Lissencephaly, generic term

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Abstract
Key-words
Definition/Classification
Etiology
Classic lissencephalies
Lissencephaly variants
Cobblestone lissencephalies
Bibliography

Abstract
The term lissencephaly, which describes a "smooth" brain, refers to rare malformations that share the absence of normal circumvolutions of the cerebral cortex. There are several types of lissencephaly, and a consensus has been reached for a classification based on associated malformations and etiologies. On the basis of this classification, five major groups of lissencephalies can be recognized:
- Classic lissencephalies (previously known as type 1 lissencephalies), which include: lissencephaly due to LIS1 gene mutation (type 1 isolated lissencephaly and Miller-Dieker syndrome), lissencephaly due to doublecortin (DCX) gene mutation, lissencephaly, type 1, isolated, without known genetic defects
- Lissencephaly X-linked with agenesis of the corpus callosum (ARX gene)
- Lissencephaly with cerebellar hypoplasia
- Microlissencephaly
- Cobblestone lissencephaly or cobblestone dysplasia (also known as type 2 lissencephaly), which includes Walker-Warburg syndrome or HARD(E) syndrome, Fukuyama syndrome and Muscle-Eye-Brain (MEB) disease.
In classic lissencephalies and variants (lissencephaly X linked with agenesis of the corpus callosum; lissencephaly with cerebellar hypoplasia; microlissencephaly), brain MRI shows thickened cortex (10 to 20 mm) and microscopy usually reveals a four-layered cortex, whereas normal cortex consists of six layers. Abnormal cortical thickness and the anarchic cytoarchitectony result from a defective neuronal migration during embryogenesis. In contrast with classic lissencephalies, variants are characterized by extracortical anomalies (total or partial agenesis of the corpus callosum, and/or severe cerebellar hypoplasia). Cobblestone lissencephaly, characterized by a disorganized and unlayered cortex, results from an abnormal organogenesis of the brain.
Children with lissencephaly present with swallowing and feeding difficulties, muscular spasms, seizures (especially with infantile onset) and a severe psychomotor delay.
The incidence of classical lissencephalies and cobblestone lissencephalies has been estimated to 1.2 in 100.000 births and 1 in 100,000 births, respectively.

Key-words
Lissencephaly, extracortical anomalies, thickened cortex, ARX1,DCX, fukutin, POMGNT1, POMT1

Definition/Classification

The term lissencephaly, which describes a "smooth" brain, refers to rare malformations that share the absence of normal circumvolutions of the cerebral cortex. There are several types of lissencephaly, and a consensus has been reached for a classification (Dobyns and Leventer, 2003) based on associated malformations and etiologies. On the basis of this classification, five major groups of lissencephalies can be recognized:

- Classic lissencephalies (previously known as type 1 lissencephalies), which include: Lissencephaly due to *LIS1* gene mutation (type 1 isolated lissencephaly and Miller-Dieker syndrome); Lissencephaly due to *doublecortin* (*DCX*) gene mutation, Lissencephaly, type 1, isolated, without known genetic defects
- Lissencephaly X linked with agenesis of the corpus callosum (*ARX* gene)
- Lissencephaly with cerebellar hypoplasia
- Microlissencephaly
- Cobblestone lissencephaly or cobblestone dysplasia (also known as type 2 lissencephaly), very different from the four other groups. This group includes Walker-Warburg syndrome or HARD(E) syndrome, Fukuyama syndrome and Muscle-Eye-Brain disease.

Etiology

In classic lissencephaly and its variants (lissencephaly X linked with agenesis of the corpus callosum; lissencephaly with cerebellar hypoplasia; microlissencephaly), the abnormal cortical thickness and the anarchic cytoarchitectony result from a defective neuronal migration during embryogenesis, given that cortical neurons normally migrate from their site of formation to their final destination between weeks 12th and 16th of development.

Cobblestone lissencephaly, characterized by a disorganized and unlayered cortex, results from an abnormal organogenesis of the brain, and more particularly of the glia limitans, which leads to complex neuronal migration disorders. Smooth appearance of the brain may be completely absent, hence the term “cobblestone complex” suggested by Dobyns.

Classic lissencephalies

Classic lissencephalies are a genetically heterogeneous group, with clinical features ranging from agyria (complete absence of circumvolutions) to pachygyria (thick cortical layer with few circumvolutions and shallow sulci). Brain MRI shows thickened cortex (10 to 20 mm, whereas normal cortical thickness is about 2.5 to 4 mm). Microscopy usually reveals a four-layered cortex, whereas normal cortex consists of six layers. Classical lissencephalies are neither associated with microcephalia, nor with major anomalies of the corpus callosum or cerebellum. Although the cortex is mainly affected, partial agenesis of the corpus callosum, and vermis hypoplasia may be seen in few patients, especially those carrying the *double cortine* (*DCX*) gene mutation.

Children affected with the Miller-Dieker syndrome present with mild dysmorphic facial features (high forehead, retrognathia).

The incidence of classic lissencephalies has been estimated to 1.2 per 100.000 births.

Classic lissencephalies might be caused by a deletion in the region 17p13, which encompasses *LIS1* (microdeletion responsible for the Miller-Dieker syndrome), a point mutation in the *LIS1* gene, a mutation of *DCX* on chromosome Xq22, or they may be of unknown etiology. Type I lissencephaly, isolated, without identified genetic anomaly is a diagnosis of exclusion, when neither associated malformations, nor family history is retrieved, in the absence of mutations of genes known to be involved in other classical lissencephalies (*LIS1*, *DCX*).

Lissencephaly variants

Lissencephaly variants (lissencephaly X-linked with agenesis of the corpus callosum; lissencephaly with cerebellar hypoplasia; microlissencephaly) share with classic lissencephalies the ethiopathogeny and the abnormal aspects and organisation of the cortex. However, in contrast with classic lissencephalies, variants are characterized by extracortical anomalies. Lissencephaly, of variable extent, is associated with a total or partial genesis of the corpus callosum, and a severe cerebellar hypoplasia, which affects mainly the vermis.

This group is currently being dismembered.

X-linked lissencephaly with absent corpus callosum and ambiguous genitalia (XLAG) is a form of X-linked lissencephalies with agenesis of the corpus callosum. It is characterized by a thinner cortex than in the classical form (5-10 mm). Clinical features include severe epilepsy of neonatal onset, hypospadias, ambiguous genitalia and poor temperature regulation. XLAG result from defects in the *ARX* gene. Carrier females in affected families may display isolated agenesis of the corpus callosum.

Microlissencephaly differs from classical lissencephaly and other variants by the presence of a severe microcephaly. They result from an abnormal neuronal proliferation or survival combined to neuronal migration disorders. Two main types of microlissencephalies are recognized: the type A (previously called the Norman-Roberts syndrome with no infratentorial anomalies and the type B (or Barth syndrome), which is associated with a severe hypoplasia of the cerebellum and corpus callosum.

Cobblestone lissencephalies

Cobblestone lissencephalies are characterized by a bumpy or granular aspect of the brain surface, associated with shallow sulci (hence the aspect of a lissencephaly), abnormal myelination of the white matter, which may have a cystic appearance in proximity of the cortex, enlarged ventricles, brainstem hypoplasia, cerebellar especially vermis hypoplasia. In contrast with classic lissencephalies, the brain is typically lined by a neuroglial layer.

The most common form is characterized by the association of hydrocephaly (H), agyria (A) (complete absence of circumvolutions), and retinal dysplasia (RD), with or without encephalocele (E). All these features explain the acronym HARD(E), a syndrome also known as Walker-Warburg syndrome, which is usually lethal within the first months of life. In 20% of cases, HARD(E) syndrome has been associated with a mutation of the *POMT1* gene, which maps to 9q34. Mutations in the *fukutin* gene are exceptionally retrieved. Type II lissencephalies also include the Fukuyama disease (congenital muscular dystrophy due to a mutation in fukutin on 9q31 and the muscle-eye-brain (MEB) disease, caused by mutations in *POMGNT1* gene, which has been mapped to 1p34-p33. Reliable population data to estimate the incidence at birth are not available, but these diseases are rare, with approximately 1 case in 100,000 births.

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