Inborn errors of metabolism leading to neuronal migration defects

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Abstract
The development and organisation of the human brain start in the embryonic stage and is a highly complex orchestrated process. It depends on series of cellular mechanisms that are precisely regulated by multiple proteins, signalling pathways and non-protein-coding genes. A crucial process during cerebral cortex development is the migration of nascent neuronal cells to their appropriate positions and their associated differentiation into layer-specific neurons. Neuronal migration defects (NMD) comprise a heterogeneous group of neurodevelopmental disorders including monogenetic disorders and residual syndromes due to damaging factors during prenatal development like infections, maternal diabetes mellitus or phenylketonuria, trauma, and drug use. Multifactorial causes are also possible. Classification into lissencephaly, polymicrogyria, schizencephaly, and neuronal heterotopia is based on the visible morphologic cortex anomalies. Characteristic clinical features of NMDs are severe psychomotor developmental delay, severe intellectual disability, intractable epilepsy, and dysmorphisms. Neurometabolic disorders only form a small subgroup within the large group of NMDs. The prototypes are peroxisomal biogenesis disorders, peroxisomal ß-oxidation defects and congenital disorders of O-glycosylation. The rapid evolution of biotechnology has resulted in an ongoing identification of metabolic and non-metabolic disease genes for NMDs. Nevertheless, we are far away from understanding the specific role of cortical genes and metabolites on spatial and temporal regulation of human cortex development and associated malformations. This limited understanding of the pathogenesis hinders the attempt for therapeutic approaches. In this article, we provide an overview of the most important cortical malformations and potential underlying neurometabolic disorders.

KEYWORDS
cerebral cortex development, neuronal migration disorders, neurometabolism, peroxisome biogenesis disorders, peroxisomal ß-oxidation defects, O-glycosylation disorders.
1 | INTRODUCTION

The central nervous system (CNS) is the most complex structure of the human organism with a multitude of distinct cell types, arranged in well-defined, interacting substructures. Its development begins early during foetal life and is virtually completed only in late adolescence. The complexity of its overall structure and the subtly balanced interactions of single genes and non-genetic factors makes the CNS susceptible, especially in early developmental stages, for disturbances, which can result in a broad range of disorders. CNS malformations are clinically and genetically heterogeneous and can occur due to many interfering effects such as monogenetic disorders including inborn errors of metabolism (IEM) or because of damaging factors during prenatal development such as maternal infections, maternal metabolic disorders (eg, diabetes mellitus, phenylketonuria, hypothyroidism), trauma or drug use. Multifactorial causes are also possible. Consequences of an abnormal CNS development are neuronal tube defects (anencephaly, encephalocele), abnormalities of midline brain structures (eg, septo-optic dysplasia, agenesis/dysgenesis of the corpus callosum), cortical malformations (agyria, pachygyria, polymicrogyria, cobblestone, schizencephaly, heterotopia), abnormal brain volume (microcephaly, megalencephaly), and hydrocephalus. In general, the time point of prenatal interference determines the type of abnormality.

IEM comprise a heterogeneous group of disorders that affect many essential metabolic pathways involved inter alia in carbohydrate, amino acid, and fatty acid metabolism and/or the functionality of peroxisomes, lysosomes, mitochondria, and other organelles. The resulting accumulation of toxic intermediates, the reduced ability to synthesise metabolites or the defects in energy supply can severely interfere with the complex and finely tuned process of early brain development. This review gives an overview of the current concept of neuronal migration and, in particular, the diverse appearances of neuronal migration defects due to monogenetic IEMs.

1.1 | Brain development and neuronal migration

The development of the human brain including global structures and fine architecture is a highly complex orchestrated process involving temporally coordinated consecutive steps that dynamically interact with each other (Figure 1). It begins at gestational week 2 to 3 with the formation of the neuronal tube, which is then processed into the basic functional entities of the human brain. Particularly important for the further brain development are cell migration processes leading to the distinct spatial positioning of different types of neurons, which forms the defined multi-layer cortical architecture along with its characteristic folded appearance of gyri and sulci (Figure 2A). During cortical development, cells of the ventricular and subventricular zones of the telencephalon proliferate to generate precursor cells for neuronal and glial cells, which, in the further course, first migrate and then differentiate to form the distinct laminar sheets of the human cerebral cortex. The latter shows an “inside-out” composition with layers comprising specific neuronal cell types, which means that later migrating neurons have to cross the overlying already established layers to reach their final destination (Figure 2B). To control this process, radial glial fibres form a structural scaffold guiding newly formed neurons through the developing cortex. This review will focus on neuronal migration disorders (NMD) caused by metabolic disturbances.

2 | NEURONAL MIGRATION DISORDERS

Continuous advances in molecular genetic testing and imaging methods result in an explosive increase in the elucidation of previously undiagnosed or even undescribed diseases with cortical malformations. More than 500 different diseases with NMD are currently known. These are rare diseases with an estimated incidence of 1:100,000-1:250,000 newborns. Typical and frequent clinical symptoms pointing to NMD are severe psychomotor developmental delay, severe intellectual disability, an intractable epilepsy, and dysmorphisms. Affected brain structures are characteristically the cerebral and cerebellar cortex and the corpus callosum.
Disturbances in neuronal migration include a wide spectrum of disorders with various phenotypical manifestations. Subtypes are currently classified based on visible morphologic anomalies of the cortex (Figure 3).

2.1 Classification

Disturbances in neuronal migration include a wide spectrum of disorders with various phenotypical manifestations. Subtypes are currently classified based on visible morphologic anomalies of the cortex (Figure 3).

2.1.1 Lissencephaly spectrum (Agyria, Pachygyria, Cobblestone)

Malformations leading to agyria (no gyri) and pachygyria (few gyri) are characterised by a thickened cortex with less than six layers and an absent or reduced formation of gyri and sulci. (Figures 3B and 4A)

I) Classical lissencephaly (type 1 lissencephaly): Classical lissencephaly is characterised by a thickened cortex with a disturbed composition of the cortical layers often together with other malformations. It is frequently associated with mutations in genes encoding components of cytoskeletal structures.

II) Cobblestone lissencephaly (type 2 lissencephaly) (Figure 4C): Cobblestone lissencephaly shows an absent or diminished sulcation together with an uneven, “cobblestone-like” surface, due to neuroglial over migration through gaps in the basement membrane into the arachnoid space leading to the development of an extracortical layer. The cortex is usually less thickened compared with classical lissencephaly. Cobblestone type II lissencephaly is mainly associated with O-glycosylation defects.
2.1.2 | Polymicrogyria

Polymicrogyria is an etiologically heterogeneous disorder that can be caused by congenital infections, hypoxia, inflammation of the microvasculature, peroxisomal defects and different other genetic defects. It is characterised by an excessive number of small gyri and a disturbed cortical layering.2–5 (Figures 3C and 4B)

2.1.3 | Schizencephaly

Schizencephaly is an extremely rare cortical malformation characterised by a cleft lined with dysplastic grey matter extending from the ependyma to the pia mater. Depending on stricter definitions, sometimes only clefts filled with CSF are considered as schizencephaly.2,8,9 The aetiology is heterogeneous
and remains unknown for the majority of cases.\textsuperscript{9} (Figures 3D and 4D)

\textbf{2.1.4 | Neuronal heterotopias}

Grey matter heterotopias are characterised by a band (Figure 3E: Subcortical band heterotopia [SBH]) or nodules (Figure 3F: Periventricular nodular heterotopia) of neurons within the normally underlying white matter, either separated from the outer layer by cell-sparse areas or extending from the cerebral mantle from the pia to the ependyma.\textsuperscript{2,4,5} It is frequently associated with mutations in genes encoding components of cytoskeletal structures.\textsuperscript{5} (Figures 3E,F and 4E)

\textbf{2.2 | IEM with neuronal migration defects}

Monogenetic IEMs with NMDs are a rather small subgroup within the wide-ranging group of neuronal migration defects. In praxis, neuronal migration defects are typically divided into the histopathological or cMRI-based categories mentioned above, although their underlying genetic causes can differ widely. IEMs are extremely heterogeneous regarding disease genes, affected metabolic pathways, clinical courses, and outcomes. The precise pathophysiological processes for diverse organ manifestations including NMD are mostly unknown. Possible IEM-related causes for neuronal migration defects are, in varying degrees, the accumulation of toxic metabolites due to metabolic blocks, evasion to alternative metabolic pathways with harmful intermediates, a deficiency of building material for anabolic processes, and defects in energy production. Even within a distinct monogenetic disease, wide clinical spectra without simple genotype-phenotype correlations are possible.

Various pathophysiological causes can lead to the same but not to a specific pattern of neuronal migration defects. This pattern usually does not reflect the specific metabolic disturbances but rather the time when the interfering effect occurs. Depending on the disease, the inheritance patterns are mostly autosomal recessive but X-chromosomal recessive or mitochondrial genome heredity is also possible. The prototypes of neuro-metabolic disorders associated with neuronal migration defects are peroxisomal disorders (peroxisome biogenesis disorders [PBD], peroxisomal ß-oxidation defects) and congenital disorders of O-glycosylation. NMDs have also been sporadically described in other neuro-metabolic disorders—nevertheless, not as a consistent feature.

Disease-specific changes in the metabolic profile of individual patients can be used to diagnose an IEM with NMD. Affected genes, phenotype MIM numbers, and the biochemical and histopathological abnormalities associated with inborn IEM leading to neuronal migration defects are listed in Table 1.

\textbf{2.2.1 | Zellweger syndrome spectrum and ß-oxidation defects}

Peroxisomes are heterogeneous organelles bounded by a single membrane. They can be found ubiquitously in almost all human cells and contain a wide variety of enzymes that contribute to a multitude of metabolic key pathways like fatty acid alpha and beta-oxidation or oxygen metabolism.\textsuperscript{10} Peroxisomes include more than
| Table 1 | Inborn errors of metabolism leading to neuronal migration defects: genes, phenotype and biochemical abnormalities |
|---------|--------------------------------------------------------------------------------------------------------|
|         | Genes | Phenotype MIM number | Biochemical and histopathological abnormalities |
| Peroxisomal disorders |  |  |  |
| Peroxisome biogenesis disorders (Zellwegersyndromespectrum, ZSS) | PEX1 | 602136 | VLCFA↑, PH/PR↑, D/THCA↑, PL↓ |
| | PEX2 | 170993 |  |
| | PEX3 | 603164 |  |
| | PEX5 | 600414 |  |
| | PEX6 | 601498 |  |
| | PEX10 | 602859 |  |
| | PEX11beta | 603867 |  |
| | PEX12 | 601758 |  |
| | PEX13 | 601789 |  |
| | PEX14 | 601791 |  |
| | PEX16 | 603360 |  |
| | PEX19 | 600279 |  |
| | PEX26 | 608666 |  |
| Disorders with single peroxisomal protein defects | ACOX1 | 264470 | VLCFA↑, PH/PR(N), D/THCA(N), PL(N) |
| | HSD17B4 | 261515 | VLCFA↑, PH/PR↑, D/THCA↑, PL(N) |
| O-glycosylation defects |  |  |  |
| Walker Warburg syndrome (WWS) | POMT1 | 236670 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | POMT2 | 613158 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| Fukuyama congenital muscular dystrophy (FCMD) | FKTN | 253800 | CK: Age < 6 years: 10-60x above normal Age ≥ 7 years: 5-20x above normal Bedridden individuals: normal, abnormal alpha-dystroglycan staining on muscle biopsy |
| Muscle eye brain disease (MEB) | POMGNT1 | 253280 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | POMGNT2 | 614830 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| Acetylglicosaminyltransferase-like protein (LARGE) disease | LARGE1 | 613154 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| Fukutin-related protein (FKRP) | FKR | 613153 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | DAG1 | 616538 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | B4GAT1 | 615287 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | B3GALNT2 | 615181 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | POMK | 615249 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | ISP D | 614643 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |
| | RXYLT1 | 615041 | CK↑, abnormal alpha-dystroglycan staining on muscle biopsy |

(Continues)
50 enzymes, which catalyse a variety of reactions, both anabolic and catabolic. Anabolic functions include the biosynthesis of either phospholipids and cholesterol, which are important for the formation of brain myelin. Catabolic functions include the beta-oxidation of long-chain fatty acids and hydrogen peroxide-based respiration, which is important in the degradation of toxic substances that can either interfere with proper brain formation or damage brain structures. The crucial role of peroxisomes is reflected in the large number of severe human diseases, the majority with CNS abnormalities. Peroxisomal disorders are subdivided into two major categories. The first category includes PBD with disturbances in peroxisome formation resulting in multiple metabolic abnormalities. It includes Zellweger syndrome spectrum (ZSS). The second category is that of disorders with single peroxisomal protein defects and includes beta-oxidation defects. The genetic basis of PBD is mutations in one of the at least 14 PEX genes. For all other peroxisomal disorders, the genetic basis is mutations in the genes encoding the impaired peroxisomal enzyme/protein.

### Table 1 (Continued)

| Genes                  | Phenotype MIM number | Biochemical and histopathological abnormalities                                      |
|------------------------|----------------------|---------------------------------------------------------------------------------------|
| ATP6V0A2-related cutis laxa | ATP6V0A2 219200      | +/- CDG-II Isoelectric focusing of transferrin, abnormal ApoCIII isoelectric focusing |
| Pyruvate dehydrogenase (PDH) deficiency | PDHA1 312170          | Lactate(†), pyruvic acid†, alanine†, ammonia†,                                       |
| Glutaric aciduria type 2 (multiple acyl coenzyme A dehydrogenase deficiency) | ETFA 231680, ETFB 231680 | Organic acids: glutaric acid, dicarboxylic acids, C4-C18 carnitine†                  |
| Nonketotic hyperglycinemia (NKH) | AMT 605899, GLDC 605899, GCSH 605899 | Glycine†, CSF/plasma glycine ratio†                                                   |
| D-2-hydroxyglutaric aciduria | D2HGDH 600721       | Organic acids: D-2-hydroxyglutaric acid†, 2-ketoglutarate†                           |
| Smith-Lemli-Opitz syndrome | DHCR7 270400         | Cholesterol†, 7 and 8 -dehydrocholesterol†                                           |
| Menkes disease          | ATP7A 309400         | Copper†, ceruloplasmin†                                                              |
| Fumaric aciduria        | FH 606812           | Organic acids: Fumaric acid†, malic acid†, succinic acid†                            |

Abbreviations: CK, creatine kinase; D/THCA: di/trihydroxycholestanoic acid; PH, phytic acid; PL, plasmalogens; PR, pristanic acid; VLCFA: very long-chain fatty acid; †, elevated concentrations (CSF or blood or urine); †, decreased concentrations (CSF or blood or urine); +, feature present; −, feature not present.
**Clinical Severity**

| (A) | (B) | (C) | (D) | (E) |
| --- | --- | --- | --- | --- |

**FIGURE 5** Neuroimaging findings in peroxisomal disorders. (PBD; A-C, E) and ß-oxidation defects (D). The images are arranged in order of decreasing clinical severity. A, bilateral perisylvian polymicrogyria (white arrow) and slight cerebral atrophy with widening of the lateral ventricles, age 6 weeks, B, pachygyria (white arrow) as well as peritigonal white matter (WM) signal hypointensity on T1-weighted image, age 3 years and 11 month, C, widespread, patchy leukodystrophy and atrophy notably of the cerebral WM with enlarged lateral ventricles, age 17 years and 6 month, d) extensive leukodystrophy comprising cerebral and cerebellar WM, 3 years and 7 month, e) germinolytic cyst (white arrow), infant. In A, C, D axial T2-weighted and in B, axial T1 weighted image, in E, sagittal T1 weighted image.

Magnetic resonance imaging (cMRI)\(^{21-25}\) (Figure 5). In patients with severe PBD as well as with peroxisomal ß-oxidation defects ACOX1 and DBP,\(^{23,26}\) the characteristic findings are perisylvian polymicrogyria and frontoparietal pachygyria. In addition, brain atrophy, delayed myelination of the supratentorial white matter and germinolytic cysts in the caudatothalamic region can be present. In patients with milder PBD phenotypes, the characteristic finding is a progressive leukencephalopathy; the presence of migrational abnormalities is rare.

So far, studies in mouse models did not reveal a direct correlation between peroxisomal ß-oxidation or other peroxisomal pathway or metabolites like very long-chain fatty acids and NMD. Thus, not only functional peroxisomes but also other metabolic or non-metabolic factors are necessary for an undisturbed cortical development in mice and humans.\(^{27,28}\)

### 2.2.2 Congenital disorders of glycosylation

Congenital disorders of glycosylation (CDG) comprise a phenotypically heterogeneous group of genetically determined metabolic disorders that are characterised by disturbances in glycosylation reactions. Glycosylation is a crucial post-translational, and often complex, process; therefore, disturbances lead to a broad variety of multi-system disorders with a large spectrum of symptoms. More than 100 different types have been reported and their number is still increasing.\(^{29}\) CDGs can be divided into various subgroups depending on their underlying affected glycosylation pathways.

**Dystroglycanopathies (O-glycosylation defects)**

Dystroglycan is a component of the dystrophin-glycoprotein complex linking the actin cytoskeleton to the extracellular matrix.\(^{30}\) One of its subunits, α-dystroglycan, serves as a membrane-associated receptor for extracellular matrix proteins such as laminin. The extensive glycosylation of α-dystroglycan is a prerequisite for its functional activity. Dystroglycan contains O- and N-glycosylation sites, whereby the O-glycosylation is responsible for its laminin-binding activity.\(^{31}\) At present, autosomal recessive inherited mutations in 13 genes are published, which are associated with disturbances of α-dystroglycan glycosylation and NMD [DAG1 (OMIM 12839), POMT1 (OMIM 607423), POMT2 (OMIM 607439), POMGNT1 (OMIM 606822), LARGE (OMIM 603590), POMGNT2 (OMIM 614828), B4GAT1 (OMIM 605517), B3GALNT2 (OMIM 610194), POMK (OMIM 605862), FKTN (OMIM 607440), FKRP (OMIM 606596), ISPD (OMIM 614631), TMEM5 (OMIM 615041)]. Overall, dystroglycanopathies present variable manifestations with early to adult-onset forms and with limited genotype-phenotype correlation.\(^{32}\) O-glycosylation defects are phenotypically closely related with overlapping and merging symptom spectra\(^{33}\) (Figure 6). The clinical severity declines from the devastating Walker Warburg syndrome (WWS), through Fukuyama congenital muscular dystrophy (FCMD), muscle eye brain disease (MEB) and N-acetylglucosaminyltransferase-like protein (LARGE) disease to fukutin-related protein (FKRP) disease that can cause a more severe dystroglycanopathy with cerebral and ocular malformations and a less severe limb-girdle muscular dystrophy. A common clinical feature of these genetically
heterogeneous disorders is a congenital muscular dystrophy accompanied by brain and eye abnormalities. Severe forms are mainly characterised by extensive brain malformations with typical cobblestone type II lissencephaly and pontocerebellar hypoplasia while less severe manifestations may have a normal cortical pattern. Children affected with the most severe form, the WWS die within the first year of life, others may survive several decades. Characteristic diagnostic features of neuronal migration defects, which are caused by dystroglycanopathies are summarised in Table 1.

Cutis laxa

Cutis laxa are heterogeneous conditions whose shared characteristic is a loose, redundant, and wrinkly skin. The primary causes are often mutations in genes coding for structural proteins, nevertheless several metabolic disorders resulting in cutis laxa have also been described. One of these forms is the autosomal recessive cutis laxa 2A (ATP6V0A2-related cutis laxa, ATP6V0A2 (OMIM 611716)). ATP6V0A2 encodes an organelle proton pump. Biochemical characteristics of the ATP6V0A2-related cutis laxa are combined N- and O-glycosylation defects leading to an abnormal transferrin isoelectric focusing pattern (Table 1). Indicative of severe variants are distinct facial dysmorphisms, neurological impairment including seizures and cobblestone dysgenesis due to abnormal neuronal migration.35-37

2.2.3 Others

NMDs have also been described in other neurometabolic disorders. However, the description of findings, which may be related to neuronal migration disorders, mostly represent single observations and are not consistent features of the particular disease. An example is pyruvate dehydrogenase (PDH) deficiency due to mutations in one of the two subunits PDHA1 (PDHA1, OMIM 300502) and PDHB (PDHB, OMIM 179060) of the mitochondrial pyruvate dehydrogenase multienzyme complex.38 Four reported cases showed NMD at autopsy by macroscopic and histological analysis. One of the two PDHA1 cases had parieto-occipital pachgyria and polymicrogyria whereas the other had periventricular nodular heterotopias. The two PDHB cases had frontal pachgyria. Zand et al reported a further newborn PDH deficient case with neuronal migration defects.39 Prenatal and postnatal cMRI as well as an autopsy revealed pachgyria, polymicrogyria, and focal heterotopia in the right frontal lobe.

For glutaric aciduria type 2 (multiple acyl-coenzyme A dehydrogenase deficiency, MIM 231680), an autosomal recessive disorder of fatty acid and amino acid oxidation, pachgyria was reported for two infants on autopsy.40 In nonketotic hyperglycaemia, a disorder of glycine metabolism, cortical malformations have been described, including pachgyria and gyral simplification on cMRI, respectively.41 Gyration abnormalities have also been seen in D-2-hydroxyglutaric aciduria, a neurometabolic
disorder with two genetic subtypes \([D2HGDH, (OMIM 609186); IDH2 (OMIM 147650)]\), which is characterised by an accumulation of D-2-hydroxyglutarate in body fluids.\(^{43}\) Parieto-occipital pachygyria was reported in one patient\(^{44}\) and delayed gyration in 10 out of 17 patients.\(^{44,45}\)

Migration defects have also been reported in Smith-Lemli-Opitz syndrome (\(DHCR7, (OMIM 602858)\) and Menkes disease (\(ATP7A, (OMIM 300011)\).\(^{46}\) A pachygyria on CT scan and at autopsy could be revealed in single patients with Smith-Lemli-Opitz syndrome, an autosomal recessive disorder caused by a genetic defect in cholesterol biosynthesis.\(^{47,48}\) In Menkes disease, caused by an impaired copper metabolism, cortical laminations were shown in three patients in microscopical studies of brain autopsy tissue.\(^{49}\) For fumaric aciduria (\(FH, (OMIM 136850)\)), an autosomal recessive disorder caused by an impaired fumarate hydratase, an enzyme that catalyses the transformation of fumarate into malate in the Krebs cycle, diffuse polymicrogyria on cMRI was reported for one infant\(^{50}\) and eight infants.\(^{51}\)

Depending on the IEM various biochemical markers can provide diagnostic information about the potential underlying genetic defect (Table 1).

### 3 SUMMARY AND CONCLUSION

Formation and folding of the cerebral cortex during embryonic development depends on complex cellular mechanisms that are precisely regulated by multiple proteins, signalling pathways and non-protein-coding genes. Malformations of cortical development lead to a wide range of neurodevelopmental disorders. A small subgroup of these are neurometabolic disorders. Neuronal migration defects are very specific for peroxisomal biogenesis disorders, the peroxisomal \(\beta\)-oxidation defects \(ACOX1\) and \(DBP\) and for congenital disorders of \(O\)-glycosylation. Although the rapid evolution of biotechnology has resulted in an ongoing identification of metabolic and non-metabolic disease genes for cerebral cortex development, we are far away from understanding the specific role of cortical genes and metabolites on the spatial and temporal regulation of human cortex development and associated malformations. Thus, future challenges are to understand these genetic and non-genetic regulatory processes and to develop therapeutic approaches accordingly. Since cerebral malformations manifest during embryonic and foetal development future foetal gene or enzyme replacement therapies in conjunction with postnatal treatments might be an option.

### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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