Malformations of cortical development: clinical features and genetic causes

Renzo Guerrini, William B Dobyns

Lancet Neurol 2014; 13: 710–26
Published Online
June 3, 2014
http://dx.doi.org/10.1016/S1474-4422(14)70040-7

Department of Neuroscience, Pharmacology and Child Health, Children's Hospital A Meyer and University of Florence, Florence, Italy (Prof R Guerrini MD); **Stella Maris Foundation Research Institute, Pisa, Italy** (Prof R Guerrini); **Departments of Pediatrics and Neurology, University of Washington, Seattle, WA, USA** (Prof W B Dobyns MD); **and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA** (Prof W B Dobyns)

Correspondence to:
Prof Renzo Guerrini, Children's Hospital A Meyer, 50141 Firenze, Italy
r.guerrini@meyer.it

Malformations of cortical development are common causes of developmental delay and epilepsy. Some patients have early, severe neurological impairment, but others have epilepsy or unexpected deficits that are detectable only by screening. The rapid evolution of molecular biology, genetics, and imaging has resulted in a substantial increase in knowledge about the development of the cerebral cortex and the number and types of malformations reported. Genetic studies have identified several genes that might disrupt each of the main stages of cell proliferation and specification, neuronal migration, and late cortical organisation. Many of these malformations are caused by de-novo dominant or X-linked mutations occurring in sporadic cases. Genetic testing needs accurate assessment of imaging features, and familial distribution, if any, and can be straightforward in some disorders but requires a complex diagnostic algorithm in others. Because of substantial genotypic and phenotypic heterogeneity for most of these genes, a comprehensive analysis of clinical, imaging, and genetic data is needed to properly define these disorders. Exome sequencing and high-field MRI are rapidly modifying the classification of these disorders.

Introduction

The development of the human cerebral cortex is a complex and tightly organised process. Disruption of any of the overlapping steps that contribute to this process can result in a wide range of developmental disorders. Many of these disorders are recognised as malformations in studies of brain imaging and collectively comprise a class of disorders that we designated as malformations of cortical development (MCD). This term was introduced to include disorders with defective cortical development in which the cortical ribbon itself appears normal (specifically some types of microcephaly, megalencephaly, and heterotopia).[1]

The classification scheme for MCD is based on the developmental steps at which the process is first disturbed, the underlying genes and biological pathways disrupted, and—when more objective data are not available—imaging features.[1–4] This system classifies MCD into three major groups that recapitulate the main developmental steps as malformations of cell proliferation, neuronal migration, or postmigrational cortical organisation and connectivity. The ideal classification should (and eventually will) rely on knowledge of biological pathways, which is not available at present. Indeed, recent advances suggest that boundaries between disorders of neuronal proliferation, migration, or subsequent cortical organisation are fading, as emphasised by the recent identification of a broad range of malformations with mutations in *WDR62*, *DYNC1H1*, and *TUBG1*.[5–8] These findings support the notion that MCD-related genes are implicated in many developmental stages that are genetically and functionally interdependent.

In this Review, we address the most difficult issues with classification, review the most common clinical presentations across MCD, provide detailed descriptions of the most common and conceptually important MCD, and discuss the genes associated with these malformations. We address these points from both a general perspective and a more specific phenotype-based approach for the most common of these disorders.

See Online for appendix

Limits in classification of MCD

Although the classification of MCD has advanced substantially during the past decade, in practice only a few categories are used, including lissencephaly, polymicrogyria, schizencephaly, focal cortical dysplasia (FCD), and periventricular nodular heterotopia. However, emerging evidence suggests that MCD are far more heterogeneous than this classification suggests, especially cases of irregular or pebbled cortical surfaces that are usually classified as polymicrogyria, even when the typical curvilinear microsulci are not seen. One example is so-called bilateral frontoparietal polymicrogyria. Reports both before and after identification of *GPR56* as the causal gene of this MCD showed a cobblestone-type cortical malformation associated with defects in the pial basement membrane.[9,10] This disorder is now referred to as bilateral frontoparietal cobblestone malformation, but use of the term polymicrogyria persists.

Individuals classified as having polymicrogyria have such diverse clinical courses and outcomes, causes and recurrence risks, associated malformations and syndromes, and imaging and neuropathological abnormalities as to render the term no more specific than that of intellectual disability. Further, the borders between MCD now classified as separate malformations have become blurred, because the new tubulinopathies can present as either lissencephaly-like or a polymicrogyria-like MCD (appendix). Enough data have accumulated to allow reclassification of some polymicrogyria-like MCD as malformations due to generalised abnormal transmantle migration, similar to classic lissencephaly.[4]

MCD would ideally be classified with use of a comprehensive approach that includes data from several different disciplines. However, this system is difficult because specialties such as molecular genetics generate large amounts of new data, whereas other specialties such as neuropathology and developmental neurobiology lag behind, unless surgical removal of affected human tissues is possible or animal models are available.[11–14]

Brain imaging

Most MCD can be differentiated by moderate-to-high-quality MRI scans (figure 1). The key features to look for include distribution and severity of the MCD, the cortical surface and border between white and grey matter (smooth or irregular), cortical thickness, and associated brain malformations. We summarise the key differences in imaging of different MCD in the appendix. Our preliminary experience suggests that ultra-high-field 7 Tesla imaging will improve characterisation of localised forms of polymicrogyria and FCD (figure 2), although its usefulness to detect regions of abnormal cortical development after negative standard 3T MRI has not been systematically assessed yet.

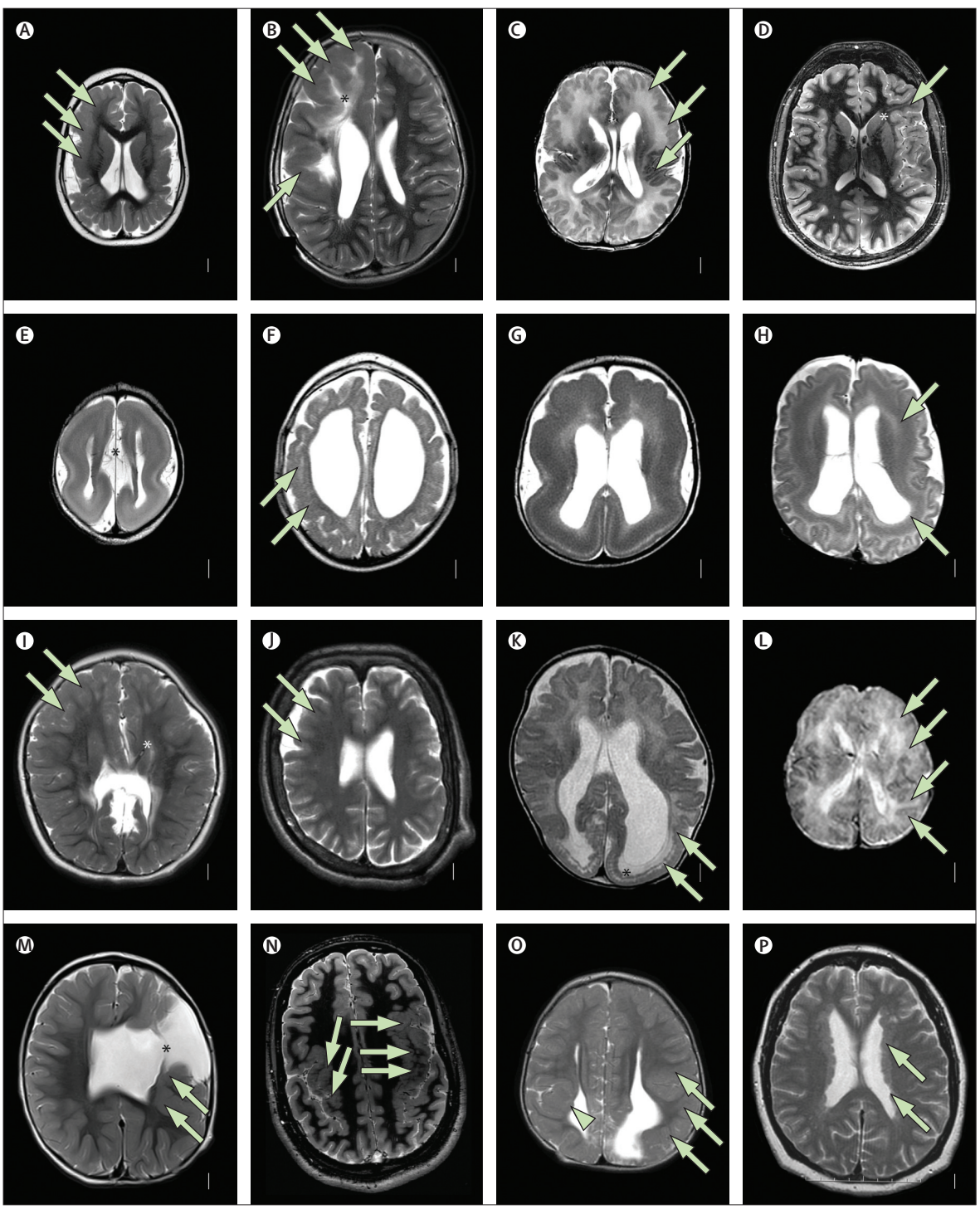

Figure 1: **Axial T2-weighted images at the level of the mid-lateral ventricles showing different malformations of cortical development**
Malformations of cortical development include severe congenital microcephaly with a polymicrogyria-like cortical malformation (A), right-sided dysplastic megalencephaly (hemimegalencephaly; B), megalencephaly and frontal-perisylvian polymicrogyria (C), focal cortical dysplasia type 2b (D), severe lissencephaly with cerebellar hypoplasia and absent corpus callosum (E), polymicrogyria-like cortical malformation in a tubulinopathy (F), grade 3 classic lissencephaly (G), diffuse subcortical band heterotopia in a female brain (H), frontal predominant cobblestone malformation in muscle-eye-brain disease (I), frontal predominant cobblestone malformation in autosomal recessive cutis lax (J), posterior predominant cobblestone mutation in a child with congenital muscular dystrophy (K), peroxisomal cortical malformation in Zellweger syndrome (L), classic schizencephaly with a left frontal open-lip cleft (M), perisylvian polymicrogyria imaged at 7 T (N), posterior periventricular nodular heterotopia with overlying polymicrogyria (O), and bilateral diffuse periventricular nodular heterotopia (P). Further description is provided in the appendix. Long arrows show representative areas of cortical malformation (A–D, F, I–O), subcortical band heterotopia (H), or periventricular nodular heterotopia (P). The short arrow shows a small periventricular nodular heterotopia (O). Asterisks denote abnormal white matter (B), focal transmantle dysplasia (D), wide inter hemispheric space due to absent corpus callosum (E), a shunt (I), and an open-lip cleft (M).

Download English Version:

https://daneshyari.com/en/article/3066573

Download Persian Version:

https://daneshyari.com/article/3066573

Daneshyari.com