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Review

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328045).

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Received 18 September 2021
Accepted 2 January 2022

To cite: Fernández-Eulate G, Carreau C, Benoist J-F, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2021-328045

ABSTRACT

Neurometabolic diseases are a group of individually rare but numerous and heterogeneous genetic diseases best known to paediatricians. The more recently reported adult forms may present with phenotypes strikingly different from paediatric ones and may mimic other more common neurological disorders in adults. Furthermore, unlike most neurogenetic diseases, many neurometabolic diseases are treatable, with both conservative and more recent innovative therapeutics. However, the phenotypical complexity of this group of diseases and the growing number of specialised biochemical tools account for a significant diagnostic delay and underdiagnosis. We reviewed all series and case reports of patients with a confirmed neurometabolic disease and a neurological onset after the age of 10 years, with a focus on the 36 treatable ones, and classified these diseases according to their most relevant clinical manifestations. The biochemical diagnostic approach of neurometabolic diseases lays on the use of numerous tests studying a set of metabolites, an enzymatic activity or the function of a given pathway; and therapeutic options aim to restore the enzyme activity or metabolic function, limit the accumulation of toxic substrates or substitute the deficient products. A quick diagnosis of a treatable neurometabolic disease can have a major impact on patients, leading to the stabilisation of the disease and cease of repeated diagnostic investigations, and allowing for familial screening. For the aforementioned, in addition to an exhaustive and clinically meaningful review of these diseases, we propose a simplified diagnostic approach for the neurologist with the aim to help determine when to suspect a neurometabolic disease and how to proceed in a rational manner. We also discuss the place of next-generation sequencing technologies in the diagnostic process, for which deep phenotyping of patients (both clinical and biochemical) is necessary for improving their diagnostic yield.

INTRODUCTION

Inborn errors of metabolism with neurological manifestations, or neurometabolic diseases, are a group of heterogeneous genetic disorders that share in common the alteration of specific aspects of the cellular metabolism, ultimately leading to disease. Often first described by paediatricians, the more recently reported adult-onset forms have phenotypes sometimes considerably different from paediatric ones, which may mimic other more common neurological disorders in adults, thus justifying a specific approach.[1–3] Adult-onset neurometabolic diseases are individually rare, numerous, heterogeneous and frequently show complex clinical presentations. These reasons, in addition to the myriad of specialised biochemical diagnostic tools available,[4] account for a significant diagnostic delay and underdiagnosis.[5] However, unlike many other neurogenetic diseases, a substantial part of neurometabolic diseases can be successfully treated, with both conservative and more recently approved innovative therapeutics. Early recognition and diagnosis of a treatable neurometabolic disease can have a major impact for patients, leading to the stabilisation of the disease or even the regression of some signs and symptoms, halting unnecessary diagnostic investigations, and allowing for family screening and treatment of presymptomatic carriers.

For all of the aforementioned, an overview of adult-onset neurometabolic diseases will be outlined, from important general considerations to phenotypical descriptions focused on treatable diseases. Furthermore, a simplified diagnostic approach for the adult neurologist will be presented, with the aim to help determine when to suspect a neurometabolic disease and how to further proceed in a rational manner.

METHODS

Search strategy and selection criteria

Neurometabolic diseases are a group of genetic disorders that share in common the alteration of the cellular metabolism, ultimately leading to disease including neurological manifestations. This definition has its limitations, given that many neurological diseases may be associated to changes in cellular metabolism that participate in some degree to the pathogenesis of the disease. Within the aim of a pragmatic clinical approach, this review will consider as a neurometabolic disease those that can be either diagnosed on characteristic biochemical abnormalities, indicating an alteration of an specific metabolic pathway, and/or those that may respond to treatments aimed at correcting a given metabolic dysfunction.[6] In order to review all adult-onset neurometabolic diseases, we first searched PubMed for article abstracts published in English, French and Spanish using the search terms “inborn errors of metabolism”, “metabolic disease” and “neurometabolic disease”, and reviewed the book by Hollak and Lachmann in 2016[7] to assemble all adult-onset neurometabolic diseases, including patients from any ethnic origin (see online supplemental material 1). Furthermore, we consider as ‘adult onset’ those

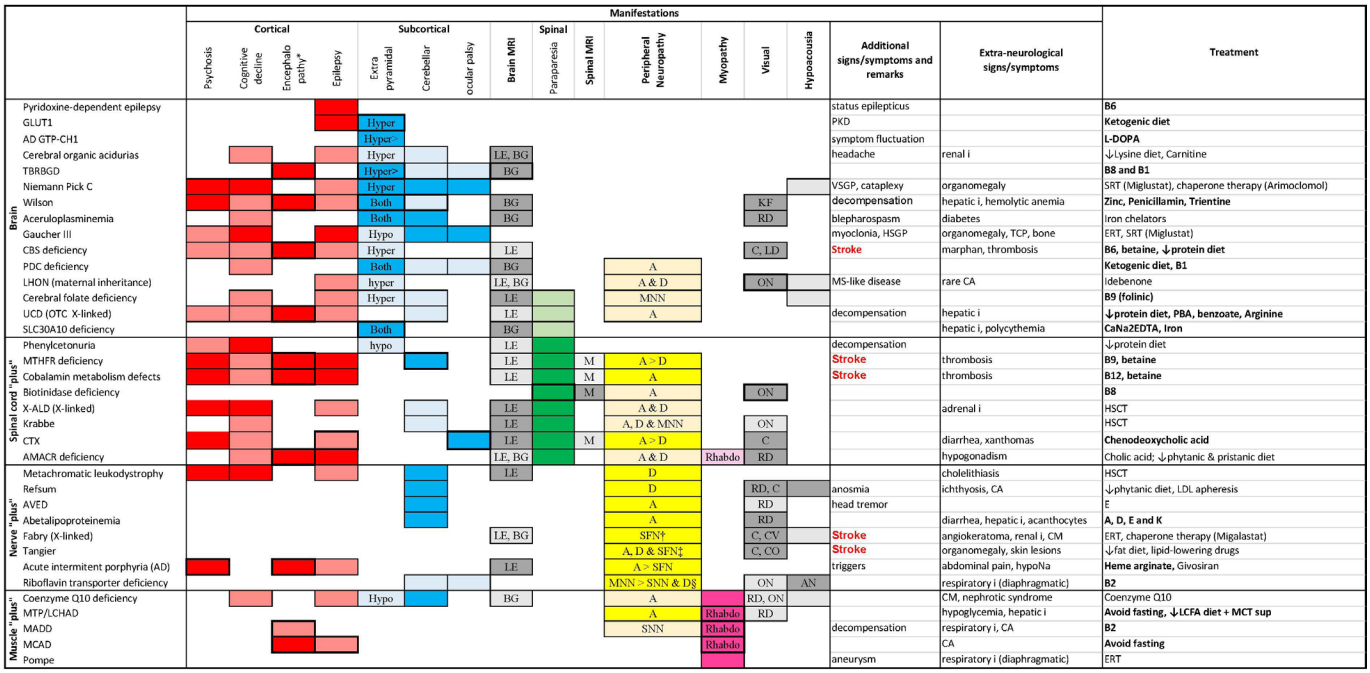

Figure 1 Neurological and extraneurological manifestations of treatable adult-onset neurometabolic diseases. Neurometabolic diseases are classified according to their neurological systematisation: brain: encephalic involvement; spinal cord 'plus': associated spinal cord involvement; nerve plus: associated nerve involvement; muscle plus: associated muscle involvement. The boxes have been coloured according to the topography of the manifestation: red for cortical, blue for subcortical, green for spinal cord, yellow for peripheral nerve and pink for muscle manifestations. Dark colours correspond to 'major' manifestations, whereas dull colours correspond to 'minor' manifestations (see text). When the box is framed in bold, it means that the manifestation in question may be acute/subacute in presentation. Extrapyramidal involvement is hypokinetic when it corresponds to parkinsonism and hyperkinetic in the case of dystonia chorea or ballismus. Cobalamin metabolism defect: predominantly clbC and cblB deficiency. *Acute or subacute change in mental status (confusion or coma). †Compressive neuropathy. ‡Pseudo-syringomyelic syndrome, multifocal demyelinating polyneuropathy with conduction blocks. §Cranial neuropathy. The authors have created and have permission to use the image. A, axonal; AD GTP-CH1,autosomal dominant GTP cyclohydrolase 1; AMACR, alpha-methylacyl-CoA racemase; AN, auditory neuropathy; AVED, ataxia due to vitamin E deficiency; BG, basal ganglia signal abnormality; C, cataract; CA, cardiac arrythmia; CBS, cystathionine beta-synthase; CM, cardiomyopathy; CO,corneal opacities; CTX, cerebrotendinous xanthomatosis; CV, cornea verticillata; D, demyelinating; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; HSGP, horizontal supranuclear gaze palsy; hyper, hyperkinetic; hypo, hypokinetic; I, insufficiency; KF, Keyser-Fleisher ring; LCFA, long-chain fatty acid; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency; LD, lens dislocation; LDL, low-density lipoprotein; LE, leucoencephalopathy; LHON, Leber hereditary optic neuropathy; M, myelitis (spinal MRI T2 hyperintensities); MADD,multiple acyl-CoA dehydrogenase deficiency; MCAD, medium-chain acyl-coenzyme A dehydrogenase deficiency; MCT, medium-chain triglyceride; MNN, motor neuronopathy; MS, multiple sclerosis; MTHFR, methylenetetrahydrofolate reductase; MTP, mitochondrial trifunctional protein deficiency; ON, optic neuropathy; OTC, ornithine transcarbamylase; PBA, phenylbutyrate; PDC, pyruvate dehydrogenase complex; PKD, paroxysmal kinesigenic dyskinesia; RD, retinal dystrophy; Rhabdo, rhabdomyolysis; SFN, small-fibre neuropathy; SNN, sensory neuronopathy; SRT, substrate reduction therapy; TBRBGD, thiamin and biotin responsive basal ganglia disease; TCP, thrombocytopenia; UCD, urea cycle disorder; VSGP, vertical supranuclear gaze palsy; X-ALD, X-linked adrenoleucodystrophy.

patients with a genetically confirmed neurometabolic disease and an onset of neurological symptoms after 10 years since patients with a given neurometabolic disease and an onset of progressive neurological symptoms after this age usually present a rather homogeneous phenotype, which differs from earlier-onset forms.[8–10] We did not exclude as adult onset those patients with subtle and non-progressive symptoms before the age of 10 years of age that could go overlooked, such as mild intellectual disability.

Subsequently, we undertook a focused search in PubMed for articles in those same languages, using each previously identified adult-onset neurometabolic disease as a search term, with the aim to refine the adult-onset neurometabolic diseases selection and to identify those where a disease-modifying therapy is currently available (figure 1 and online supplemental material 2). We collected all clinical, MRI, biochemical and therapy data concerning these diseases. Although numerous and different classifications exist, these treatable adult-onset neurometabolic diseases were classified and presented in a clinically relevant manner, meaning that disorders with similar clinical characteristics and common biochemical tests were grouped together.

REVIEW

KEY CONCEPTS IN NEUROMETABOLIC DISEASES

Pathophysiology

Neurometabolic diseases are often due to an enzyme deficiency or dysfunction, potentially causing substrate accumulation upstream of the enzymatic block and a lack of downstream product synthesis (figure 2). If the accumulation of substrates is toxic at abnormally high concentrations, it may be responsible for clinical manifestations.[6] These manifestations may be acute, as in ammonium accumulation in urea cycle disorders (UCDs)[11] or haeme precursors' accumulation in acute intermittent porphyria,[12] and/or progressive, as in the case of lysosomal storage disorders (LSD).[13] Furthermore, the toxic accumulation may also be due to a transport defect (as in Wilson and

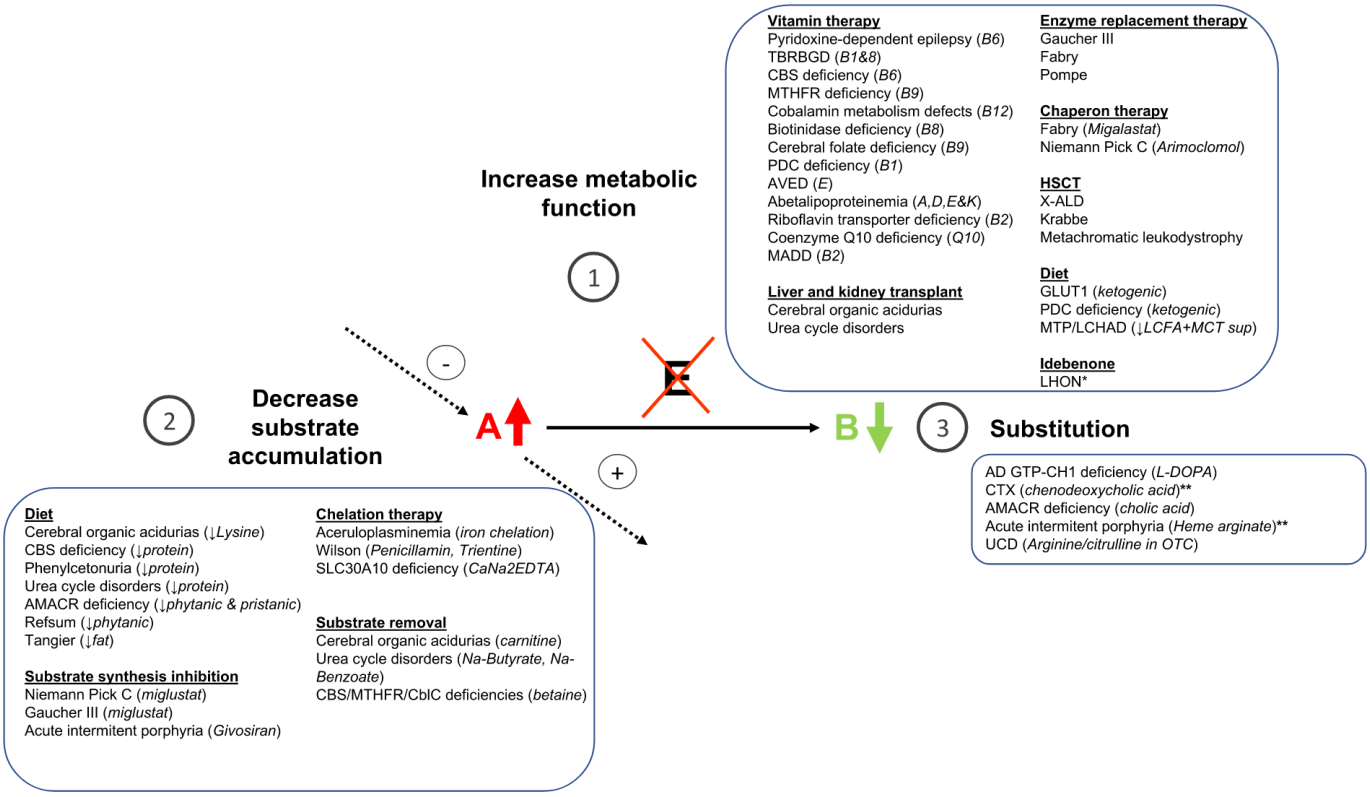

Figure 2 Schematic representation of the pathophysiology and potential therapeutic strategies in neurometabolic diseases. In blue squares are specific treatments within the three main therapeutic strategies and the diseases where the treatment is indicated. *Treatment is also a free-radical scavenger. **Treatment will also decrease substrate accumulation by downregulating its synthesis. The authors have created and have permission to use the image. A, substrate; AD GTP-CH1, autosomal dominant GTP cyclohydrolase 1; AMACR: alpha-methylacyl-CoA racemase; AVED, ataxia due to vitamin E deficiency; B, product; cblC, cobalamin C; CBS, cystathionine beta-synthase; CTX, cerebrotendinous xanthomatosis; E, enzyme; HSCT, haematopoietic stem cell transplantation; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; LHON, Leber hereditary optic neuropathy; MADD, multiple acyl-CoA dehydrogenase deficiency; MCAD, medium-chain acyl-coenzyme A dehydrogenase; MTHFR, methylenetetrahydrofolate reductase; MTP, mitochondrial trifunctional protein deficiency; OTC, ornithine transcarbamylase; PDC, pyruvate dehydrogenase complex; TBRBGD, thiamin and biotin responsive basal ganglia disease; X-ALD, X-linked adrenoleucodystrophy.

aceruloplasminaemia). In other neurometabolic diseases, it is the deficiency in a given enzymatic product that leads to disease, either directly, as in neurotransmitter synthesis disorders,[14] or indirectly, due to impaired downstream cellular function like in pyruvate dehydrogenase complex (PDC) deficiency (in this case, in addition to lactic acidosis).[15] Moreover, due to the complexity of metabolic networks, a deficiency in a given enzyme can also lead to less schematic metabolic derangements with both indirect increased toxic compounds as well as deficient ones. The observed enzyme deficiency is not always due to an anomaly of the enzyme itself, but it can also be explained by a defect in substrate or enzyme transport to the catabolic site (as in X-linked adrenoleucodystrophy (X-ALD) where peroxysomal transport of very long chain fatty acids is impaired)[16]; by a deficiency in a protein with the function of bringing in proximity the enzyme and its substrate (as in saposin deficiency, responsible for a metachromatic leucodystrophy with arylsulfatase normo-function)[17]; or by an alteration in the metabolism of a vitamin required for the synthesis of a cofactor essential for the correct functioning of the enzyme (as the impaired synthesis of the 5-methyltetrahydrofolate, the active form of folate occurring in methyltetrahydrofolate reductase (MTHFR) deficiency and leading to the subsequent altered methionine synthase activity responsible for hyperhomocysteinaemia and hypomethioninaemia).[10]

Biochemical tools

Compared with other neurogenetic diseases, the diagnostic approach in neurometabolic diseases relies in the use of very numerous biochemical tests.[4] These may be the measurement of one or a set of metabolites through a single test (such as total homocysteine or amino acid chromatography, respectively), of an enzymatic activity or of a functional test such as the mitochondrial respiration. Those tests may be performed in different fluids or tissues (including blood, urine, CSF, muscle or cultured cells, mainly skin-derived fibroblasts). Some biochemical studies are broad and point towards an overall alteration of a metabolic pathway; thus, additional analysis may be needed to identify the specific location of the metabolic block. These should also help guide and/or interpret the genetic study, whether it is Sanger sequencing of a specific gene or next-generation sequencing (NGS) of a metabolically oriented panel of genes.[18] For example, an abnormal profile of blood acylcarnitines is suggestive of an altered mitochondrial beta-oxidation of fatty acids, and the nature of the specific abnormal acylcarnitines can point toward a specific enzyme within this pathway. Other biochemical studies can only screen for a specific neurometabolic disease, such as blood cholestanol in cerebrotendinous xanthomatosis (CTX), or the different specific enzymatic activities in LSDs, among which only the subgroups of mucopolysaccharidoses and oligosaccharidoses, almost exclusively of paediatric onset, can be screened

as a whole by analysing mucopolysaccharids and oligosaccharids in urine.[19]

Therapeutic strategies

Unlike most non-metabolic neurogenetic diseases, many neurometabolic diseases are treatable[6]; that is, the natural history of the disease can be modified by a specific therapeutic intervention. Some innovative treatments have been very recently proved to be efficient, and many therapeutic trials are ongoing in the field of neurometabolic diseases. Several and sometimes complementary therapeutic approaches exist (figure 2):

1. Restoration of a minimal enzymatic activity. It can be achieved by iterative intravenous infusion of the deficient enzyme as in Fabry and Pompe disease, known as *enzyme replacement therapy (*ERT).[20 21] However, ERT is frequently unable to cross the blood–brain barrier and therefore has little impact on neurological symptoms. Various strategies are currently being studied to overcome this caveat, and recently, the intraventricular administration of ERT has been shown to be effective in neuronal ceroid lipofuscinosis type 2.[22] Depending on the neurometabolic disease, increasing the enzyme activity may be possible through other strategies than ERT: (1) the administration of a *high-dose vitamin or an enzymatic cofactor*, such as vitamin B6 (pyridoxine) in certain forms of classic homocystinuria (cystathionine beta-synthase deficiency)[23]; (2) the administration of a *molecule with a chaperone effect* that will limit enzyme degradation, like migalastat in Fabry disease or arimoclomol in Niemann-Pick C disease (that increases heat shock protein expression)[24 25]; (3) *haematopoietic stem cell transplant* of cells expressing a normal activity of the deficient enzyme, whether allogenous (classically used in X-ALD, Krabbe disease and metachromatic leucodystrophy)[26–28] or ex vivo genetically modified autologous stem cells expressing the deficient enzyme in a supraphysiological manner (recent trials have demonstrated the efficacy of this latter strategy in children with X-ALD and metachromatic leucodystrophy)[29 30]; and (4) liver and/or kidney transplant with restricted indications in organic acidurias and UCDs. Without directly acting on enzyme activity, some treatments similarly aim to support the deficient metabolic function: this mainly concerns defects of energy metabolism (Glut1 deficiency, PDC deficiency and mitochondrial beta-oxidation disorders) for which specific ketogenic diets can restore energy production, bypassing the altered energetic pathway.
2. Limiting or decreasing the accumulation of substrates upstream of the enzymatic block. This can be achieved by a specific *diet or regime*, such as the limitation of protein intake in UCDs and the consequent reduction of the ammonemia[11]; by a *detoxifying drug* which binds to these substrates and limit their toxicity or facilitate their elimination, as is the case for sodium benzoate in UCDs[31]; or, still in UCDs, by extrarenal depuration to decrease ammoniaemia in the context of severe disease decompensation. In LSDs, drugs that inhibit the endogenous synthesis of these accumulated substrates can be used, which are known as *substrate reduction therapy*, like miglustat in Niemann-Pick C disease, which inhibits the ganglioside synthesis pathway.[32] Similarly, a novel RNA interference therapeutic targeting hepatic delta-aminolevulinate synthetase 1 messenger RNA prevents the accumulation of haeme precursors in acute intermittent porphyria.[33]
3. The *supply or substitution of the deficient product* downstream of the deficient enzymatic reaction, such as L-dopa supplementation in autosomal dominant GTP cyclohydrolase I deficiency, also known as Segawa's disease or dopa-sensitive dystonia.[34]

WHEN TO SUSPECT A NEUROMETABOLIC DISEASE IN ADULTS AND HOW TO PROCEED

As mentioned previously, early recognition and diagnosis of a treatable neurometabolic disease is particularly important. We will follow the algorithm presented in figure 3, which is the result of the exhaustive review of the literature added to the clinical experience of the authors, and should therefore be interpreted as such as it will not replace clinical reasoning for each individual patient. In practice, the adult neurologist can encounter three situations.

Characteristic presentation of a given neurometabolic disease

In some situations, the presenting phenotype may be *immediately suggestive of a given adult-onset neurometabolic disease* (as described in figure 1 for treatable diseases): the specific biochemical and/or genetic test should be performed directly.

Genetic presentation or atypical acquired presentation

More frequently, *the clinical picture suggests a genetic disease* (family history of similar symptoms, parental consanguinity or a very chronic course), *or a commonly acquired aetiology is suspected in the first place but there are atypical features* leading to consider other less common disease mimics. In these situations, a neurometabolic aetiology should be considered if some of the following 'red flags' are present:

1. *Multiple neurological manifestations*, either involving several different neuroanatomical structures (eg, the association of epilepsy, indicating supratentorial disfunction, and cerebellar ataxia, indicating infratentorial involvement), or associated extraneurological signs and symptoms (visual, auditory, cardiac, hepatobiliary or endocrine). This is usually the case for most neurometabolic diseases. However, some more specific features can be found in particular subgroups of adult-onset neurometabolic diseases: in mitochondrial diseases (progressive external ophthalmoplegia, ptosis, stroke-like episodes, sensory neuronopathy, optic neuropathy, retinopathy, cataracts, sensorineural deafness and diabetes),[35] in LSDs (supranuclear gaze palsy, hepatosplenomegaly, facial dysmorphia and osteoarticular deformities)[13] and in peroxisomal disorders (demyelinating polyneuropathy, retinopathy, cataract, sensorineural deafness, facial dysmorphia and osteoarticular deformities).[36]
2. *Acute or subacute neurological manifestations occurring in a context of basal metabolism modification* and/or increased energy demand, such as weight loss, prolonged fasting, drastic modification of diet, surgery, infection or drugs. This can occur in aminoacidopathies,[37] disorders of energy metabolism (including mitochondrial respiratory chain and beta-oxidation disorders),[38] disorders of vitamin metabolism[23] and porphyrias.[12]
3. *Principal types of brain MRI findings* (figure 4):
   - A demyelinating cerebral white matter disorder with confluent, bilateral and more or less symmetrical T2 hyperintensities, in the absence of vascular risk factors, can suggest certain LSDs (Krabbe disease with involvement of the cortico-spinal tracts,[39] metachromatic leucodystrophy with frontal-predominant periventricular hyperintensities),[40] a specific peroxisomal disorder: X-ALD (with contrast enhancement in the inflammatory phase

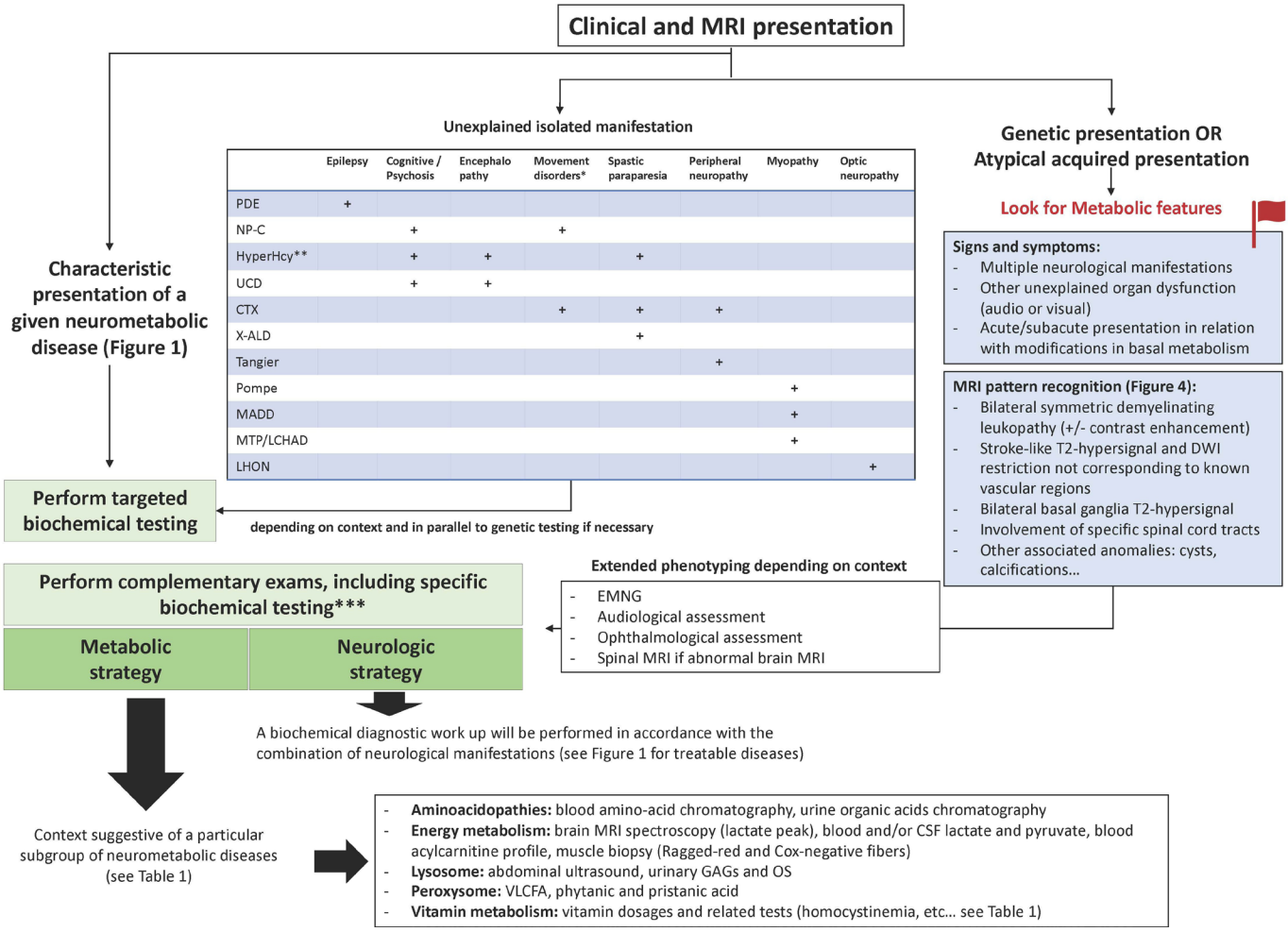

Figure 3 Recommended algorithm to identify and evaluate adult patients with suspected neurometabolic diseases. *Movement disorders include extrapyramidal manifestations as well as isolated ataxia. **Genetic hyperhomocystinaemias include CBS deficiency, MTHFR deficiency and cobalamin metabolism defects. ***In parallel with diagnostic NGS if available or followed by confirmatory genetic testing if positive diagnostic work-up. The authors have created and have permission to use the image. CBS, cystathionine beta-synthase; CSF, cerebrospinal fluid; CTX, cerebrotendinous xanthomatosis; DWI, diffusion-weighted imaging; EMNG, electromyoneurography; GAG, glycosaminoglycan; HyperHcy, hyperhomocysteinaemia; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; LHON, Leber hereditary optic neuropathy; MADD, multiple acyl-CoA dehydrogenase deficiency; MTP, mitochondrial trifunctional protein deficiency; NGS, next-generation-sequencing; NP-C, Niemann-Pick type C; OS, oligosaccharides; PDE, pyridoxine-dependent epilepsy; UCD, urea cycle disorder; X-ALD, X-linked adrenoleucodystrophy; VLCFA, very long chain fatty acids.

of the disease),[41] several 'cerebral' organic acidurias (with periventricular hyperintensities and possible involvement of the U-fibres),[42 43] as well as other diseases (see figure 1 for treatable ones) including CTX (with involvement of the dentate nuclei or the peridentate cerebellar white matter).[44] Furthermore, the presence of a bilateral and symmetrical often longitudinally extensive involvement of specific spinal cord tracts (such as subacute combined degeneration), associated or not with cerebral involvement, may also suggest a diagnosis of a treatable neurometabolic disease such as CTX, disorders of homocysteine remethylation (MTHFR deficiency and cobalamin C deficiency)[45] and biotinidase deficiency.[46]

– A bilateral and symmetrical involvement of the deep grey matter or basal ganglia. These abnormalities can be seen in several disorders of energy metabolism including mitochondrial respiratory chain disorders (producing a Leigh syndrome if associated with encephalopathy),[47] PDC deficiency,[48] and thiamin and biotin responsive basal ganglia disease (TBRBGD)[49]; in cerebral organic acidurias (associated or not with white matter T2 hyperintensities),[42] and in Wilson's disease.[50]

– Frequently, the brain MRI may be completely normal, and this should not rule out a neurometabolic disease if other clinical and paraclinical findings are present.

In these situations, the neurologist should first search for *subclinical signs* that may guide the diagnosis: mainly a spinal MRI in the context of a pathological brain MRI, a nerve conduction study with electromyography, an ophthalmological evaluation to detect any corneal, lens, retinal and optic nerve alterations, and an audiological evaluation including an audiogram and auditory evoked potentials (that can be abnormal in the absence of audiogram abnormalities). Second, depending on the context, perform other *complementary exams*, including *specific biochemical analysis*, according to two possible parallel diagnostic strategies:

► We will follow a "metabolic" strategy if the context is suggestive of a particular subgroup of neurometabolic diseases as previously mentioned: in this case diagnostic tests exploring

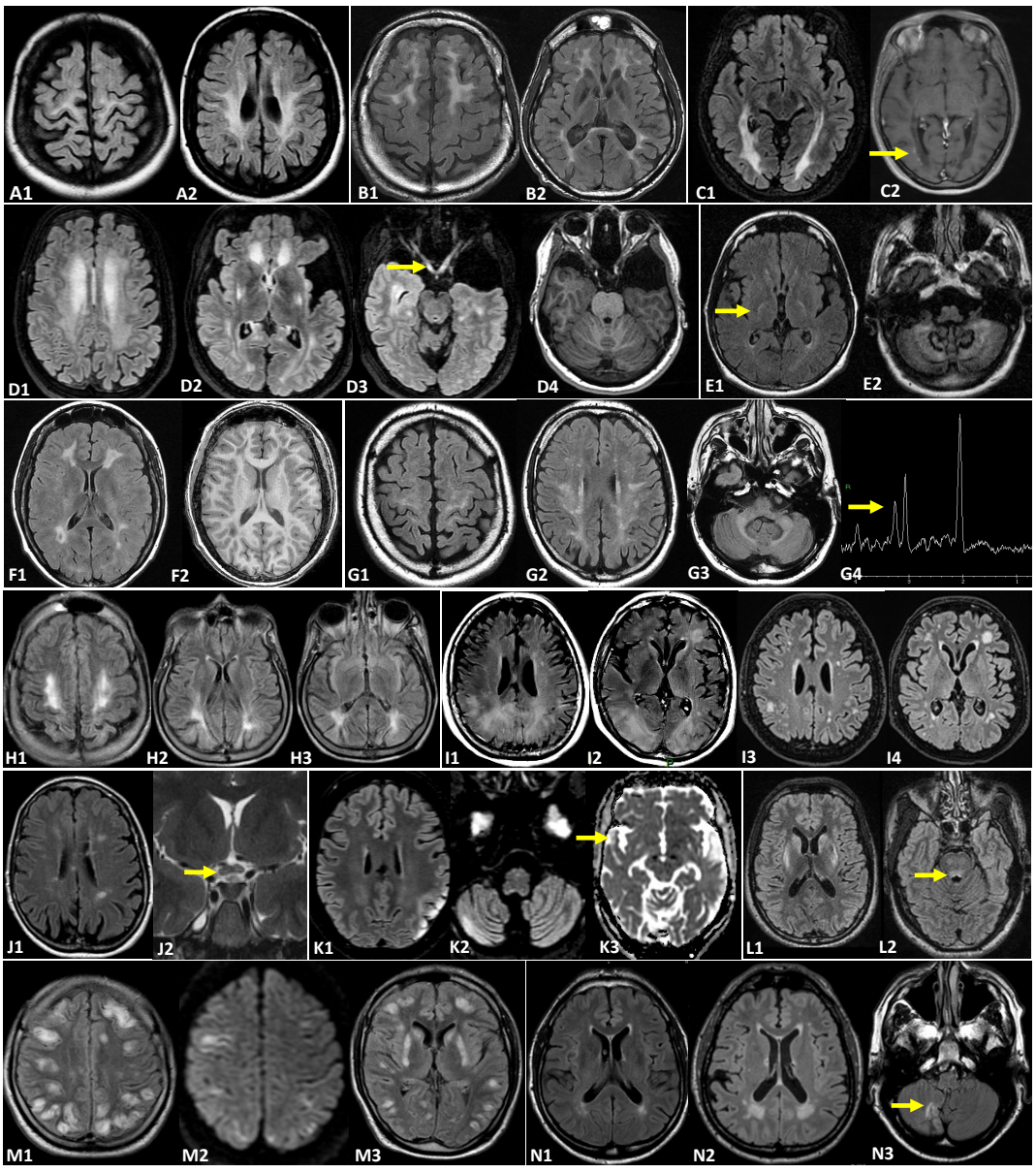

Figure 4 Brain MRI illustrating various treatable adult-onset neurometabolic diseases. All MRIs originate from adult patients (19–60 years old). Krabbe disease (A1–2): T2-FLAIR signal abnormalities involving the periventricular and deep white matter with frequent involvement of the corticospinal tract. Metachromatic leucodystrophy (B1–2): T2-FLAIR showing a diffuse leucoencephalopathy in particular around the frontal horns with sparing of subcortical U fibres leading to a 'butterfly pattern'. X-linked adrenoleucodystrophy (C1–2): posterior leucoencephalopathy on T2-FLAIR (C1) and a peripheral border of active demyelination on gadolinium enhancement on T1W sequence (C2, arrow). Glutaric aciduria type 1 (D1–4): T2-FLAIR demonstrating a diffuse periventricular and deep white matter hyperintensity with lenticular (D2) and optic pathway (D3, arrow) signal abnormalities; enlargement of the convexity of subarachnoid spaces and sylvian fissures (D2) as well as bilateral temporal hypoplasia on T1W (D4). Cerebrotendinous xanthomatosis (E1–2): T2-FLAIR hyperintensity in the posterior limbs of both internal capsules (E1, arrow) and signal abnormalities within the dentate nuclei and the deep cerebellar white matter (E2). Methylenetetrahydrofolate reductase deficiency (F1–2): periventricular white matter signal abnormalities on T2-FLAIR (F1) and T1W (F2) sequences. Cerebrospinal fluid folate deficiency (G1–4): bilateral and symmetric leucoencephalopathy on T2-FLAIR sequences involving the supratentorial white matter and middle cerebellar peduncles. Spectroscopic analysis (G4) shows a rather low level of choline. Phenylketonuria (H1–3): periventricular and deep white matter leucoencephalopathy on T2-FLAIR predominantly located within posterior regions. Acute intermittent porphyria (I1–4) can sometimes be associated with posterior reversible encephalopathy syndrome (PRES) (I1–2). Complete disappearance of the PRES syndrome (I3–4) afterwards. Leber's hereditary optic neuropathy 'plus' disease (J1–2): T2-FLAIR MS-like signal abnormalities (J1) and T2 central hyperintensity of the optic chiasma (J2, arrow). Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (K1–3): T2-FLAIR (K1–2) showing multifocal stroke-like cortical lesions in different stages of evolution involving multiple vascular territories. Increased signal on apparent diffusion coefficient MAP (K3, arrow) represents vasogenic rather than cytotoxic oedema. Wilson's disease (L1–2): bilateral and symmetrical midbrain (L2, arrow), heads of the caudate and putamen T2-FLAIR hyperintensities. Thiamin and biotin responsive basal ganglia disease (TBRBGD) (M1–3): acute episode of a diffuse vasogenic oedema with numerous hyper T2-FLAIR (M1,3) and diffusion cortical lesions (M2). The heads of the caudate and putamen (M2) are also involved. Fabry's disease (N1–N3): T2-FLAIR periventricular and deep white matter signal abnormalities. Compared with the baseline MRI (N1), the cerebral small vessel disease progresses on the 4-year follow-up MRI (N2) in a patient with no known cardiovascular disease. Ischaemic stroke sequelae of the posterior circulation (N3, arrow) can also be seen. The authors have created and have permission to use the image.T1W, T1 weighted.

Table 1 Key biochemical diagnostic tests for the diagnosis of treatable adult-onset neurometabolic diseases (clustered according to the explored metabolic pathways)

Neurometabolic disease	Key biochemical analysis	Comments
Neurotransmiter synthesis deficiency		
AD GTP-CH1 deficiency	Neurotransmitters and pterins (CSF)	Possible L-dopa trial: high efficacy
Aminoacidopathies		
Cerebral organic acidurias	Organic acid chromatography (u), amino acid chromatography (b)	
Phenylcetonuria		
Urea cycle disorders	Ammoniaemia, amino acid chromatography (b)	Possible false negative between crisis
Genetic hyperhomocystinaemia: MTHFR, cobalamin metabolism defects and CBS deficiency	Total homocysteine (b), amino acid chromatography (b)	
Lysosomal storage disorders		
Niemann-Pick- C	Cholestane-b-triol and LSM509 (b)	
Gaucher III	Leucocyte glucocerebrosidase activity and glucosylsphingosine (b)	
Krabbe	Leucocyte galactocerebrosidase activity (b)	
Metachromatic leucodystrophy	Leucocyte arylsulfatase A activity (b) and sulfatides (u)	Possible false positives or 'pseudo-deficit': urinary sulfatides and/or genetic study; possible false negatives: saposin C deficiency
Fabry	Leucocyte alpha galactosidase activity, LysoGb3 (b)	Possible false negatives in women: genetic study
Pompe	Acid alpha-glucosidase activity (b)	
Peroxysomal disorders		
X-ALD	Very long chain fatty acids (b)	Possible false negative in hemizygote women
Refsum	Phytanic acid (b)	
AMACR deficiency	Pristanic acid, DHCA, THCA (b)	
Disorders of vitamin metabolism		
Pyridoxine-dependent epilepsy	AASA, P6C, proline (b, u, CSF)	Pyridoxin trial possible
Biotinidase deficiency	Biotinidase activity (b)	
Abetalipoproteinaemia	Complete lipid analysis including apolipoproteins and Vitamine E (b)	
AVED	Vitamin E (b)	
Cerebral folate deficiency	5-Methyltetrahydrofolate (CSF)	
TBRBGD	Lactate (CSF)	Not sensitive nor specific; thiamin+biotin trial and/or genetic study
Riboflavin transporter deficiency	Acylcarnitines (b)	Poor sensitivity: genetic study
Disorders of energy metabolism		
GLUT 1	CSF:blood glucose ratio	
PDC deficiency, coenzyme Q10 deficiency, LHON	Lactate and pyruvate (CSF and b)	Significantly better sensitivity in CSF
Disorders of beta-oxydation: MADD, MCAD and MTP/LCHAD	Acylcarnitines (b)	
Metal toxicity		
Wilson	Exchangeable/free copper (b and u), ceruloplasmin (b)	
Aceruleoplasminaemia	Cerulopasmin, copper, iron and ferritin (b), copper (u)	
SLC30A10 deficiency	Manganese (b)	
Others		
CTX	Cholestanol (b)	
Acute intermitent porphyria	Porphobilinogen non-light-exposed, 5-aminolevulinic acid (u)	Poor sensitivity between crisis
Tangier	Complete lipid analysis including apolipoproteins (b)	

AASA, α-aminoadipic-δ-semialdehyde; AD GTP-CH1, autosomal dominant GTP cyclohydrolase 1; AMACR, alpha-methylacyl-CoA racemase; AVED, ataxia due to vitamin E deficiency; b, blood; CBS, cystathionine beta-synthase; CSF, cerebrospinal fluid; CTX, cerebrotendinous xanthomatosis; DHCA, dihydroxycholestanoic acid; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency; LHON, Leber hereditary optic neuropathy; LSM509, lyso-sphingomyelin 509; LysoGb3, globotriaosylsphingosine; MADD, multiple acyl-CoA dehydrogenase deficiency; MCAD, medium-chain acyl-coenzyme A dehydrogenase deficiency; MTHFR, methylenetetrahydrofolate reductase; MTP, mitochondrial trifunctional protein deficiency; P6C, Δ1-piperideine-6-carboxylate; PDC, pyruvate dehydrogenase complex; TBRBGD, Thiamin and biotin responsive basal ganglia disease; THCA, trihydroxycholestanoic acid; u, urine; X-ALD, X-linked adrenoleucodystrophy.

the suspected metabolic pathways will be performed (see figure 3 and table 1).

- In parallel, we will follow a "neurological" strategy where the biochemical diagnostic work up will be performed in accordance with the combination of neurological manifestations (see figure 1 for treatable diseases). Three main criteria are to be used to judge if a biochemical test can be useful for the patient: the consistency of the clinical presentation as a whole with the tested disease, the invasiveness and reliability (in terms of sensitivity and specificity) of the test, and the existence of a treatment. In this line figure 1 shows the different clinical manifestations of all potentially treatable adult-onset neurometabolic diseases categorised as major (if they are frequent or predominant within the clinical picture, and potentially be found isolated) or minor (if infrequent, even subclinical and rarely found isolated), as well as acute or chronic onset. Table 1 specifies the limitations of some screening tests. In the case of a treatable neurometabolic disease, it is probably legitimate to test not only if the presentation is reminiscent of the disease but also if it is merely compatible.

Unexplained isolated manifestation

Finally, some neurometabolic diseases may have an *unspecific isolated neurological manifestation* without the aforementioned clinical and paraclinical hints, compatible with either a genetic or acquired aetiology. For example, adrenomyeloneuropathy (the spinal form of X-ALD) can present as an isolated spastic paraparesis,[51] and rarely, this is may also be the case for CTX.[52] Niemann-Pick type C disease may present with isolated psychosis or a movement disorder.[8] Certain neurometabolic diseases, like Tangier (possibly mimicking chronic idiopathic demyelinating polyneuropathy) or Pompe disease, may present with isolated neuromuscular signs and symptoms.[53 54] In these cases, if the diagnosis is not obvious after first-line investigations, it may be useful to carry out a biochemical analysis of the possible neurometabolic diseases, in parallel to the relevant genetic study if necessary (eg, a 'spastic paraplegia' panel).

The recommended diagnostic approach is summarised in figure 3. If a biochemical test was to be positive, an evaluation by a specialist in the field should be considered to interpret the result within the clinical context and to guide the subsequent diagnostic process, whether further biochemical studies are needed or a genetic study can be undertaken. It should be noted that for some neurometabolic diseases, no reliable biochemical diagnostic test is available, and it is the genetic study alone that can confirm the disease. In these cases, it may be possible to perform a therapeutic test, of outmost importance in the case of neurometabolic diseases with possible acute/subacute presentations where benefit from early treatment can be dramatic. This is the case for TBRBGD and riboflavin transporter deficiency.[23] Finally, the clinician should take into account the prevalence of individual neurometabolic diseases in their region, as well as the frequency of consanguinity and the presence of founding mutations.

PLACE FOR NGS GENE TECHNOLOGIES AND METABOLOMICS IN THE DIAGNOSIS OF NEUROMETABOLIC DISEASES

Neurometabolic diseases are predominantly, but not exclusively, single-gene recessive disorders. NGS technologies now allow for rapid and inexpensive large-scale genomic analysis of rare diseases.[55] The first and most widespread technology is that of a panel of genes, allowing for the sequencing of hundreds of known genes implicated in neurometabolic diseases. If available, an alternative to gene panels is the sequencing of the entire set of protein-coding sequences or exome, known as wide exome sequencing or to directly sequence the entire 6 billion base pair human genome through wide genome sequencing. NGS has facilitated the detection of new gene–phenotype associations, expanding the clinical spectrum of already established Mendelian disorders.[18] All of the aforementioned has increased our ability to correctly diagnose patients, has decreased diagnostic delay and reduced overall diagnostic expenses.[56] Furthermore, NGS will also allow to detect genetic modifiers that could explain the phenotypical heterogeneity encountered within patients suffering from the same disease, even among siblings carrying the same pathogenic variants.[57]

However, the increased genetic resolution and complexity of the data comes with an increased detection of variants of unknown significance. This is why a combined approach with deep phenotyping of patients is needed. Concerning intellectual deficiency with a suspected metabolic origin, both clinical and biochemical phenotyping reached a high diagnostic yield of 68%,[18] whereas similar exome studies without deep phenotyping usually result in a lower diagnostic yield of around 16%.[58] To fit with this strategy, NGS, if easily available, could be performed in parallel to targeted biochemical phenotyping in patients with suspected neurometabolic diseases in the context of our proposed diagnostic approach. Complementary biochemical tests may also be needed once NGS results are available to help in the interpretation of variants of interest.

In addition, biochemical phenotyping could also be enlarged by metabolomics, establishing a comprehensive biochemical profile.[59] The high-dimensional nature of the data amassed through metabolomics requires the use of dedicated preprocessing platforms and multivariate analysis or even machine learning tools to classify the findings.[60] This untargeted approach has the potential to direct the diagnosis among varied and unspecific manifestations and to diminish the number of specific biochemical tests, thus reducing the overall cost.[61] In addition, it could provide complementary biochemical data to assist in the interpretation of genetic variants from NGS gene studies.[62] Although these metabolomics approaches are powerful, they have not yet been translated into clinical practice.

CONCLUSIONS

Adult neurometabolic diseases encompass a heterogeneous set of conditions for which we have presented a synthetic overview of the different phenotypes, especially for those with a currently available treatment, as well as a simplified diagnostic approach. Nevertheless, this practical knowledge is bound to change over the next years, with the identification of new neurometabolic diseases, the report of new phenotypes for known ones, the accessibility of untargeted diagnostic tools (genomics and metabolomics) and the discovery of new treatments for currently untreatable neurometabolic diseases. We hope that this review will increase awareness of this group of diseases and allow for an efficient and rational use of the biochemical tests available in the diagnosis of neurometabolic diseases, ultimately leading to prompt diagnosing and early treatment of patients.

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Contributors Concept and design, drafting of the manuscript: GF-E, CC YN. Administrative, technical, or material support: CC, NS and FL. Supervision: GF-E and YN. Acquisition, analysis or interpretation of data, critical revision of the manuscript for important intellectual content: all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests YN reported grants from Takeda and Orchard therapeutics and has received honoraria from Sanofi Genzyme and Orphazyme. No other disclosures were reported.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary material 1: List of all adult-onset neurometabolic diseases. In bold, those with a disease-modifying therapy currently available in clinical practice. Adapted from: *Hollak CE, Lachmann R, editors. Inherited metabolic disease in adults: A clinical guide. Oxford University Press; 2016.*

DISORDERS OF CARBOHYDRATE METABOLISM

Glycogen storage disorders 0-XIII, including **Pompe**, Cori/Forbes, Andersen or Adult polyglucosan body disease and McArdle disease

Galactosemia

GLUT1 deficiency

DISORDERS OF MITOCHONDRIAL ENERGY METABOLISM

Pyruvate dehydrogenase complex deficiency

Disorders of mitochondrial energy metabolism: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), Myoclonic epilepsy with ragged-red fibers (MERRF), Neurogenic weakness with ataxia and retinits pigmentosa (NARP), Leigh syndrome (subacute necrotizing encephalomyelopathy), **Leber hereditary optic neuropathy (LHON)**, Progressive external ophtalmoplegia (PEO), Kearns-Sayre syndrome (KSS), Sensory ataxic neuropathy, dysarthria and ophtalmoparesis (SANDO), Myoclonic epilepsy, myopathy, sensory ataxia (MEMSA), Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Fatty acid oxidation: Carnitine deficiency carnitine palmitoyltransferase 1A (CPT1A) deficiency, carnitine-acylcarnitine translocase (CACT) deficiency, carnitine palmitoyltransferase 2 (CPT2) deficiency, Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, **Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Mitochondrial trifunctional protein (MTP) deficiency**, **Medium-chain acyl CoA dehydrogenase (MCAD) deficiency**, Short-chain enoyl-CoA dehydrogenase (SCAD) deficiency, 3-hydroxyacyl-CoA dehydrogenase (HADH) deficiency

Electron transfer defects: **Multiple acyl-CoA dehydrogenase (MADD) deficiency**

Riboflavin metabolism defects: **Brown-Vialetto-Van Laere (BVVL) syndrome**, FAD synthetase deficiency, MFT deficiency 81

Disorders of ketogenesis and ketolysis: 3-hydroxyl-3-methylglutaryl-CoA (HMG-CoA) synthase deficiency, HMG-CoA lyase deficiency

Disorders of creatine metabolism: AGAT deficiency, GAMT deficiency, CrT defect

Coenzyme Q10 deficiency

DISORDERS OF PROTEIN METABOLISM

Phenylketonuria

Maple syrup urine disease, Proionic acidemia, Methlymalonic acidemia and Isovaleric acidemia

Urea cycle disorders, Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

Citrin deficiency

Cystathionine beta-synthase deficiency or Homocystinuria

Cerebral organic acidurias: Glutaric aciduria type I and 2-hydrohyglutatic acidurias

Lysinuric protein intolerance and Hartnup disease

DISORDERS OF VITAMIN METABOLISM
Biotinidase deficiency
Disorders of cobalamin: CblC and others
Folate metabolism: Methylenetetrahydrofolate reductase (MTHFR) deficiency
Disorders of thiamin metabolism: Biotin-thiamin responsive basal ganglia disease

NEUROTRASMITTERS
Succinic semialdehyde dehydrogenase deficiency
Adult-onset monoamine disorders: **Autosomal dominant GTP cyclohydrolase deficiency**
Brain serotonin deficiency

DYSLIPIDEMIAS
Tangier disease
Abetalipoproteinemia

BILE ACID SYNTHESIS DEFECTS
Cerebrotendinous xanthomatosis
Spastic paraplegia (SPG) type 5

DISORDERS OF PURINE METABOLISM
Lesch-Nyhan disease and variants

PORPHYRIAS
Acute intermittent porphyria

MINERAL AND METAL METABOLISM DISORDERS
Disorders of copper and iron metabolism: Neuroferritinopathy, **Wilson disease, Acerulopasminemia**
Disorders of manganese metabolism: **SLC30A10 deficiency**

LYOSOMAL STORAGE DISORDERS
Fabry disease
Gaucher disease type III
GM1-gangliosidosis type II and III
GM2-gangliosidosis (Tay-Sachs and Sandhoff disease)
Krabbe disease
Metachromatic leukodystrophy (ARSA and Saposin-C deficiency)
Niemann type C
Pompe disease
Neuronal Ceroid Lipofuscinosis (mainly CLN2, CLN3, CLN4, CLN5, CLN6, CLN7, CLN11, CLN13).
Sialidosis or Mucolipidosis type 1

PEROXISOMAL DISORDERS

X-linked adrenoleukodystrophy and adrenomyeloneuropathy
Refsum disease
2-methylacyl-CoA racemase (AMACR) deficiency

CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

Only some genes like *DPGAT1* congenital myasthenia

Supplementary material 2: List of references for Figure 1 and Table 1.

Neurotransmiter synthesis deficiency	
AD GTP-CH1 deficiency	Wijemanne 2015; Trender-Gerhard 2009; Hyland 2008 [1–3]
Aminoacidopathies	
Cerebral organic acidurias	Gelener 2020; Tabarestani 2020; Mainka 2020; Tsai 2017; Pierson 2015; Herskovitz 2013; Marcel 2012; Karatas 2010; Angle 2008; Periasamy 2008; Kulkens 2005; Bahr 2002; Fujitake 1999 [4–16]
Phenylcetonuria	Chen 2019; Wang 2018; Tufekcioglu 2016; Rosini 2014; Vockley 2014; Bilder 2013; Kasim 2001 [17–23]
Urea cycle disorders	Anderson 2020; Koya 2019; Panza 2019; Bigot 2017; Maillot 2016; Anstey 2015; Atiq 2008; Maillot 2007; Tuchman 2001 [24–32]
Genetic hyperhomocystinemia : MTHFR or Cobalamin metabolism defects and CBS deficiency	Marelli 2021; Vieira 2020; Wei 2020; Weber Hoss 2019; Gales 2018; Morris 2017; Norris 2017; Stabler 2013; Michot 2008; Kelly 2003; Powers 2001 [33-43]
Lysosomal storage disorders	
Niemann Pick-C	Sitarska et Lugowska 2019; Nadjar 2018; Lazzaro 2016; Maubert 2013 [44–47]
Gaucher III	Leurs 2018; El-Beshlawy 2017; Stirnemann 2017; Mistry 2015; Grabowski 2015; Ben Rhouma 2012; Vellodi 2009; Guimaraes 2002; Charrow 1998; Neil 1979 [48–57]
Krabbe	Xia 2020; Cousyn 2019; Zhang 2018; Escolar 2017; Liao 2017; Adachi 2016; Debs 2013 [58–64]
Metachromatic leukodystrophy	Van Rappard 2015; Hahn 1982 [65,66]
Fabry	Ortiz 2018; Curiati 2017; Smid 2015; Ghali 2012; Hegemann 2006 [67–71]
Pompe	Hossain 2018; Chan 2016; Young 2003; Umapathysivam 2001 [72–75]

Peroxysomal disorders	
X-ALD	Rattay 2020; Mannari 2020; Shamim 2017 [76–78]
Refsum	Stepien 2016; Bompaire 2015; Wanders 2011; Britton 1989 [79–82]
AMACR deficiency	Smith 2010; Kapina 2010; Clarke 2004; McLean 2002; Ferdinandusse 2000 [83–87]
Disorders of vitamin metabolism	
Pyridoxine-dependent epilepsy	Osman 2020; Xue 2019 [88,89]
Biotinidase deficiency	Radelfahr 2020; Van Winckel 2020; Van Iseghem 2019; Wolf 2019; Deschamps 2018; Yilmaz 2017; Bottin 2015; Cowan 2010 [90–97]
Abetalipoproteinemia	Lee 2014; Nagappa 2014; Zamel 2008 [98–100]
AVED	El Euch-Fayache 2014; Cavalier 1998; Finckh 1995; Gotoda 1995 [101–104]
Cerebral folate deficiency	Pope 2019; Masingue 2019; Sadighi 2012 [105–107]
TBRBGD	Tabarki 2013; Kono 2009 [108,109]
Riboflavin transporter deficiency	Carreau 2020; Foley 2014 [110,111]
Disorders of energy metabolism	
GLUT 1	Leen 2013; Afawi 2010; Veggiotti 2010 [112–114]
PDC deficiency, Coenzyme Q10 deficiency	Pavlu-Pereira 2020; Rahman 2012; Sedel 2008; Quinzii 2007; Mellick 2004; Ogasahara 1989 [115–120]
LHON	Ciron 2018; Carelli 2017; Martikainen 2016; Pfeffer 2013; Palace 2009; McFarland 2007; Gilhuis 2006; Horvath 2000; Nikoskelainen 1995 [121–129]
Disorders of beta-oxydation: MADD, MCAD and MTP/LCHAD	Nadjar 2020; Chen 2019; De Biase 2017; Wang 2016; Grunert 2014; Rosenbohm 2014; Liewluck 2013; Schatz 2010; Lang 2009; Abdenur 2001; Van Hove 1993 [130–140]
Metal toxicity	

Wilson	Yong 2019; Guillaud 2018; Bandmann 2015; Roberts 2008; Ferenci 2007 [141–145]
Aceruleoplasminemia	Marchi 2019; Kono 2012 [146,147]
SLC30A10 deficiency	Quadri 2012; Tuschl 2012; Gospe 2000 [148–150]
Others	
CTX	Makary 2018; Sasamura 2018; Degos 2016; Nakashima 1994; Leitersdorf 1993 [151–155]
Acute intermitent porphyria	Simon 2018; Kevelam 2016; Bonkovsky 2014; Hervé 2010 [156–159]
Tangier	Hooper 2020; Mercan 2018 [160,161]

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