Miller-Dieker Syndrome

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Abstract
Miller-Dieker Syndrome (MDS) is a contiguous gene deletion syndrome of chromosome 17p13.3, characterised by classical lissencephaly (aka lissencephaly type 1) and distinct facial features. Additional congenital malformations can be part of the condition. Children with MDS present with severe developmental delay usually have epilepsy and feeding problems are common. The lissencephaly represents the severe end of the spectrum with generalized agyria, or agyria and some frontal pachygyria. Visible and submicroscopic deletions of 17p13.3 including the LIS1 gene are found in almost 100% of patients.

Keywords
Miller-Dieker Syndrome, classical lissencephaly, lissencephaly type 1, *LIS1* gene, microdeletion, chromosome 17

Definition
Miller-Dieker Syndrome (MDS) is a contiguous gene deletion syndrome of chromosome 17p13.3, characterised by classical lissencephaly (aka lissencephaly type 1) and distinct facial features. Additional congenital malformations can be part of the condition.

Differential diagnosis
The main differential diagnosis is isolated lissencephaly sequence (ILS), also characterised by classical lissencephaly. However additional dysmorphic facial features or anomalies are mild to absent. ILS can be associated with mutations in both the *LIS1* gene (chr. 17p13.3) and *DCX* gene (encoding doublecortin, chr. Xq22.3). MDS is solely due to monosomy of 17p13.3, involving the *LIS1* gene.
Additional features, not typical of MDS, can be related to an unbalanced chromosomal translocation with monosomy 17p, and trisomy of another chromosomal area (see below).

Frequency
MDS is undoubtedly a rare condition. The only published (1991) data on the prevalence of classical lissencephaly (lissencephaly type 1) comes from a Dutch study, reporting 11.7 per million live births. The more widespread use of MRI and increasing recognition of this neuronal migration disorder suggest, that the incidence and prevalence are probably higher. In the author's experience about 25 – 30% of patients with classical lissencephaly have MDS.

Clinical features
Pregnancy can be associated with a history of polyhydramnios, intrauterine growth retardation, and reduced fetal movements. Children with MDS present with severe developmental delay. They do not learn to sit independently or walk,

and their development remains at the 3 – 6 month level. Generalised hypotonia is a prominent feature early in life, with increasing spasticity as the patients get older. Epilepsy can be present at birth, and usually presents within the first 6 months of life, often as infantile spasms. Feeding and swallowing problems are common, and can be complicated by aspiration pneumonia. The head circumference is small to normal at birth, but older patients are usually microcephalic. Typical facial features seen in MDS include a high forehead, most noticeable in early infancy and childhood, bitemporal hollowing, vertical furrowing of the forehead when crying, flattened ear helices, mild hypertelorism, epicanthic folds, a short nose with a depressed nasal root and anteverted nares, prominent lateral nasal folds, a round philtrum and upper lip with a thin, downward facing vermillion border, a flat midface, and a small chin. Additional features include a sacral dimple, cryptorchidism in males, cardiac anomalies and omphaloceles. Structural renal anomalies, contractures, and clinodactyly have also been reported.

Classical lissencephaly at the severe end of the spectrum is seen on cerebral imaging, with generalised agyria (LIS grade 1) or agyria with some frontal pachygyria (LIS grade 2). The cortex is thick; well above the normal 3mm. Additional features include posterior enlargement of the lateral ventricles (colpocephaly), and hypoplasia of the corpus callosum. Midline calcifications in the area of the 3rd ventricle have been described. The failure of the opercula to fold over the insula results in the "figure of eight" appearance seen on imaging. The posterior fossa structures usually look normal.

Management

Management of children with MDS is symptomatic. To avoid the complications of feeding and swallowing problems (poor nutritional state, aspiration pneumonia), nasogastric tubes and gastrostomies (more long-term solution) can be utilised. Seizure control is important. Previously, death was usually expected to occur within the first few years of life. However with improved seizure management, and use of gastrostomies to treat feeding problems, children with MDS now often have a longer survival. A small minority of patients with MDS, who have lived into their early teens, are known to the author.

Etiology

MDS is a chromosomal deletion syndrome on chromosome 17p13.3, and this was first recognised in 1983. Prior to this MDS was considered to be an autosomal recessive condition, as familial recurrences had been reported. However these families were subsequently found to have chromosomal rearrangements, predisposing balanced carriers to have offspring with monosomy of 17p13.3.

Almost 100% of patients with the diagnosis of MDS have a deletion of 17p13.3. About 50% have a microscopically visible deletion, and the remainder has a submicroscopic deletion. In about 12% of patients the deletion is the result of a familial chromosomal rearrangement. The author is not aware of germline mosaicism having been reported to date, and the empiric recurrence risk for sporadic deletions is very low (well below 1%).

In patients with MDS the 17p13.3 deletions are generally larger than those seen in patients with ILS and deletions in the same area. A recent study narrowed the critical region that differentiates MDS from ILS down to 400kb. Patients with MDS tend to have classical lissencephaly at the most severe end of the spectrum, which is not normally seen in patients with ILS, although deletions or mutations of the *LIS1* gene are responsible for the lissencephaly in both cases. Deletion of two additional genes, *CRK* and *14-3-3ε*, telomeric to *LIS1* was found to be associated with the most severe lissencephaly grade. Creation of a recent mouse model suggests a role for *14-3-3ε*.
in cortical development, and deletion of this gene as well as *LIS1* could explain the more severe lissencephaly phenotype of MDS compared to that of ILS.

Genetic counselling

The recurrence risk for MDS is very low, as the chromosomal deletion is usually a de novo event. However if it is associated with a familial reciprocal translocation, the recurrence risk for an abnormal live born can be as high as 33%. There appears to be a higher incidence of monosomy 17p and MDS than trisomy 17p, which has a milder phenotype.

Antenatal diagnosis

Prenatal diagnosis is available and consists of fetal chromosomes analysis by karyotyping or FISH, on chorion villus sampling or amniocentesis. Classical lissencephaly can usually only be recognised on imaging after 28

weeks of pregnancy, as cerebral gyri are not fully developed prior to this gestation.

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