Migration disorders and heterotopia: A pictorial review

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Authors: M. Reiss-Zimmermann, J. Fuchs, L. Schomerus, A. Merkenschlager, D. Weber, I. Sorge, W. Hirsch; Leipzig/DE
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Learning objectives

To illustrate the spectrum of migration disorders. To outline the advantages and limitations of MRI. Short up-to-date excursion on treatment concepts.

Background

Migration disorders (MD) are increasingly recognized as an important cause of epilepsy and developmental delay. Up to 40% of children with refractory epilepsy have a cortical malformation [1]. MD encompass a wide spectrum of disorders related to abnormal cortical development with varied genetic etiologies, anatomic abnormalities, and clinical manifestations.

Cerebral cortical development involves a set of highly complex and organized events, including neural stem cell proliferation, migration, and finally neuronal differentiation. Disruption of these various stages may result in MD [2]. The pathogenesis of these malformations is multifactorial: genetic mutations or environmental insults, whether acquired in utero at different stages of brain development, or during the perinatal or postnatal period after corticogenesis may all contribute to the development of these syndromes [3,4]. The timing, severity, and type of environmental influences, as well as genetic factors, will ultimately determine the type and extent of malformation syndrome. Research in delineating the genetic and molecular basis of these disorders has given a greater insight into the underlying pathogenesis of not only the malformation, but also the process involved in normal cortical development. Different mutations of the same gene can cause different phenotypes, based on the degree of protein dysfunction (so termed genotype-phenotype correlation). Loss or disruption of the functional domains within a gene ultimately determines the phenotype of the disorder.

Diagnosis of MD is important, since Patients who fail three antiepileptic medications are less likely to have their seizures controlled with additional trials of medications and therefore epilepsy surgery should be considered.

Imaging findings OR Procedure details

Image findings

With recent advantages in neuroimaging, there is a significant increase in the recognition of MD as a cause of epilepsy and neurologic dysfunction [2,6,7]. Morphologically and using MR imaging studies, malformations can be divided into generalized, lateralized, or focal - depending on their characteristic features and their distribution. However, this classification does not necessarily take into consideration the different pathogenetic mechanisms underlying these malformations [5].
Apart from this more clinical related MRI based classification, MRI can provide further information on these malformations. From a strict anatomical localization, these malformations can also be divided in three main neuroanatomic groups. A third classification is the syndromic approach to the developmental malformations. This approach is useful because it can provide a clinical framework that generates specific therapeutic strategies.

A fourth classification will be used in this article to outline the main migration disorders, which can be subdivided in disorders due to abnormal neurogenesis, neuronal migration, neuronal migration arrest and neuronal organization.

The examination protocol should always include high resolution T1- and T2-w sequences in adequate slice orientation to display the neuroanatomy. Turbo-inversion recovery-Sequences (TIR) can be helpful to diagnose heterotopia. Contrast agent is only needed to exclude other differential diagnoses.

**I - Disorders due to abnormal neurogenesis**

The balance between cell proliferation and cell death determines the ultimate number of neurons or glia in the developed brain. Diffuse pertubations in this delicate balance result in microcephaly or macrocephaly. Focal disruptions (typical due to mosaicism) can lead to focal cortical dysplasia.

**Microcephaly** refers to a head circumference that is more than 2 standard deviations below the population mean. It may result from abnormal cell division or proliferation. A number of processes can cause microcephaly and are often accompanied by involvement of other organ systems [2].

**Hemimegalencephaly** or unilateral megalencephaly is a rare condition, which is characterized by enlargement of one hemisphere or part of it (IMA 1 on page 10). It can also be accommodated by overgrowth of parts or the whole ipsilateral body. Pathology typically reveals cortical dysplasia, white matter abnormalities, abnormal cell types, and polymicrogyria [8]. Due to this significant brain malformation, patients typically have mental retardation and almost always have epilepsy that can become intractable.

**Focal cortical dysplasia** is probably the most common form of focal development disorder diagnosed in patients referred for intractable epilepsy and covers a spectrum of conditions in which the neuropathologic and electroclinic presentations and the surgical outcomes vary [9,1]. Cortical dysplasia can be subclassified according to the pattern of gyral involvement. The differentiation of multifocal dysplasia from hemimegalencephaly may be difficult in some cases. The typical MRI findings (IMA 2 on page 11, IMA 3 on page 11) in these patients consist of focal areas of cortical thickening, with poor underlying gray-white matter differentiation and shallow sulci [9].

**II - Disorders due to abnormal neuronal migration**

Grey matter heterotopia is relatively common congenital anomalies that usually cause a patient to present seizures and variable developmental retardation [10-12]. Heterotopia can be subdivided...
mainly into two different groups: Periventricular heterotopia (IMA 4 on page 11) refers to nodules of neurons found along the ventricular wall of the lateral ventricles, with an apparently normal cerebral cortex. The diagnosis of this disorder requires isointensity of periventricular tissue with normal grey matter as well as the lack of surrounding edema on all sequences examined, allowing distinction from the subependymal nodules of tuberous sclerosis [13]. Although focal subcortical band heterotopia (IMA 5 on page 12) is less common, it is more associated with contralateral pyramidal signs and focal motor convulsions. MRI of the brain demonstrates two parallel layers of gray matter (the so called "double cortex" syndrome): a thin outer ribbon and a thick inner band, separated by a very thin layer of white matter between them. The severity of epilepsy and developmental delay is directly correlated with the degree of migration arrest, as indicated by the thickness of the subcortical band heterotopia [14].

The classic Lissencephaly (Type I) refers to the loss of the normal gyri and sulci of the brain. The severity of the malformation may range from agyria and pachygyria, to subcortical band heterotopia with a relatively normal gyral pattern. Patients usually have severe mental retardation, epilepsy, and often also have microcephaly. MRI demonstrates an hourglass configuration with areas of pachygyria and agyria and a shallow Sylvian fissure. Differences in the location of involvement may be used to differentiate between different mutations causing lissencephaly.

III - Disorders due to abnormal neuronal migration arrest

Cobblestone Lissencephaly (Type II) is a way more complex malformation, consisting of agyria, pachygyria or polymicrogyria, thickening of the cortex and edematous or cystic changes of the white matter. Aqueductal stenosis with hydrocephalus, vermian hypogenesis, patchy abnormal white matter signal, and agenesis or hypogenesis of the corpus callosum can also be seen. This form of lissencephaly refers to the nodular appearance of the cerebral cortex caused by disorganization of the cortical layers, and over migration of neurons through the pial surface of the brain into the leptomeninges. It is also associated with various eye abnormalities and congenital muscular dystrophies (Fukuyama muscular dystrophy, Walker-Warburg-Syndrome) [15,16].

IV - Disorders due to abnormal neuronal organization

Polymicrogyria (IMA 6 on page 12) is the presence of an excess number of abnormally small gyri that produce an irregular cortical surface, either focal of diffuse, unilateral or bilateral. Bilateral involvement is frequently seen, with a symmetric or asymmetric distribution, affecting the frontal, fronto-parietal, parieto-occipital, perisylvian, and mesial occipital regions. The outermost cortical layer commonly fuses, which leads to an appearance of an overly smooth cortical surface. MRI demonstrates thick cortex that can be interpreted as pachygyria. However, cortical thickness is less than that observed in pachygyria. The sulci are shallow and the underlying white matter may show an abnormal T2-signal. Polymicrogyria can be localized to one hemisphere and may also be one of the underlying pathologic changes in patients with hemimegalencephaly.

The term Schizencephaly is used to describe gray-matter-lined clefts in the cerebral hemispheres extending from the cerebral cortex to the ventricle and is typically lined by polymicrogyric cortex [17]. Schizencephaly can be unilateral (IMA 7 on page 13) or bilateral (IMA 8 on page 13) and tends to
involve the insular, precentral, and postcentral regions [15]. The clefts may be in apposition to each other (closed lip or Type I schizencephaly, IMA 9 on page 14) or separated (open lip or Type II schizencephaly, IMA 10 on page 14). Whereas Type II can easily be displayed by MRI, Type I is hard to diagnose, often consisting of tiny excavations of the ventricle only. Also, absent or deficient septum pellucidum maybe seen.

Images linked within the text of this section:

![Images](image_url)

**Fig.**: Using coronal T1w IR (A) and axial T2w (B+C) imaging to display a bilateral "closed lip" schizencephaly and a lobar holoprosencephaly.
Fig.: Displaying a Hemimegalencephaly on the left side in T1-weighted (B) and T2-weighted (A) images.
Fig.: Using axial T2w imaging (A+B) to display bifrontal subcortical band heterotopia.

Fig.: Displaying a bilateral nodular periventricular heterotopia using coronar T1 IR (A) and axial T2w (B) imaging

Fig.: Using coronal T1w IR (A), axial (B) and sagittal (C) T2w imaging to display a left-sided frontal "open lip" schizencephaly, a holoprosencephaly and thinning of the corpus callosum. Furthermore polymicrogyria can be found occipital (B).
**Fig.**: Displaying a unilateral thickening of the insular cortex on the right side in a patient with known symptomatic focal epilepsy (A - T1w IR, B - T2*w axial imaging)

**Fig.**: Axial imaging (A+B - FLAIR, C - contrast enhanced T1w), displaying a large developmental venous anomaly (DVA) frontoparietal on the right side and cortical thickening of the adjacent gyri.
**Fig.:** Displaying occipital polymicrogyria and right-sided veriventricular heterotopia (A - T2w, B - T1w, C - Tw IR)

**Fig.:** Using coronal T1w IR (A), axial T1w (B) and axial T2w (C) imaging to display a large left-sided "open lip" schizencephaly and a smaller one on the right side. Furthermore gliotic periventricula changes can be found (C)
Fig.: The images display a fetal MRI with T2w images, revealing an "open li" schizencephaly of the occipital horn of the lateral ventricle on the right side.

Additional images for this section:
**Fig. 1:** Displaying a Hemimegalencephaly on the left side in T1-weighted (B) and T2-weighted (A) images.

**Fig. 2:** Displaying a unilateral thickening of the insular cortex on the right side in a patient with known symptomatic focal epilepsy (A - T1w IR, B - T2*w axial imaging)

**Fig. 3:** Axial imaging (A+B - FLAIR, C - contrast enhanced T1w), displaying a large developmental venous anomaly (DVA) frontoparietal on the right side and cortical thickening of the adjacent gyri.
**Fig. 4:** Displaying a bilateral nodular periventricular heterotopia using coronar T1 IR (A) and axial T2w (B) imaging.

**Fig. 5:** Using axial T2w imaging (A+B) to display bifrontal subcortical band heterotopia.
**Fig. 6:** Displaying occipital polymicrogyria and right-sided veriventricular heterotopia (A - T2w, B - T1w, C - Tw IR)

**Fig. 7:** The images display a fetal MRI with T2w images, revealing an "open li" schizencephaly of the occipital horn of the lateral ventricle on the right side.
**Fig. 8:** Using coronal T1w IR (A), axial T1w (B) and axial T2w (C) imaging to display a large left-sided "open lip" schizencephaly and a smaller one on the right side. Furthermore gliotic periventricula changes can be found (C).

**Fig. 9:** Using coronal T1w IR (A) and axial T2w (B+C) imaging to display a bilateral "closed lip" schizencephaly and a lobar holoprosencephaly.
**Fig. 10:** Using coronal T1w IR (A), axial (B) and sagittal (C) T2w imaging to display a left-sided frontal "open lip" schizencephaly, a holoprosencephaly and thinning of the corpus callosum. Furthermore polymicrogyria can be found occipital (B).
Conclusion

With recent advances in neuroimaging, there is a significant increase in the recognition of MD, which is of importance in treatment of symptomatic epilepsy, including offering surgical options when appropriate, and neurodevelopmental delay. The mechanisms underlying these malformations are complex, heterogeneous, and poorly understood. MRI has contributed by improving our understanding of these malformations through clinico-MRI correlations [5].

Personal Information

Please, feel free to contact me:  
Martin Reiss-Zimmermann  
Dpt. of Pediatric Radiology  
University Hospital Leipzig  
Liebigstr. 20  
04103 Leipzig  
Germany  
email: martin.reiss-zimmermann@medizin.uni-leipzig.de  
internet: http://www.uni-leipzig.de/paedrad

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