Neurometabolic disorders

Five new things

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Abstract

Purpose of review: To present emerging issues in neurometabolic disorders, with an emphasis on the diagnostic workup of patients with suspected neurometabolic disorders and some future challenges in the care for these patients. **Recent findings:** Next-generation sequencing and next-generation metabolic screening increase the speed and yield of the diagnostic process in neurometabolic disorders. Furthermore, they deepen our insights into the underlying disease mechanisms. Care of adult patients with neurometabolic disorders is an expanding subspecialty, especially in internal medicine and neurology.

Summary: We briefly discuss some novel genetic and biochemical laboratory techniques and changing insights in the molecular basis of disease, and illustrate the importance of MRI pattern recognition in the diagnostic process. Furthermore, we discuss gene therapy that is cautiously entering the field, and pay attention to the new field of (transition of) care for adult patients with inborn errors of metabolism.

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Because inborn metabolic diseases—as a group—are difficult to define,¹ it seems reasonable neither to give a precise definition of neurometabolic disorders nor to review the many different neurologic signs and symptoms with which they may present. We will instead describe Five new things in the field of neurologic disorders that are caused by genetic defects in cell metabolism. A tremendous modern diagnostic armamentarium has enabled early diagnosis of many of these rare disorders, as well as the recognition of dozens of new ones. Although most diseases can nowadays only be treated symptomatically, disease-specific treatment strategies are visible on the horizon for some.

To understand the diagnostic and therapeutic advances, one may want to keep the classical concepts of inborn errors of metabolism in mind, since they offer the principal paradigms for the basic understanding of this intriguing group of diseases (figure 1). Genes involved in inborn errors of metabolism generally encode enzymes (catalyzing biochemical reactions), cofactors (supporting enzymes), and transmembrane transporters. Absent or abnormal functioning of

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Figure 1 Mechanisms of disease

Deficient enzyme activity of 1 of the 3 enzymes involved in dopamine biosynthesis, or lack of their cofactors tetrahydrobiopterin and pyridoxine (depicted with an asterisk), leads to neuronal dopamine shortage and thus compromised dopaminergic neurotransmission. In patients with aromatic amino acid decarboxylase (AADC) deficiency, a novel metabolite (3-O-methyldopa), otherwise not found in healthy persons, can be detected in body fluids. Treatment options can directly target the underlying molecular defect. Examples are drugs that replenish the missing metabolite (L-dopa for tyrosine hydroxylase deficiency), drugs that substitute the missing end product (dopa-agonists for all dopamine biosynthesis defects), vitamin supplementation to augment residual enzyme activity (pyridoxine for AADC deficiency), and gene therapy (for AADC deficiency, see text).

such proteins leads to accumulation (before the metabolic block) or deficiency (after the block) of metabolites. Eventually novel metabolites occur that are formed in alternative, otherwise unused pathways. Accumulation of metabolites leads to storage disorders with filling of cell compartments and tissues, as can be encountered in some lysosomal storage disorders. Accumulation can, alternatively, lead to intoxication, like coma in hyperammonemia due to urea cycle defects. Depending on the metabolic pathway that is involved, and the tissues in which this pathway is relevant, clinical symptomatology occurs in one or more organs.

Advances in laboratory diagnosis

Modern DNA sequencing technologies, generally referred to as next-generation sequencing (NGS), are tools in the diagnosis of known neurogenetic disorders, while they are also leading to the discovery of the molecular basis of many new disorders. NGS comprises a variety of techniques, allowing targeted analysis of relevant gene panels for different disease groups

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(e.g., epilepsies and movement disorders) or untargeted DNA analysis. Untargeted analysis can cover all coding regions of the DNA (whole exome sequencing), but may, besides the coding regions, even include the noncoding regions (whole genome sequencing; for further reading, see reference 2). In daily clinical practice, the choice between single gene testing or NGS (gene panel, exome, and genome sequencing) will strongly depend on their availability and costs, but also on the patient's phenotype, and additional information from the family history. A recognizable disorder will generally lead to Sanger sequencing of the causative gene. Ideal candidates for NGS are patients with nonspecific but clearly definable phenotypes linked to dozens of genes, like, e.g., hereditary spastic paraplegia, especially when they are from large families with multiple affected members. The latter allows segregation analysis in a pedigree to help distinguish gene variants from disease-causing mutations.

The fact that many novel genes, discovered by NGS, encode proteins with unknown functions seriously mystifies the relationship between the mutated gene and the patient's disorder. The same problem may also be encountered when novel variants are found in known genes. Following the rapidly growing availability of genetic tests in clinical practice, there is a need for advanced functional techniques to study the biological effect of gene alterations. In other words, functional studies are necessary to bridge the gap between the abnormal genetic code and the diseased patient. Conventional biochemical techniques provide information on specific groups of metabolites (amino acids, organic acids), and have proven to be useful in diagnosing known and discovering novel disorders based on specific metabolic fingerprints. Powerful holistic techniques, however, are currently entering the field. In analogy to the novel genetic techniques, they have been coined next-generation metabolic screening and omics techniques (e.g., metabolomics, lipidomics).

3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like (MEGDEL) syndrome is a unique Leigh-like disorder with dystonia and deafness, 3-methylglutaconic aciduria, and a highly characteristic brain MRI pattern (see next paragraph and figure 2).^{3,4} With exome sequencing, mutations in the *SERAC1* gene were identified as the underlying course.⁵ This gene was known to contain a lipase domain but its exact role in human metabolism was unknown. With lipidomics techniques on cell extracts of patients, it was possible to demonstrate abnormal concentrations of specific phospholipids.⁵ This result was among the first steps towards the identification of the SERAC1 protein as a key player in phosphatidylglycerol remodeling, essential for both mitochondrial function and intracellular cholesterol trafficking. The article illustrates the power of combining different modern techniques, namely NGS (identifying the gene), classic metabolomics (demonstrating 3-methylglutaconic aciduria), and novel lipidomics (characterizing specific phospholipids), for unraveling the molecular basis of diseases and the complexity of normal brain metabolism.

The human metabolome consists of more than 10,000 small molecules (metabolites). Classic, targeted metabolomics, e.g., analysis of amino acids or organic acids, is a mainstay in the diagnostic workup of inborn errors of metabolism and during follow-up (monitoring of therapy). Untargeted metabolomics techniques are currently being developed in several genetic and metabolic laboratories in addition to these conventional analyses.⁶ They aim to identify and quantify a vast majority of all metabolites in body fluids or cell extracts. Proton nuclear

Figure 2 Characteristic and recognizable MRI patterns of some well-known, prototypic neurometabolic disorders and some novel disorders

(A, B) X-linked adrenoleukodystrophy with characteristic dorsal predominance and involvement of the corpus callosum. MRI (age of patient: 10 years) depicts 3 zones of different disease activity: the central, burnt-out zone, the contrast-enhancing inflammatory zone, and the outermost zone of demyelination extending with finger-like T2 hyperintensity beyond the enhancing middle zone. (C, D) Metachromatic leukodystrophy with characteristic involvement of the corpus callosum and a so-called tigroid pattern of radiating stripes of more normal signal within the abnormal white matter (age of patient: 2 years).¹⁸ (E–K) Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate is characterized by selective involvement of brainstem and spinal cord tracts (age of patient: 10 years): the pyramidal tract over its entire length in corona radiata (K), posterior limb of the internal capsule (J), pons and medulla (F–I), sensory tracts in the dorsal columns (E, F), lemniscus medialis (I), corona radiata (K), the superior (I) and inferior (G, H) cerebellar peduncles, the anterior spinocerebellar tracts at the level of the medulla (lateral, in F), and the intraparenchymal trigeminal nerve (I).¹¹ (L, M) The eye of the tiger sign in a 15-year-old adolescent with neurodegeneration with brain iron accumulation due to *PANK2* gene mutations. MRI shows T2-hyperintense foci within the T2-hypointense pallidum, the former assumedly resulting from tissue destruction, the latter from iron deposition. (N, O) The putaminal eye in 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome. There is a characteristic temporal pattern of basal ganglia changes with initial T2 hyperintensity of the pallidum, followed by T2 hyperintensity and swelling of caudate and putamen when normal signals of the mid-dorsal putamens look like eyes in the putamen (N, O; MRI at age 15 months). Ultimately, atrophy of the basal ganglia as well as cerebellum and cerebral hemispheres occurs.⁴ MRI sequences: T2: A, C–K, L–N; fluid-attenuated inversion recovery: O; T1 plus contrast: B.

magnetic resonance (MR) spectroscopy is an untargeted technique that has relatively limited sensitivity but nevertheless has been successful in identifying several novel inborn errors of metabolism.^{7,8} Current, ultramodern high-resolution mass spectrometers have a much higher sensitivity, reaching a detection limit in the low nanomolar range.⁶ Similarly, untargeted lipidomics techniques allow identification and quantification of the several thousand different lipid species that are present in the human body.⁶

Advances in neuroradiology

During the past decades, major technical improvements and the availability of modern MRI apparatus in large parts of the world have substantially contributed to early recognition of

neurometabolic disorders as a group. Meanwhile, it has become clear that individual disorders may have characteristic, eventually pathognomonic MRI abnormalities (figure 2).^{9–11} MRI pattern recognition has proven to be a fruitful starting point in the diagnostic process, in the best case directly leading to targeted laboratory workup of the suspected metabolic pathway and gene. Such a straightforward approach reduces the length of the diagnostic process, may prevent the patient from being exposed to unnecessary procedures, may eventually lead to the early recognition of a treatable disorder, and last but not least will save costs. Besides this, MRI pattern recognition has also been at the basis of the definition of many new neurometabolic disorders (figure 2).^{9–11} Relatively novel MR techniques, like diffusion-weighted imaging, are contributing to the growing understanding of the disease mechanisms that underlie white matter pathology based on changes of water molecule motility in the extracellular space.¹² Proton MR spectroscopy gives new insights into in vivo brain composition and metabolism, complementary to classic (ex vivo) metabolic studies in body fluids and tissues, and can as such be used for diagnostic purposes and therapeutic monitoring, e.g., in disorders of creatine transport and metabolism.^{13,14}

Changing biochemical and genetic concepts

Interestingly, some of the above-mentioned discoveries have forced us to rethink the basic principles of Mendelian inheritance in man. A single gene is generally linked to one clinical phenotype, sometimes with a broad phenotypic spectrum but always transmitted via one of the classic modes of inheritance (autosomal dominant or recessive, X-linked, or maternal). In this context, many neurometabolic disorders follow an autosomal recessive mode of inheritance with asymptomatic carriership of both parents. Similarly, in families with X-linked recessive disorders, female carriers are generally considered to remain without symptoms. Although these rules of thumb are still applicable to most genes and disorders, a growing number of important exceptions have appeared on the horizon.

Mutations of the *ABCD1* gene, encoding the peroxisomal transporter of very long-chain fatty acids (VLCFA), cause X-linked adrenoleukodystrophy (X-ALD). Elevated plasma and tissue concentrations of VLCFA are the biochemical hallmark of X-ALD and lead to a wide disease spectrum in boys and adult men, ranging from isolated adrenal insufficiency to fatal cerebral demyelination (illustrated in figure 2).¹⁵ For several decades, it has been noticed that the general rule for X-linked recessive disorders (female carriers remain asymptomatic) does not hold true for X-ALD carriers. Recently it has even been shown that X-ALD carriers are highly likely to develop symptoms, mostly related to myelopathy.¹⁶ In contrast to the invariable increase of plasma VLCFA levels in male patients with X-ALD, up to almost 1/3 of the female carriers have normal plasma VLCFA concentrations. Taking all pitfalls into account, female X-ALD carriers are at risk to remain unrecognized and diagnosed with other disorders, eventually followed by inappropriate therapeutic choices.¹⁶ It is of interest that there is still controversy over whether the most logical underlying disease mechanism, namely skewed X-inactivation, predicts the symptomatic status of X-ALD carriers.

Recently, it has been discussed that mutations in the *ALDH18A1* gene, encoding an enzyme essential in proline and ornithine biosynthesis, account for a wide phenotypic spectrum ranging from autosomal dominant, pure hereditary spastic paraplegia (HSP) to complex HSP with intellectual disability, with or without cutaneous abnormalities and cataract, and an autosomal recessive mode of inheritance.¹⁷ The *ALDH18A1* gene is only one example of a growing number of genes associated with autosomal recessive as well as dominant disorders (table). As already shortly touched on for X-ALD, the traditional explanations for differences in phenotypes (e.g., levels of residual enzyme activity correlate with disease severity) generally are not satisfactory; in most cases, further studies will be necessary to unravel the cellular mechanisms underlying these phenomena.

Table Examples of genes that are associated with neurologic disorders with autosomal dominant (or de novo heterozygous) occurrence as well as autosomal recessive inheritance patterns

Gene	Protein function	Dominant disorder, or de novo mutation	Recessive disorder
AFG3L2	Subunit of a mitochondrial protease complex; binding partner of paraplegin (see below)	SCA28 ²³	Spastic ataxia and neuropathy ²⁵
		Optic atrophy and ID ²⁴	
ALDH18A1	Enzyme; proline and ornithine biosynthesis from glutamate	Pure HSP (SPG9) ^{17,26}	Complex HSP (ID, spasticity, cataract, cutis laxa) ^{28,17}
		Cutis laxa and progeroid features ²⁷	
GRID2	Glutamate receptor subunit δ -2	Congenital cerebellar ataxia ²⁹	Complex ARCA ^{29,30}
KIF1A	Axonal transport of synaptic vesicles	ID, spasticity, cerebellar atrophy, optic nerve atrophy, peripheral neuropathy, epilepsy ³¹	HSAN-II ³⁵
		PEHO syndrome ³²	
		Neurodegenerative disorder ³³	Complex HSP (spasticity, cerebellar ataxia, peripheral neuropathy; SPG30) ³⁶
		Pure HSP ³⁴	
NALCN	Ion channel	CLIFAHDD syndrome ³⁷	INAD with facial dysmorphism ³⁸
REEP2	Shaping of the endoplasmic reticulum	Pure HSP ³⁹	Pure HSP ³⁹
SPG7	Paraplegin; assembles with AFG3L2 to form a mitochondrial protease complex (see above)	Isolated optic neuropathy or complex HSP (spasticity $\pm$ cerebellar ataxia $\pm$ optic neuropathy) ⁴⁰	Complex HSP (spasticity, cerebellar ataxia, optic neuropathy; SPG7) ⁴²
		PEO $\pm$ cerebellar ataxia ⁴¹	PEO with spastic ataxia ⁴¹
			Pure cerebellar ataxia ⁴³
SPTBN2	Cytoskeletal protein; β -III spectrin	SCA5 ^{44,45}	ARCA ^{45,46}

Abbreviations: ARCA = autosomal recessive cerebellar ataxia; CLIFAHDD = congenital contractures of the limbs and face, hypotonia, and developmental delay; HSAN = hereditary sensory and autonomic neuropathy; HSP = hereditary spastic paraplegia; ID = intellectual disability; INAD = infantile neuroaxonal dystrophy; PEHO = progressive encephalopathy, edema, hypersarhythmia, and optic atrophy; PEO = progressive external ophthalmoplegia; SCA = spinocerebellar ataxia; SPG = spastic paraplegia.

Therapeutic advances

Neurometabolic disorders can be treated at 3 logic disease-specific levels (see also figure 1). First, gene therapy would replace the mutated DNA code by healthy copies, and thus offer affected cells the opportunity to produce normal protein again. Second, enzyme replacement therapy would supply the body with the protein that is lacking. Third, interventions at the metabolite level aim to decrease the flux through the pathway (in defects that lead to accumulation or toxicity), or to replenish substrates to compensate for deficiencies. Typical challenges encountered in therapy development are the difficult accessibility of the CNS and safety issues because of its vulnerability. Furthermore, early timing of therapeutic interventions is of utmost importance because of the limited regenerative capacity of the brain.

From all new developments in the field of therapies for neurometabolic disorders, the recent advances in gene therapy might fit the best in this article. Although heavily hyped in the early 1990s as the answer to many genetic diseases, gene therapy has only lived up to its promises during the last few years. Many safety issues have finally been resolved, and strategies for gene delivery to the brain (which generally rely on adeno-associated virus [AAV] as a vehicle) have

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markedly improved. Consequently, gene therapy nowadays seems within reach for some neurometabolic disorders.

Metachromatic leukodystrophy (MLD) is a fatal white matter disorder affecting the central and peripheral system, generally, but not exclusively presenting in the paediatric population.¹⁸ MLD can be recognized based on its typical MRI pattern (figure 2), and diagnosis is straightforward by demonstrating deficient arylsulfatase A (ARSA) enzyme activity in leukocytes, and *ARSA* gene mutation analysis.¹⁸ So far, no disease-specific treatment is available for MLD. In an open-label, single-arm, phase I/II clinical study, French investigators assess the safety and efficacy of *ARSA* gene transfer in the brain of children with MLD. Patients at a presymptomatic or early disease stage are given 12 simultaneous injections of the investigational product in the white matter of both cerebral hemispheres through image-guided tracks (for details, see www.clinicaltrials.gov [identifier: NCT01801709]). The preliminary results of this study are cautiously reported to be promising (personal communication, 15 Years Center for Childhood White Matter Disorders symposium, Amsterdam, the Netherlands, October 2015).

In contrast to MLD, where large brain areas are affected and investigators logically aim for global gene delivery, other neurometabolic disorders may benefit from injections targeted to small brain areas (local gene delivery). The latter has been performed in aromatic amino acid decarboxylase (AADC) deficiency, an autosomal recessively inherited defect of neurotransmitter biosynthesis.^{19,20} AADC catalyzes the final step in the biosynthesis of dopamine (depicted in figure 1) as well as serotonin. This disorder can be diagnosed based on measurement of abnormal neurotransmitter metabolites in CSF, demonstrating AADC enzyme deficiency in plasma, and *AADC* gene mutation analysis. Most patients have an infantile-onset, severe neurologic disorder dominated by a complex movement disorder. AADC deficiency is notoriously difficult to treat, and subsequently, life expectancy is seriously reduced.¹⁹ The first experiences with *AADC* gene delivery to the human brain originate from adult neurology, where patients with Parkinson disease have experimentally had intrastriatal infusion of an AAV vector containing the *AADC* gene.²¹ The investigators aimed to increase the capacity of putaminal neurons to synthesize dopamine from levodopa, in an attempt to successfully treat patients with lower (orally administered) doses of levodopa and thus prevent the typical side effects associated with higher doses.²¹ In AADC deficiency, *AADC* gene delivery to the substantia nigra would theoretically be the ultimate, curative treatment strategy, replacing the inherited mutated gene by normal copies. Following the technical advances in the context of Parkinson disease, and with a relatively high incidence of AADC deficiency in Taiwan, gene therapy has further been developed and applied in pediatric patients with AADC deficiency by Taiwanese investigators.²⁰ While the first, short-term results show beneficial motor responses, a second gene therapy trial for AADC deficiency is being prepared in the United States.

Transition of care

All above-mentioned developments have led to a growing exposure to neurometabolic disorders in clinical practice as well as in the scientific community, and subsequently have considerably

increased the awareness for these disorders in children and also in adults. Moreover, improved survival of children with classical phenotypes, and the recognition of late-onset disorders presenting in adulthood, lead to an absolute increase of numbers of adult patients with neurometabolic disorders. The care for these patients is a rather new and expanding subspecialty, especially in internal medicine and neurology. The Society for the Study of Inborn Errors of Metabolism (SSIEM) Adult Metabolic Physicians Group has recently stressed the growing need for multidisciplinary services specialized in the care of adults with inborn errors of metabolism.²² In their article, they report the distribution of the many different disorders in a large European multicenter cohort of more than 6,000 adults, in order to anticipate facilities and staffing needed in these and other future centers. The most common diseases followed by these specialized clinics were phenylketonuria (20.8% of all patients), mitochondrial disorders (14%), and lysosomal storage disorders like Fabry disease (8.9%) and Gaucher disease (4.2%). Although many of them are not primary neurologic disorders, most threaten normal brain functioning in the long run as part of their natural history if left untreated or during phases of acute decompensation. Since all these disorders are very rare, most neurologists are not familiar with cell metabolism in general and metabolic medicine in particular, and training programs and congresses for residents and seniors in neurology generally do not cover this topic in much detail, many challenges can be expected. Health care professionals, neurologists, and pediatricians, who are now or in the future will be responsible for the transition of neurologic care for these vulnerable teenagers and adult patients, should not wait but anticipate these challenges. While doing so, they can look forward to the discovery of an intriguing world that helps us to understand not only many different, complex neurologic diseases, but also the metabolic basis for normal brain functioning.

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Neurometabolic disorders: Five new things

- Next-generation sequencing and next-generation metabolic screening increase the speed and yield of the diagnostic process in neurometabolic disorders and deepen our insights into the underlying disease mechanisms.
- Recognition of disease-specific MRI patterns is of great importance: it leads to targeted and swift diagnostic workup, prevents the patient from being exposed to unnecessary, eventually invasive procedures, may eventually lead to the early recognition of a treatable disorder, and saves costs.
- Some neurometabolic disorders follow the classic autosomal recessive mode of inheritance, but can also be transmitted as an autosomal dominant trait in other families.
- Gene therapy is cautiously entering the field as an experimental treatment option for neurometabolic disorders.
- The care of adult patients with inborn errors of metabolism is still in its infancy, and future professionals in this field may anticipate many challenges.

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AUTHOR CONTRIBUTIONS

M.A.W., I.H., and R.A.W. wrote the manuscript. M.A.W. and R.A.W. created figure 1 and table 1. M.A.W. and I.H. created figure 2.

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