis was offered to other relatives at risk, and enabled first trimester prenatal diagnosis in a subsequent pregnancy of the proband’s mother. A fetus with the balanced pericentric inversion was detected, and a healthy infant has subsequently been born.

It is clearly important to distinguish between sporadic 17p deletions and those resulting from cryptic familial rearrangements which have a high recurrence risk in order to provide accurate genetic counselling. In our case the availability of a definitive first trimester prenatal diagnosis was an important factor in the couple’s decision to embark upon a further pregnancy. The value of FISH for diagnosis, investigation of relatives, and prenatal diagnosis in this family supports the recommendation of Kuwano et al.\(^\text{25}\) that FISH analysis should be performed in all parents of children with MDS resulting from submicroscopic deletions to detect subtle rearrangements associated with a high recurrence risk.

A permanent cell line of one of the balanced inversion carriers is available at St Mary’s Hospital, Manchester via Dr H Kingston.


