Structure, Function and Genes: What Can We Learn from MRI

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Summary

Malformations of cortical development represent a major cause for medically refractory epilepsy, cognitive disability and delayed development. Modern neuroimaging enabled their in vivo differentiation and classification in three big categories based on the abnormal step of neuronal development: malformations due to abnormal neuronal proliferation, migration and organization. In the recent years there has been an enormous progress in identifying causative genetic defects of malformations of cortical development. Tuberous sclerosis is an autosomal dominant malformation caused by mutations in either *TSC1* or *TSC2* genes, comprising about 80% of all cases. Periventricular nodular heterotopia, a migrational abnormality is frequently X-linked caused by mutation in *Filamin A* gene; rarely it is autosomal recessive (*ARFGEF2 gene*). Subcortical laminar heterotopia is also commonly X-linked with mutation in *DCX* gene; other genetic causes include *LIS1* and *TUBA1A* mutations.

Polymicrogyria is associated with different conditions including prenatal infectious or ischaemic injury. Among its known genetic causes are numerous microtubule-associated genetic defects (*TUBB2B, TUBA8, TUBB3, TUBA1A*). Other genetic causes include autosomal recessive mutations of *GPR56, OCLN, KIAA1279, COL18A1, TBR2* and X-linked *SRPX2*.

Novel discoveries of *WDR62* gene and tubulin mutations have finally challenged the concept of one gene – one mechanism – one malformation and at the same time they shed some more light on the pathophysiology of brain malformations. It has been demonstrated that different mutations of *WDR62* gene may cause a wide spectrum of MCD including microcephaly, pachigyria, lissencephaly, polymicrogyria, schizencephaly, dysgenesis of corpus callosum, hippocampal and cerebellar abnormalities, blurring the border between disorders of neuronal proliferation, migration and organization.

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Key words: Malformations of cortical development, genes, MRI, epilepsy

Struktur, Funktion und Gene: Was sehen wir im MRT?

Malformationen kortikaler Entwicklung sind eine wichtige Ursache für therapierefraktäre Epilepsien, kognitive Behinderungen und Entwicklungsverzögerungen. Die moderne Neuroradiologie ermöglicht die In-vivo-Diagnostik und Klassifizierung in drei grosse Kategorien basierend auf dem abnormen Schritt der neuronalen Entwicklung: Fehlbildungen aufgrund von Störungen der Proliferation, Migration und Differenzierung. In den letzten Jahren wurden enorme Fortschritte bei der Identifizierung ursächlicher genetischer Defekte für Fehlbildungen der kortikalen Entwicklung gemacht. Die tuberöse Sklerose ist eine autosomal-dominante Erbkrankheit, die durch Mutationen im Bereich des *TSC1*- oder *TSC2*-Gens verursacht wird, die etwa 80 % aller Fälle ausmachen. Bei der periventrikulären nodulären Heterotopie handelt es sich in der Regel um eine Migrationsstörung mit Mutationen im X-chromosomal lokalisierten *Filamin-A*-Gen, in seltenen Fällen werden autosomal-rezessiv vererbte Formen festgestellt (Mutationen im *ARFGEF2*-Gen). Bei der subkortikalen laminaren Heterotopie liegt ebenfalls häufig eine Mutation im X-chromosomal lokalisierten *DCX*-Gen vor. Weitere genetische Ursachen sind *LIS1*- und *TUBA1A*-Mutationen.

Polymikrogyrie wird mit verschiedenen Ursachen in Verbindung gebracht, wie z. B. pränatalen Infektionen oder Ischämien. Zu den bekannten genetischen Ursachen gehören verschiedene Mikrotubuli-assoziierte Gendefekte (*TUBB2B, TUBA8, TUBB3, TUBA1A*). Weitere genetische Ursachen umfassen autosomal-rezessiv vererbte Mutationen von *GPR56, OCLN, KIAA1279, COL18A1, TBR2* sowie des X-chromosomal lokalisierten *SRPX2*.

Die Neuentdeckung des *WDR62*-Gens und von Tubulinmutationen haben das Konzept „Ein Gen – ein Mechanismus – eine Fehlbildung“ endgültig in Frage gestellt und erweitern gleichzeitig die Kenntnisse über die Pathophysiologie von Hirnfehlbildungen. Es wurde gezeigt, dass verschiedene Mutationen des *WDR62*-Gens ein breites MCD-Spektrum verursachen können, einschliesslich Mikrozephalie, Pachygyrie, Lissenzephalie, Polymikrogyrie, Schizenzephalie, Dysgenesie des

des Corpus callosum sowie Anomalien von Hippocampus und Zerebellum, wodurch die Grenzen zwischen Störungen der Proliferation, Migration und Differenzierung verwischen.

Schlüsselwörter: Fehlbildungen der kortikalen Entwicklung, Gene, MRT, Epilepsie

Structure, fonction et gènes : ce que l'IRM peut nous apprendre

Les malformations du développement cortical (MDC) représentent une cause majeure d'épilepsie réfractaire aux traitements, de déficience cognitive et de retards de développement. L'imagerie cérébrale moderne a permis leur diagnostic in vivo et leur classification en trois grandes catégories selon le stade de survenue des troubles dans le développement neuronal : malformations liées à la prolifération, à la migration et à l'organisation des cellules neuronales. Ces dernières années, d'énormes progrès ont été réalisés en matière d'identification des anomalies génétiques responsables de malformations du développement cortical. La sclérose tubéreuse de Bourneville est une maladie autosomique dominante provoquée par des mutations au niveau des gènes *TSC1* ou *TSC2*, représentant environ 80 % de tous les cas. L'hétérotopie nodulaire périventriculaire est généralement liée à une malformation survenant lors de la migration neuronale par mutation du gène de la *filamine A* situé sur le chromosome X. Dans de rares cas, elle présente une forme autosomique récessive (mutations du gène *ARFGEF2*). L'hétérotopie laminaire sous-corticale est elle aussi souvent liée au chromosome X et entraînée par mutation du gène *DCX* ; les mutations de *LIS1* et *TUBA1A* sont d'autres causes génétiques rencontrées.

La polymicrogyrie est associée à différentes conditions, telles que les infections prénatales ou les lésions ischémiques. Diverses anomalies génétiques en lien avec les microtubules (*TUBB2B, TUBA8, TUBB3, TUBA1A*) figurent au nombre des causes génétiques connues de cette malformation, auxquelles s'ajoutent les mutations autosomiques récessives de *GPR56, OCLN, KIAA1279, COL18A1, TBR2* et du gène *SRPX2* localisé sur le chromosome X.

Les découvertes récentes concernant le gène *WDR62* et les mutations de la tubuline ont définitivement remis en question le concept « un gène – un mécanisme – une malformation » tout en éclairant d'un jour nouveau la physiopathologie des malformations cérébrales. Il a été démontré que différentes mutations du gène *WDR62* peuvent entraîner un large éventail de MDC, telles que microcéphalie, pachigyrie, lissencéphalie, polymicrogyrie, schizencéphalie, agénésie du corps calleux, ou encore des anomalies hippocampiques et cérébelleuses, brouillant de fait les limites entre troubles de la prolifération, de la migration et de l'organisation des cellules neuronales.

Mots clés : malformations du développement cortical, gènes, IRM, épilepsie

Introduction

In the recent years there has been a tremendous progress in discovering genetic causes of malformations of cortical development (MCD) shedding light on their pathopsysiology and at the same time challenging the current classification of MCD and shaking the hypothesis of one gene – one mechanism – one malformation [1, 2].

MCD represent a major cause of medically refractory epilepsy in children and adults [3-5]. Other clinical features include delayed developmental milestones, cognitive impairment, neurological deficits, and reduced life span in some cases [6, 7]. MCD etiology is very heterogenous: some have known genetic causes, represent part of genetic syndromes, may occur as isolated cases or be caused by exogenous factors. MCD are classified based upon three overlapping steps of neuronal development: I) neuronal proliferation, II) neuronal migration, III) late migration / cortical organization [6]. The process of neuronal development is dynamic and more than one step may occur at the same time during gestation and early postnatal life. Increased or decreased proliferation of cortical neurons at early stages of brain development results in microcephaly, macrocephaly, tuberous sclerosis, focal cortical dysplasia (FCD) type II, hemimegalencephaly or dysplastic tumors (ganglioglioma, dysembryoplastic neuroepithelial tumor) – MCD of category I. MCD of category II – e.g. periventricular nodular heterotopia (PNH) or subcortical band heterotopia (SBH) are caused by disruption of neuronal migration from ventricular areas, where neurons proliferate, to cortical surface. Polymicrogyria (PMG), schizencephaly and FCD type I represent MCD of category III with aberrant late migration/cortical organization (lamination, gyration) [6]. The most widely used MCD classification was first created in 1996 and was based mainly on their radiological features [8]. Since then three amendments were proposed by the same group of authors and with the time more genetic information has been incorporated in this classification [6, 9, 10]. However, the pace of gene discovery is far more rapid compared to the speed of amendments of the classification which renders the nomenclature already outdated as it has been published.

Despite the great progress in discovering causative genetic defects of MCD, their diagnosis in everyday clinical practice is largely based on MRI. In unclear or "non-lesional" cases, special imaging protocols and computational MRI post-processing techniques are required for enabling the detection of some MCD [11-16]. The widely utilised MRI sequences for epilepsy patients who may harbour an MCD include high resolution T1-weighted 3-D images with and/or without intravenous contrast application, axial and coronal T2-weighted, T1-weighted

inversion recovery, T2-weighted fast fluid attenuated inversion recovery (FLAIR) performed using either 1.5 or 3 Tesla magnets. According to different studies that correlated presurgical MRI findings with postsurgical histology, up to 40% of MCD, especially FCD, may be missed on routine MRI [17, 18]. Voxel-based MRI post-processing techniques may increase the detection rate of FCD type II up to 17% [16]. It is of decisive importance who reads and interprets the MR images of epilepsy patients with potential MCD as a cause of their seizures: The combination of a dedicated MRI protocol and an expert neuroradiologist compared to standard MRI sequences and non-expert radiologist increases the chances of detecting an epileptogenic lesion dramatically from 39% to 91% (von Ortzen 2002). The same applies to imaging / histology correlation which is much more precise (89%) when an expert neuroradiologist interprets an epilepsy dedicated MRI versus to non-expert reading of a standard MRI (22%) [19].

Precise description of brain malformations other than supratentorial MCD is crucial for taking decision on genetic testing in patients with MCD. Abnormalities of corpus callosum, basal ganglia, hippocampi and especially infratentorial structures may give important clues for potential genetic testing [20-22]. A new classification of lissencephalies has been proposed based on their combination with cerebellar malformations and some of these particular combinations have distinct genetic causes [20].

Aside from detailed imaging information, a thorough clinical description, anamnestic factors as well as pedigree tree play an important role in genetic testing of patients with MCD. This information includes craniofacial or any other dysmorphysm, other organ systems affected, psychomotor and cognitive status, developmental milestones, types of seizures, age at seizure onset, family history of epilepsy and MCD, history of abortions, etc..

Disorders of neuronal proliferation

Tuberous sclerosis and focal cortical dysplasia

Tuberous sclerosis is an autosomal dominant phacomatosis presenting on MRI with multiple cortical tubers, subependimal nodules and giant cell astrocytomas (**Figure 1**) [20, 23]. Cortical tubers are best visible on T2-weighted and FLAIR sequences; calcifications of subependimal nodules are seen on CT and T2*-weighted MRI; giant cell astrocytomas are usually enhanced by contrast substance and require surgical intervention due to a risk of CSF flow obstruction. Patients with tuberous sclerosis present frequently with early severe epilepsy with pharmacoresistant seizures, cognitive impairment and involvement of other organ systems [20, 23-25]. However, there are clinically mild cases without intellectual disability and easy to manage epilepsies. These, so called "forme fruste", cases of tuberous sclerosis have also much milder phenotype on MRI compared to "classical" appearance [26].

Tuberous sclerosis is an autosomal-dominant disorder caused by mutations in either *TSC1* or *TSC2* genes. The *TSC1* gene on chromosome 9q34 encodes protein hamartin and the *TSC2* gene on chromosome 16p13.3 codes for protein tuberin. In most cases, nonsense or frameshift mutations are seen; missense or in-frame deletions or splice mutations are observed rarely. Both genes are tumor supression genes; their products inhibit mTOR protein cascade and therefore are involved in regulation of cell growth and cycle [27, 28]. Clinical and genetic diagnoses of tuberous sclerosis are of great importance taking into consideration the risk of malignancies and the recurrence risk of about 50% in offsprings of mutations carriers. Heterozygous mutations of *TSC2* are identified in about 60% and mutations of *TSC1* in about

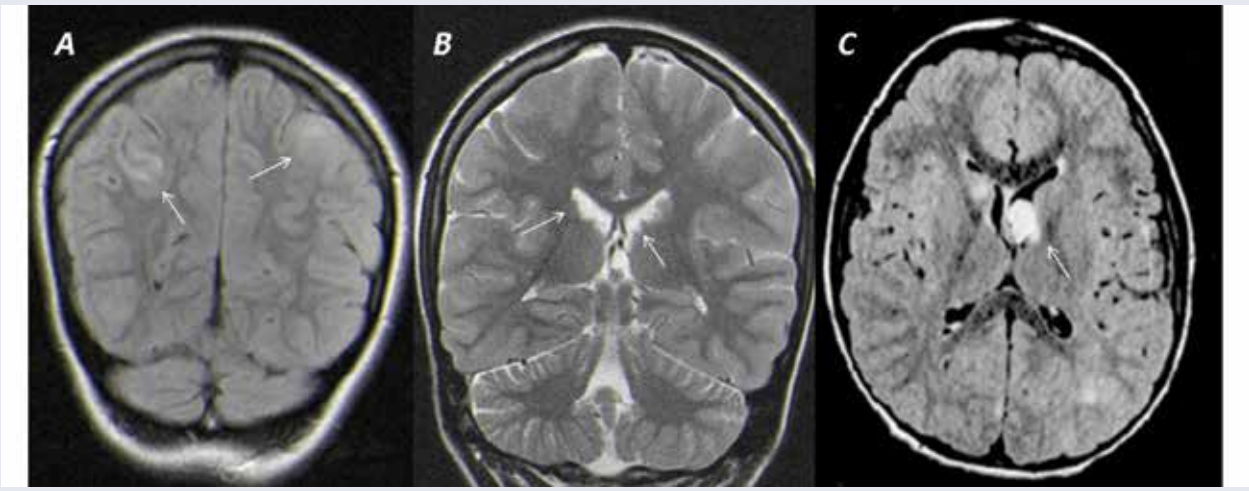

Figure 1
A: Multiple subcortical tubers with increased signal on coronal FLAIR image (arrows)
B: Subependimal nodules on T2-weighted coronal image (arrows)
C: Giant cell astrocytoma enhanced by contrast substance (arrow)

19% of patients with tuberous sclerosis [7].

Focal cortical dysplasia (FCD) is a malformation of cortical development which is histologically and by MRI appearance similar to tuberous sclerosis. FCD type IIB [29], as tuberous sclerosis, is characterised on histology by presence of balloon cells, dysmorphic and giant neurons. On MRI, FCD IIB is a cortical/ subcortical lesion (very rarely – multiple lesions) with high signal in T2-weighted and FLAIR sequences, which tapers towards the lateral ventricle (so called "transmantle" sign) [30, 31]. Earlier genetic studies suggested the role of TSC1 gene in the development of FCD [32]; however, the most recent studies have demonstrated that FCD (even multifocal FCD) are not caused by mutations in TSC genes [33]. Therefore, FCD cannot be regarded as "forme fruste" of tuberous sclerosis.

The patients with bilateral symmetrical PNH, female in the vast majority, seek the medical attention due to their seizures, which may or may not be medically intractable. The prevalence of PNH in non-epileptic patients is largely unknown as PNH has been detected accidentaly in patients imaged for causes other than epileptic seizures. There is a wide spectrum of clinical presentation: usually cognitive performance, language and motor development are within normal range, however, severe cognitive impairment and neurological disability have also been discribed in patients with PNH [7].

Heterotopic nodules display high epileptogenicity as it has been shown by invasive EEG recordings with intracranial depth electrodes placed in periventricular nodules [39]. Functional MRI demonstrated involvement of PNH in some complex cognitive tasks assessing mem-

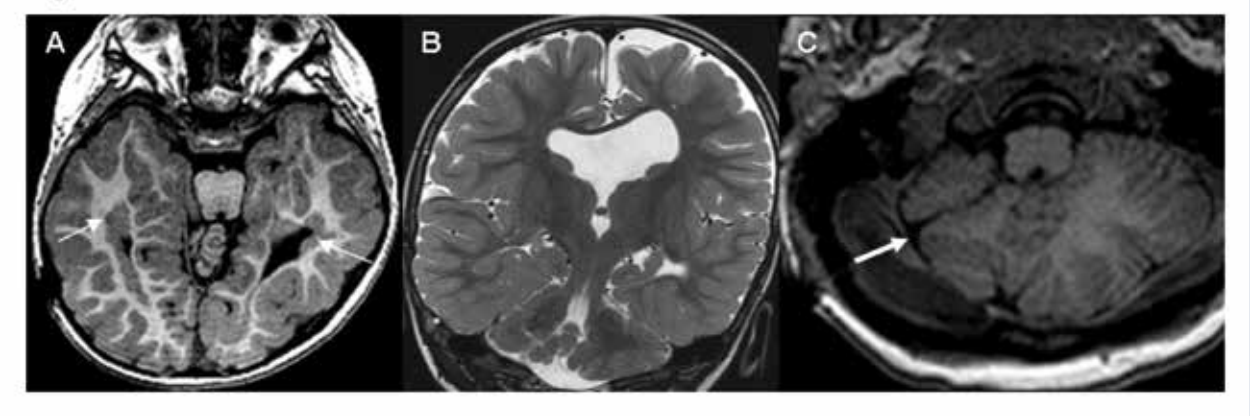

Figure 2

A: Axial T1-weighted image with bilateral periventricular nodular heterotopia along temporal horns of lateral ventricles (thin white arrows)

B: Hypoplastic/partially infolded hippocampi.

C: Cleft with overlying polymicrogyria (thick white arrows) of the right cerebellar hemisphere (right hemisphere is smaller compared to the left one)

Migrational disorders

Periventricular nodular heterotopia

Periventricular nodular heterotopia (PNH) present on MRI with multiple nodular conglomerates of ectopic grey matter assembled along the lateral ventricules. These nodules are usually bilateral and symmetrical. They are well visualised in both T1- and T2-weighted MR images (**Figure 2**). Other MRI phenotypes include unilateral single nodule PNH frequently localised in the trigonal area; so called "transmantle" heterotopia with ectopic nodules placed all the way from ventricle to the cortex; assymetric bilateral; PNH may be associated with agenesis of corpus callosum or polymicrogyria; could be predominantly perisylvian or posterior [34-37]. PNH is frequently coupled with hippocampal and/or cerebellar malformations (**Figure 2**) [22, 38].

ory and language [40]; whereas in simple motor tasks, different studies show contradicting results from nodules integrated in motor circuits to the absence of any activation [40, 41].

Virtually almost all cases of bilateral symmetrical PNH are familial. In the majority of cases it is an X-linked dominant disorder with a mutation in the *Filamin A* gene. Female preponderance, ruccurent abortions and frequent male pre- or perinatal death are common features of PNH. *Filamin A* maps to Xq28, consists of 48 exons and encodes F-actin binding cytoplasmatic phosphopritein which is involved in the locomotion of developing neurons. *Filamin A* is also important for coagulation and vascular-related functions, causing frequent combinations of PNH with cardiovascular problems (cardial valve disease, aortic dissection, etc.) and coagulopathies, for which they should be monitored. Patients with PNH and *Filamin A* heterozygous mutation carry a 50% risk of passing the mutant gene to offsprings [6, 7].

Other genes that may cause PNH in both sexes include a rare form of autosomal recessive form of PNH due to the mutation of the ADP-ribosylation factor guanine nucleotide exchange factor-2 (*ARFGEF2*) [42]. This form of PNH is associated with delayed myelination, microcephaly, severe developmental delay, cognitive impairment, early intractable seizures including infantile spasms as well as increased susceptibility to infections. *ARFGEF2* encodes for the protein which is required for vesicle and membrane trafficking from the trans-Goldgi network. Overall, PNH caused by *ARFGEF2* mutation is radiologically distinct and clinically more severe compared to PNH caused by *Filamin A* mutation [42].

Subcortical band heterotopia

Subcortical band heterotopia (SBH) or "double cortex" presents with a second layer of grey matter below cortex separated from it by a thin band of white matter. The "true" cortex itself appears on MRI either normal or thinned and/or with simplified gyration (**Figure 3**) [10, 43]. SBH may be combined with hippocampal abnormalities, infratentorial malformations, dysgenesis of corpus callosum or enlarged lateral ventricles [22, 38]. MRI post-processing may be helpful in identifying subtle forms of posteriorily predominant SBH [44]. The majority of patients with SBH present with early onset epilepsy with either focal or generalised, frequently pharmacoresistant seizures which in some instances progress to Lennox-Gastaut syndrome [45]. Severe developmental delay and mental retardation are more common compared to PNH. Women are strikingly more commonly affected than men as SBH is most frequently caused by heterozygous mutation of the X-linked *DCX* gene. Phenotypically, this mutation is frontally pronounced and rarely associated with extracerebral malformations [7]. *DCX* mutation has been also rarely described in males, who may have either SBH or classical lissencephaly. Other rather rare genetic causes of SBH include heterozygous mutation of the *LIS1* gene and *TUBA1A* gene with occipitally predominant SBH [7, 46]. It is of note that both *LIS1* and *DCX* interact with microtubules, hence the lissencephalic phenotype is caused by mutations of both genes.

Classical lissencephaly

Classical lissencephaly is related to SBH and is characterized by absent gyri (agyria; so called "smooth" brain) or decreased cortical convolutions (pachigyria) (**Figure 4**). The sulci and gyri fail to form as neurons and do not migrate properly from ventricular/subventricular zone towards the cortical plate [10, 43, 45]. The cortex is usually thick and there is usually a typical sign on T2-weighted images: a thin subcortical layer of increased signal due to the area where the cells are sparse (**Figure 4**). Classic lissencephaly is frequently associated with hippocampal abnormalities and midbrain-hindbrain malformations [22, 45].

Clinical presentation of patients with classic lissencephaly is usually severe. They are cognitively impaired, have muscle atonia or hypertonia, frequently quadriparesis, delayed milestones and most severe epileptic encephalopathies with pharmacoresistant seizures [7]. There are numerous syndromes described, most common among them is Miller-Dieker syndrome [10].

Most epilepsies in patients with classical lissencephaly are caused by *de novo* mutations of the *LIS1* (*PAFAH1B1*) gene; in about 10% of patients *DCX* mutations are seen and the minority of patients (about 1%) harbour de novo mutations in the *TUBA1A* gene [7]. Deletion of the *LIS1* gene cause the most severe phenotype with lissencephaly more prominent in posterior brain areas comprising up to 40% of all classical lissencephaly cases [47]. Missense mutations of the *LIS1* gene have

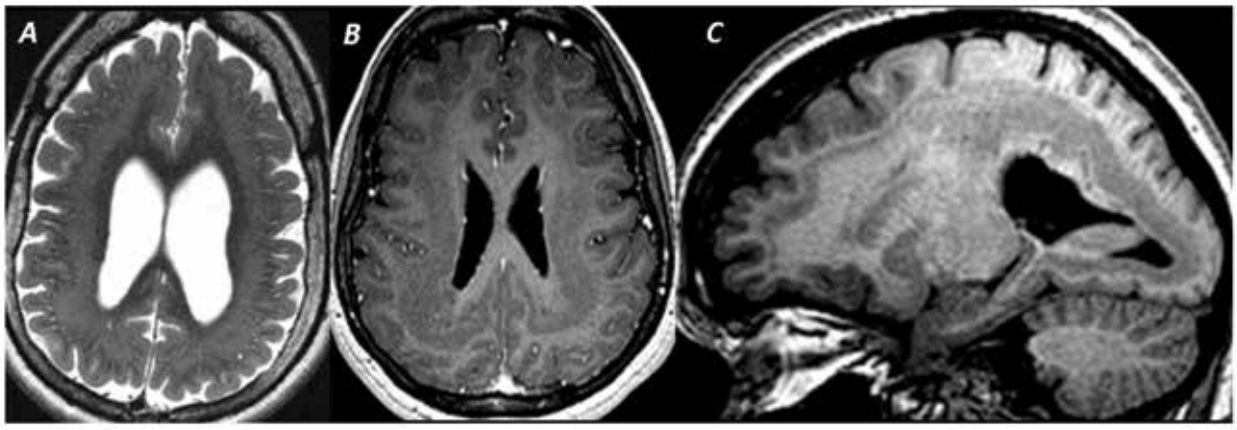

Figure 3
A: T2-weighted axial image with subcortical laminar heterotopia („double cortex") and enlarged ventricules
B: T1-weighted axial image with subcortical laminar heterotopia of posterior predominance
C: T1-weighted sagittal image with subcortical laminar heterotopia of posterior predominance

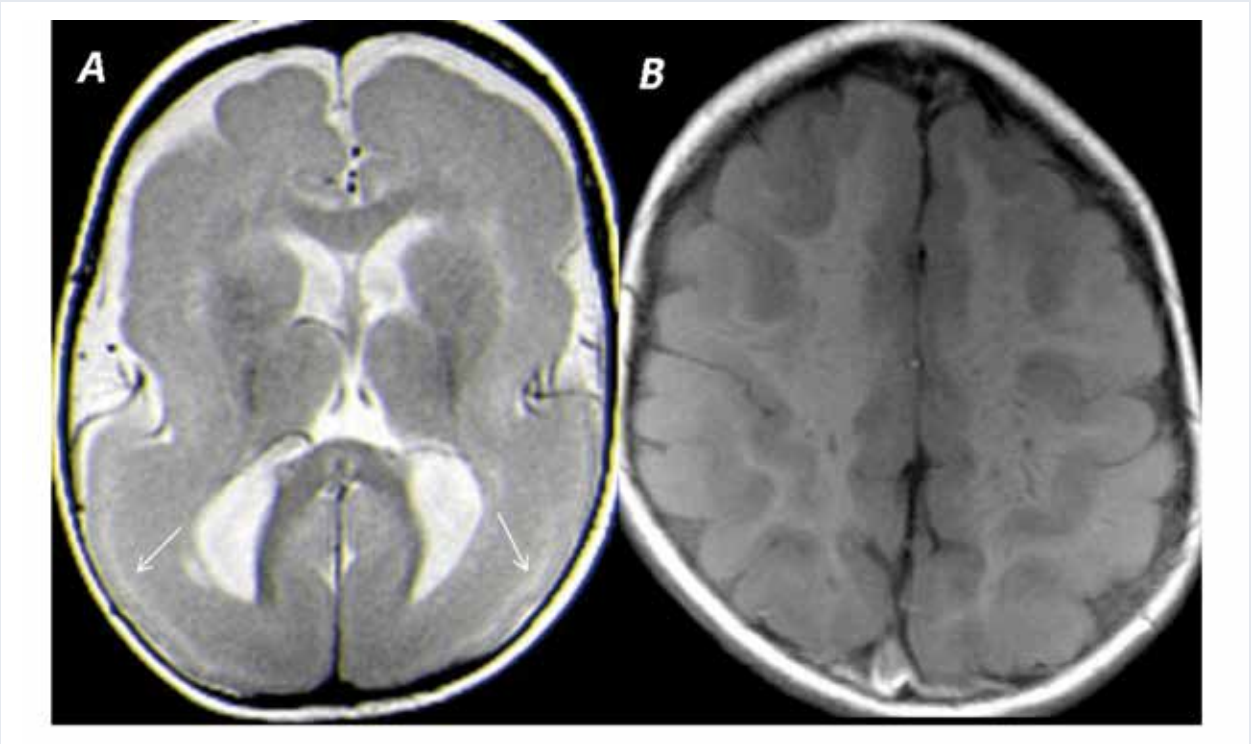

Figure 4

A: Classical lissencephaly with agyria ("smooth" brain) and steep Sylvian fissure on T2-weighted axial image. White arrows point at subcortical rim of increased signal – the area with sparse neurons

B: Pachygyria – simplified gyral pattern and thick cortex

usually less severe malformation with milder neurological and cognitive impairment [48]. Mosaic mutations of *LIS1* may also cause posteriourly pronounced SBH [49].

LIS1 encodes a protein that has essential role in locomotion of developing neurons. This protein that is similar to β-subunit of heterotrimeric G proteins has been demonstrated to co-localize with microtubules and to promote their stabilization [50].

Cobblestone malformations

Cobblestone malformations are frequently associated with congenital muscular dystrophies, so called dystroglycanopathies [10]. Among them the most common are Walker-Warburg syndrome, Fukuyama congenital muscular dystrophy and muscle-eye-brain disease. These conditions are caused by mutations of multiple genes involved in O-glycolisation of α-dystroglycan, like *FCMD, FKRP, POMT1, POMT2, LARGE, POMGnT1*[10]. The abberant formation of the basal membranes in muscles, retina and brain causes these muscular, eye and cerebral disorders. Defective cerebral basal membrane causes abnormal formation of cortical laminae and overmigration of neurons into pial surface, resulting in a typical cobblestone phenotype observed on MRI [10]. However, the MRI appearance is widely variable and presents with pachy- and agyria, polymicrogyria-like malformation, dilated ventricules, cerebellar abnormalities and callosal dysgenesis [10]. Cerebellar malformations associated with cobblestone complex seem to be most severe compared to those cerebellar abnormalities which are seen in classical or variant lissencephalies [20].

Polymicrogyria

Polymicrogyria (PMG) is characterised by irregular brain surface, multiple small gyri with excessive folding of cortical cell layers and partial fusion of gyral surfaces (**Figure 5**) [10]. On histology PMG presents with two patterns: a classical type with four distinct layers and a non-layered variety with poorly or non-laminated cortex [51, 52]. PMG may range from restricted focal cortical to widespread diffuse and generalised areas. It could be unilateral or bilateral symmetrical [10]. PMG in unusual locations, like bilateral mesio-temporal, have been described (**Figure 6**) [53]. PMG is frequently associated with schizencephaly as well as with many other different conditions and syndromes, including prenatal (either ischaemic or infectious) injury [6]. Many mutations causing PMG have been published [6]. Accordingly, the spectrum of clinical manifestations ranges from normal individuals (PMG as an incidental finding on MRI) to patients with severe epilepsy, mental retardation and neurological disability [6].

Bilateral perisylvian PMG is one of the common examples of genetically determined PMG [6]. It is usually

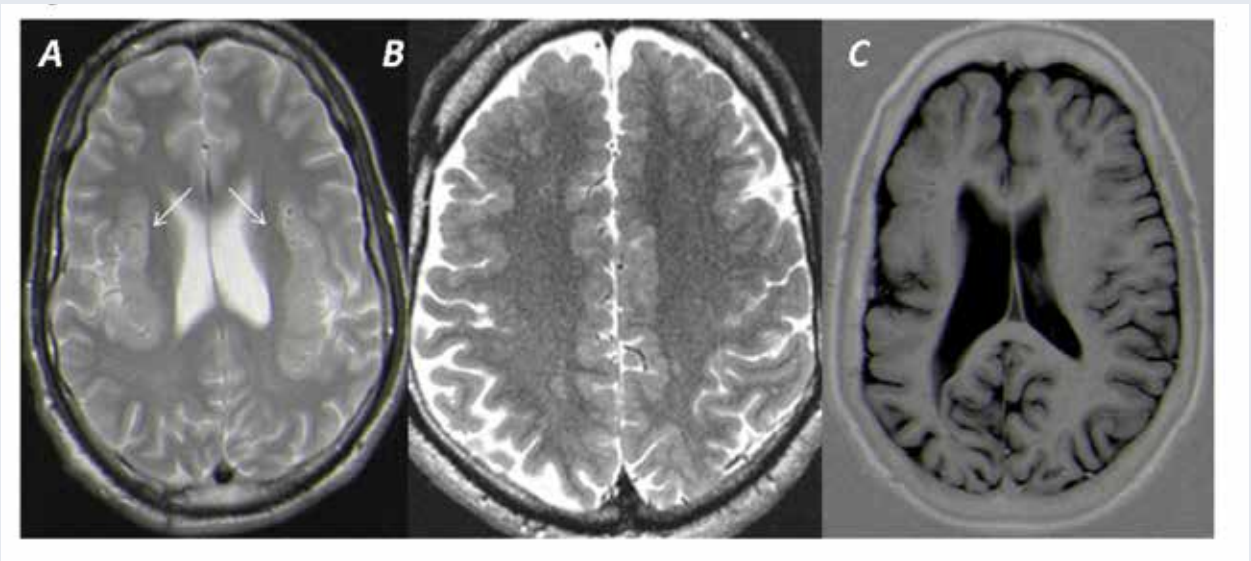

Figure 5
A: Bilateral asymmetrical perisylvian polymicrogyria (arrows),
B: ilateral fronto-parietal polymicrogyria
C: Bilateral asymmetrical perisylvian polymicrogyria

symmetrical but may vary in extent. Several families with this form of PMG have been reported although the majority of cases are sporadic. The inheritance is heterogeneous with possible autosomal recessive, autosomal dominant, X-linked recessive and X-linked dominant [54]. X-linked PMG maps in some cases to Xq28 [6]. Deletions affecting chromosomal region 22q11.2 are also common. Some patients with bilateral perisylvian PMG have facio-pharingo-glosso-mastocatory apraxia and dysarthria [55].

Overlapping malformations and mutations: challenges for classification

Congenital muscular dystrophies associated with malformations of cortical development were the first examples of phenotypical heterogeneity of malformations caused by the mutation of the same gene or even the same mutation. On the other hand, equal phenotypes had different underlying genetic abnormality.

Recent discoveries of *WDR62* gene and tubulin mutations have finally challenged the concept of one gene – one mechanism – one malformation and at the same time they shed some more light on the pathophysiology of brain malformations [56].

It has been demonstrated that different mutations of *WDR62* gene may cause a wide spectrum of MCD including microcephaly, pachigyria, lissencephaly, polymicrogyria, schizencephaly, dysgenesis of corpus callosum, hippocampal and cerebellar abnormalities, blurring the border between disorders of neuronal proliferation, migration and organization [1]. Functional studies revealed that *WDR62* transcripts and protein are enriched in neural progenitors within ventricular and subventricular zones [1]. Normal expression of *WDR62* in neocortex occurs only during the period of embryonic neurogenesis. In contrast to other known microcephaly genes, *WDR62* is not linked to centrosomes and is mainly located in the nucleus [1].

In the recent years, new genetic defects causing cobblestone malformations have been discovered. Mutations of the *GPR56* gene are known to cause bilateral frontoparietal polymicrogyria. However, in the *GPR56* knockout mouse there are regions of cortical dysorganization due to discontinuous basal lamina causing overmigration of neurons and cobblestone formation similar to those in lissencephalies [57]. Neuronal overmigration and cobblestone-like features may also be caused by missense mutation of *TUBB2B* gene, that has been known to cause asymetric frontally predominant polymicrogyria [58]. *TUBB2B* as one of the neuronally expressed tubulin genes has a distinct role in neuronal migration. These examples show how different genetic defects regulating a single mechanism may result in similar phenotypes, blurring the borders between disorders of neuronal migration and cortical organization. At the same time mutations of one gene may cause a large spectrum of malformations as it has been shown recently in *TUBB2B* and *TUBA1A* mutations [2]. In 47 patients with polymicrogyria and five patients with atypical lissencephaly, *TUBB2B* and *TUBA1A* coding regions were sequenced [2]. Four β-tubulin and two α-tubulin mutations were identified in these patients who had other associated brain abnormalities aside from polymicrogyria and lissencephaly. Among them the most consistent were dysmorphic basal ganglia and internal capsule [2]. These findings challenge the entire classification of malformations of cortical development suggesting that future nomenclatures may be based on

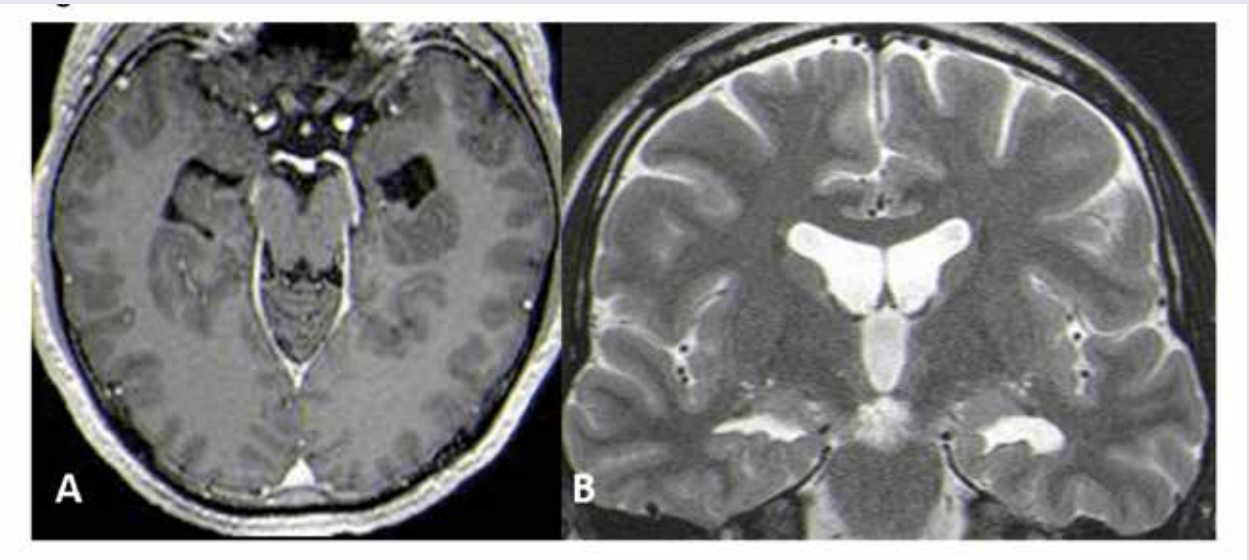

Figure 6

A: T1 axial MRP post-contrast image demonstrating bilateral enlargement of the temporal horns of the lateral ventricles, thick cortex in the mesial-temporal region bilaterally with the blurred gray-white matter junction;

B: T2 coronal image, demonstrating bilateral mesial-temporal small gyri, thick cortex and blurred gray-white matter junction

affected mechanisms of disrupted brain development rather than causative genes.

Importance of genetic testing in patients with MCD

The importance of identifying genetic causes of MCD is undeniable. It helps to define the precise diagnosis, facilitates prediction of the clinical course and prognosis. Genetic counselling of patients and their families on the risk of MCD recurrence in further generations and the question of prenatal genetic testing are possible when affected genes are identified in individual patients. Functional genetic studies allow understanding the pathophysiology of MCD and eventually leading to discovery of novel therapies for MCD.

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