Syndrome of the month

Syndromes with lissencephaly

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Earl Walker's paper in 1942 represents a detailed review of early described cases of lissencephaly and states that Owen (*On the anatomy of vertebrates*, vol 3, London: Longmans, Green & Co, 1868) is said to have introduced the term lissencephaly to describe an agyric brain, from the Greek words "lissos" (smooth) and "encephalus" (brain).¹

Further reports of lissencephaly followed by Miller,² Dieker *et al*,³ Warburg,^{4,5} and others and their contributions are recognised in syndromes now known as Miller-Dieker syndrome and Walker-Warburg syndrome.

In his detailed analysis in 1984/85, Dobyns categorised lissencephaly into different patho-

logical types, assigned these to previously described cases or syndromes, and discussed possible genetic mechanisms.^{6,7} The two main pathological types he described provide a useful basis on which to review "syndromes with lissencephaly".

Key word: lissencephaly.

Type I or classical lissencephaly

PREVALENCE

The only epidemiological data on the prevalence of type I lissencephaly come from The Netherlands, with 11.7 per million births.⁸

PATHOLOGY AND NEUROIMAGING

Type I lissencephaly results from a neuro-migrational arrest between 12 and 16 weeks' gestation, and histologically the cortex has four instead of six layers. These consist of a marginal, superficial cellular, cell sparse, and deep cellular layer.⁹ The cell sparse layer can appear as a hypodense area on computerised tomography (CT) or hyperintensity on T2 weighted magnetic resonance (MR) images, especially in the perisylvian region.¹⁰

Macroscopic abnormalities which can also be seen on neuroimaging include: agyria, mixed agyria/pachygyria or complete pachygyria, a thick cerebral cortex, incomplete opercularisation resulting in a shallow sylvian fissure and the typical "figure of eight" appearance of the brain, hypoplastic corpus callosum, persistent septum cavum pellucidum, dilatation of the posterior horns of the lateral ventricles, also known as "colpocephaly", probably because of incomplete development of the adjacent structures such as the calcarine gyri and the hippocampi, and heterotopias. Midline calcification not associated with infection can be observed in some cases and importantly the cerebellum usually appears normal (fig 1).¹¹⁻¹³

SYNDROMES

Miller-Dieker syndrome (MDS)

In patients with MDS the cerebral cortex is usually predominantly agyric with few areas of pachygyria. Perinatal problems include polyhydramnios and a low birth weight. Feeding problems and recurrent chest infections are common. Patients are generally hypotonic, although hypertonia, particularly of the limbs, can ensue. They are profoundly retarded and develop seizures in the first few months of life, which can be difficult to control.¹²

Figure 1 Classical lissencephaly (MRI scan). (Above) Axial T1 weighted SLE spin echo MR images showing agyria of the frontal and temporal lobes and pachygyria in the occipital lobes. Note shallow sylvian fissures, mild colpocephaly (short arrows), and prominent cavum vellum interposition (long arrow). (Below) Coronal T1 weighted spin echo image, showing some temporal pachygyria. Note thick cortex.

Figure 2 Characteristic face of Miller-Dieker syndrome. Note the high forehead, bitemporal hollowing, flat nasal bridge, anteverted nares, and small jaw.

Figure 3 Isolated lissencephaly sequence. Facial features relatively unremarkable. Note the short nose seen in some patients with ILS.

Figure 4 Isolated lissencephaly sequence. Facial features relatively unremarkable. Note the thin upper lip seen in some patients with ILS.

A study in 1991 from The Netherlands on type I lissencephaly showed a five year survival of 54% in those patients with complete or nearly complete agyria, which would include MDS.⁸ However, improved seizure control and the increased use of gastrostomies and thus a decrease in aspiration pneumonias will influence the survival figures.

Dysmorphic features include microcephaly, bitemporal hollowing, a high forehead, vertical furrowing which is said to be typical but is only seen in 50% of cases, epicanthic folds, a short nose with anteverted nares, dysplastic ears, thin upper lip, and small jaw. Other abnormalities

include sacral dimples, occasional cardiac defects, joint contractures, and abnormal genitalia in males (mainly cryptorchidism)¹² (fig 2).

Isolated lissencephaly sequence (ILS)

Patients with ILS usually have a mixture of agyria and pachygyria or predominantly pachygyria. In these patients the study from The Netherlands reported a five year survival of 91%.⁸

Perinatal problems are uncommon and the patients mostly present when they develop seizures; some present with developmental delay. Otherwise the clinical picture is similar to that in MDS, although patients with ILS are more likely to show some minor developmental achievements. Any progress is also influenced by the ability to control their seizures.

Patients are microcephalic and dysmorphic facial features are uncommon. Changes such as bitemporal hollowing and a small jaw can be explained by the underlying cerebral anomaly. Several patients also have a short nose and a thin upper lip. Cryptorchidism in males is common¹³ (personal observations) (figs 3 and 4).

GENETICS

In 1983 Dobyns *et al*¹⁴ first reported an association between MDS and a deletion of 17p13.3 in two families and in 1991 deletions in this area were also reported in ILS.¹⁵ In 1993 Reiner *et al*¹⁶ reported the cloning of a candidate gene they called "LIS1" (lissencephaly 1) involved in non-overlapping deletions in two MDS patients. Homology between the sequence of the 45K subunit of the platelet activating factor acetylhydrolase (PAFAH-45K) present in the bovine cerebral cortex and the protein encoded by this gene was reported.¹⁷ Subsequently it was shown that one of the cDNA clones used in the study is a chimera of partial sequences from PAFAH-45K and a 14-3-3 protein located more distally on 17p13.3 and that the PAFAH-45K gene is not the primary cause of type I lissencephaly. Further studies located the ILS critical region distal to PAFAH-45K and deletions of this region are seen in both ILS and MDS, with distal breakpoints being more telomeric in MDS. This provides further evidence for MDS being a contiguous gene syndrome explaining the additional facial dysmorphisms seen in this condition compared to ILS.¹⁸

INVESTIGATIONS AND COUNSELLING

Microscopic deletions of 17p13.3 have been reported in about 50% of patients with MDS, 12% as a result of familial rearrangements.¹²

Using fluorescent in situ hybridisation (FISH) studies, deletions were found in 92%.¹⁹

In patients with ILS, chromosome analysis did not show any deletions of 17p13.3 in a series reported by Dobyns *et al*¹³ or in our own series.²⁰ However, submicroscopic deletions using FISH have been found in increasing numbers. Our study indicated that the probe at present commercially available will show

Figure 5 Cobblestone lissencephaly (US scan). Coronal ultrasound section. Falx (small arrows), lateral ventricle (LV), cisterna magna (CM). Smooth agyric cortex (medium arrows), hypoplastic cerebellum (large arrow). Hypoplastic inferior vermis seen on sagittal sections.

Figure 6 Cobblestone lissencephaly (CT scan). Axial CT section. Severe hydrocephalus, absent septum pellucidum. Note agyric cortex (arrows) not as well visualised owing to the beam hardening/misregistration effects of the adjacent skull.

deletions in about 18% of patients with ILS.²⁰ Using additional probes and slightly revised phenotypic criteria (that is, exclusion of patients with severe congenital microcephaly) (W B Dobyns, personal communication) deletions were shown in 44% of patients with ILS.¹⁹

In patients with a deletion of 17p13.3 the recurrence to sibs will be low and prenatal diagnosis can be offered. FISH should also be undertaken on the parents in cases with submicroscopic deletions to exclude subtle rearrangements. In ILS cases where a deletion has not been shown with currently available probes the recurrence risk is about 5%.²¹

Prenatal ultrasonographic diagnosis of lissencephaly has been reported in a few cases of MDS,^{22,23} but the absence of gyral formation is unlikely to become apparent before the third trimester. Additional features like colpocephaly

may be more helpful indicators. Overall ultrasonography is not a reliable method to detect type I lissencephaly in early pregnancy.

Cases of type I lissencephaly with autosomal recessive inheritance have been observed.^{9,21} Norman *et al*²⁴ reported a patient born to consanguineous parents with two further apparently similarly affected sibs. The patient had classical lissencephaly, marked microcephaly, a low sloping forehead, and a prominent nasal bridge. Although this has been discussed as a specific syndrome and named Norman-Roberts syndrome,⁶ further convincing reports have failed to follow and now the distinction from ILS is unclear.^{9,21} At present a 25% recurrence risk should be considered in those patients with type I lissencephaly and severe congenital microcephaly in whom a deletion on 17p13.3 is not detected.

Classical lissencephaly and X linked inheritance will be discussed later.

Type II or cobblestone lissencephaly

PREVALENCE

There is no reliable prevalence data available on type II lissencephaly. It is most commonly seen in the United Kingdom as Walker-Warburg syndrome (personal observations).

PATHOLOGY AND NEUROIMAGING

Histologically, type II lissencephaly is characterised by a severely disorganised unlayered cortex with extensive neuronal and glial ectopia in the leptomeninges. These changes are seen in the cerebellum as well as the cerebrum, although to a slightly lesser degree. Macroscopically, the surface of the brain is predominantly agyric with a somewhat verrucous appearance, hence the name "cobblestone lissencephaly". In addition, areas of pachygyria and polymicrogyria are seen. The cortex is thickened, but to a lesser extent than in type I lissencephaly. The meninges are also thickened and adherent to the cortex, resulting in obliteration of the subarachnoid space and consequently hydrocephalus. Fusion of the cerebral hemispheres is also observed. The septum pellucidum and corpus callosum are hypoplastic or absent. Myelination is poor. The cerebellum is often small and the vermis hypoplastic. Other abnormalities include Dandy-Walker malformation and occipital cephaloceles^{7,11,25} (figs 5 and 6). The extent of the cerebral and cerebellar abnormalities is variable in the syndromes described below.

SYNDROMES

Essentially three syndromes have been outlined in association with type II lissencephaly: Walker-Warburg syndrome, Muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy, eye abnormalities and muscular dystrophy being the other consistent features. Muscle-eye-brain disease (MEB) has mainly been reported in the Finnish population and Fukuyama congenital muscular dystrophy (FCMD) has predominantly been seen in the

Japanese population. Walker–Warburg syndrome (WWS) and MEB differ mainly in the severity of the manifestations, these being milder in MEB, and it is suggested that they may be allelic.^{21 26 27}

Type II lissencephaly has also been seen without ocular changes or muscular dystrophy²¹ (personal observation).

Walker–Warburg syndrome

In 1989 Dobyns *et al*²⁸ published an extensive review of patients with Walker–Warburg syndrome. They all had type II lissencephaly, with hydrocephalus, cerebellar malformation, and vermian hypoplasia being the other consistent features. Eye abnormalities included retinal dysplasia, microphthalmia, colobomata, and anterior chamber abnormalities (cataracts, corneal clouding commonly secondary to a Peter anomaly, and glaucoma). Congenital muscular dystrophy was seen in all patients with a raised CK, abnormalities on EMG, and pathological changes on muscle histology.

Other abnormalities consisted of cleft lip and palate, genital anomalies in males (small penis, cryptorchidism), and occasionally congenital contractures.

Congenital macrocephaly was common and congenital microcephaly was observed particularly in patients with a posterior cephalocele, leading the authors to postulate that the cephalocele might have a “decompressive” effect. Postnatally, microcephaly was also observed after the insertion of a shunt.

Pregnancy was commonly complicated by polyhydramnios and resuscitation was often required at birth. The median survival was 9 months. All patients were profoundly retarded although some of those who survived beyond the first year showed some minor developmental achievements.

Muscle-eye-brain disease

In 1989 Santavuori *et al*²⁹ published a series of 19 patients with MEB and recently reviewed their findings in 20 patients at a workshop on congenital muscular dystrophy.³⁰

Cerebral and cerebellar malformations were consistent with type II lissencephaly, but often less severe than those seen in WWS. Hydrocephalus was present in 15 out of 20 cases. Eye abnormalities consisted predominantly of severe myopia, although glaucoma, retinal dystrophy, and cataracts were also seen. Very high visual evoked potentials were common. Congenital muscular dystrophy was a consistent feature with CK levels raised 3 to 20 times the norm, although normal in some cases in the first year of life.

Pregnancy was usually uncomplicated with infants presenting with hypotonia and feeding difficulties neonatally or in the first few months of life. All cases were mentally retarded, usually severely; however, a few did learn to walk and 50% developed some speech. Seizures were common. Survival was significantly longer than in WWS. Some of the patients seen were over 40 years of age.

Fukuyama congenital muscular dystrophy

In 1981 Fukuyama *et al*³¹ published a detailed review of patients with congenital progressive muscular dystrophy of the Fukuyama type, also known as FCMD, and in 1994 Yoshioka and Kuroki³² reviewed the findings in 48 patients.

Cobblestone lissencephaly was present in these patients. The cerebral surface showed pachygyria and polymicrogyria. Features further included mild to moderate ventriculomegaly, white matter abnormalities, and polymicrogyria of the cerebellum.

Eye abnormalities mainly consisted of myopia, although some patients had optic atrophy.

All patients had muscular dystrophy. CK levels ranged from 10 to 50 times normal with declining levels after the age of 6 years.

A higher rate of threatened miscarriages during pregnancy and postmature deliveries were reported. Hypotonia and marked mental retardation were predominant features, although some learned to walk and had meaningful speech development. Seizures were common with a much higher incidence of febrile convulsions than seen in the general population. In a recent review of 83 cases, Fukuyama reported an average survival of 18 years.³⁰

GENETICS

All three syndromes are considered to be autosomal recessive with reports of more than one affected offspring of consanguineous parents.^{28 29 33} FCMD has recently been linked to 9q31–33.³⁴ Subsequently the same group found linkage to this locus in a family of affected male sibs defined as either having FCMD or WWS.³⁵ Other groups have not found linkage of WWS or MEB to 9q31–33.²¹

A few cases of prenatal ultrasound diagnosis have been reported.^{36 37} Features, such as hydrocephalus, encephaloceles, and microphthalmia, can be detected in the second trimester and ultrasound scanning during pregnancy can be a useful diagnostic tool, especially in those families with a previously affected child.

Other syndromes with defective neuronal migration

More than 25 syndromes with lissencephaly and other disorders of neuronal migration have been delineated.²¹ Of particular interest are some recent reports of apparent X linked inheritance, which provide evidence of one or more loci on the X chromosome involved in neuronal migration, and they will therefore be briefly reviewed as part of this article.

In his review of isolated lissencephaly in 1992, Dobyns *et al*¹³ reported a patient with classical lissencephaly and an apparently balanced X;2 translocation with breakpoints at Xq22 and 2p25.

In 1994 Pinard *et al*³⁸ described two very interesting families, where the probands, both boys, had lissencephaly, one with predominant agyria and one with agyria and pachygyria and radiological appearances consistent with type I lissencephaly. Neither had a deletion of 17p13.3 on high resolution banding. One of

the mothers had a history of epilepsy, the other of poor school performance. Both had subcortical laminar heterotopias on MR imaging. One of the probands had two maternal half sisters who both had a history of epilepsy and educational difficulties. MR imaging showed subcortical laminar heterotopias, similar to those seen in their mother. The authors suggested X linked dominant inheritance in both families, with the females being less severely affected than the males.³⁸

In 1992 Zollino *et al*³⁹ reported three males and a female (first cousins) with mental retardation born to three healthy sisters. Additional features variably included characteristic facies, congenital hypotonia, microcephaly, talipes equinovarus, and hypogenitalism. In the female the developmental difficulties were less marked than in the males, and both she and one of the males had normal MRI scans. The two other males had pachygyria. Again it was postulated that this was an X linked dominant mental retardation syndrome.

Finally there is a report by Berry-Kravis and Israel⁴⁰ of a family with five affected males in two generations. Problems included psychomotor retardation, seizures, micrognathia, and micropenis. Imaging studies were available on two of the patients and showed predominantly pachygyria with some areas of agyria, absence of the corpus callosum, and ventricular dilatation. An X linked syndrome was discussed.

Conclusion

Lissencephaly is clearly a heterogeneous disorder with several loci involved in neuronal migration. The aim of this article is to review some of the well defined syndromes within the current pathological and phenotypic classification and discuss the observed inheritance patterns and genetic mechanisms, which facilitate diagnosis of affected patients and counselling of their families. The definitive phenotypic range of the syndromes will become clear as the genes responsible are cloned.

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