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What can pediatricians learn from adult inherited metabolic diseases?

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Abstract

The field of inherited metabolic diseases (IMD) has initially emerged and developed over decades in pediatric departments. Still, today, about 50% of patients with IMD are adults, and adult metabolic medicine (AMM) is getting more structured at national and international levels. There are several domains in which pediatricians can learn from AMM. First, long-term evolution of IMD patients, especially those treated since childhood, is critical to determine nutritional and neuropsychiatric outcomes in adults so that these outcomes can be better monitored, and patient care adjusted as much as possible from childhood. Conversely, the observation of attenuated phenotypes in adults of IMD known to present with severe phenotypes in children calls for caution in the development of newborn screening programs and, more largely, in the interpretation of next-generation sequencing data. Third, it is important for pediatricians to be familiar with adult-onset IMD as they expand our understanding of metabolism, including in children, such as oxysterols and glycogen metabolism. Last, the identification of common molecular and cellular mechanisms in neurodevelopment and neurodegeneration opens the way to synergistic therapeutic developments that will benefit both fields of pediatric and adult medicine. Overall, these observations underline the need of strong interdisciplinarity between pediatricians and adult specialists for the diagnosis and the treatment of IMD well beyond the issues of patient transition from pediatric to adult medicine.

KEYWORDS

adult metabolic medicine, interdisciplinarity, long-term outcomes, neurodegeneration, neurodevelopment, newborn screening, treatments

1 | INTRODUCTION

Although one of the first recognized inherited metabolic diseases (IMD) affects predominantly adults, that is, alkaptonuria identified at the end of the 19th century,[1] the field of IMD has mostly developed between the 1950s and the 2000s in pediatric medicine, except for the adult metabolic center from London created by Charles Dent

in the 1950s.[2] The society for the study of inborn errors of metabolism (SSIEM) was created in 1963 by a group of passionate pediatricians and biochemists. The onset of newborn screening (NBS) for IMD in the 1960s was also a critical factor to stimulate the creation of dedicated pediatric units for IMD. The 2000s saw the onset of the adult metabolic medicine (AMM) with a dedicated section at the SSIEM (2010), a dedicated book for IMD in AMM (2016), and a dedicated SSIEM course for AMM (2019).

Before addressing what pediatricians may learn from adult IMD, it should be acknowledged that many adult neurologists, internists, geneticists working in AMM were trained by pediatric physicians and/or biochemists working in metabolic pediatric departments. Besides their historical expertise in diagnosing and treating various inherited metabolic defects, pediatricians usually embrace IMD with a broad understanding of different organ specialties. Indeed, the challenge in IMD is mostly to link a biochemical and molecular defect to a group of symptoms regardless of the various organs and systems that may be involved. Instead, most adult neurologists, internists, endocrinologists, nephrologists, cardiologists, hepatologists are rather familiar with symptoms related to their favorite organ but apprehend with more difficulties the holistic view that is needed to do IMD medicine. Therefore, while it is now increasingly recognized that about 50% of IMD patients are adults,[3] the interdisciplinary view from pediatric IMD specialists remains a unique asset that adult IMD specialists should continue to learn from.

Similarly, pediatric IMD specialists can also gain in critical knowledge from adult IMD specialists. Encouraging AMM in all medical specialties is essential due to the rapidly expanding number of adults patients with IMD. Developing AMM is not only important for patient transition from pediatrics to adult medicine, but there are various areas in which pediatricians can improve the care of their patients and their understanding of the pathophysiology of IMD based on the growing experience in AMM.

2 | NUTRITIONAL OUTCOMES OF PATIENTS WITH IMD IN ADULTHOOD

The treatment of IMD affecting intermediary metabolism like, for example, urea cycle diseases, organic aciduria, or amino-acidopathies involve chronic special diets with restriction of proteins and maintenance of anabolism through regular glucose and lipid uptake. The long-term consequences of these special diets can be excessive weight gain, even obesity in some patients, with detrimental consequences in adolescence and adulthood, especially cardiovascular and neurological complications.[4,5] Several factors probably contribute to these nutritional side effects: (i) the partly artificial nature of these special diets, (ii) the need for regular food intake and maintained anabolism in children due to growth and higher metabolic rate, which decreases in adulthood but that is not always adjusted accordingly, (iii) the increase of calorie intake during at-risk situations for metabolic decompensations, and/or (iv) eating disorders favored by chronic diets.[6] The long-term consequences of low protein diet on bone mineralization and brain functions through aging should also be addressed.[7,8] While pediatricians and dietitians become increasingly aware of the possible deleterious impact of these special diets, the implementation of standardized and multiparametric patient assessments is essential to identify patients at risk of poor nutritional outcomes in order to adjust care during childhood and adolescence.[9]

Another concern of long-term special diets is nutrient deficiencies (e.g., vitamins and trace elements especially) favored by restriction in proteins or long chain fatty acids. While customized supplements have been developed, patients are not always compliant, sometimes due to palatability issues, and nutrient deficiencies related to special diets may cause more harm than, sometimes, the metabolic defect they intend to treat. This is illustrated, for example, in the debate for the dietary management of adult patients with phenylketonuria. While increase of phenylalanine intake with age may affect some domains of neurocognition, not necessarily perceived as impactful by patients in their daily life, long-term deficiencies of vitamin B12 secondary to low-protein diets are not without risks for the nervous system.[10,11] Similarly, chronic deficiency in certain amino acids may have implications in cognitive impairments, mood, and anxiety disorders. This is especially suspected of deficiencies in branched chain amino acids (BCAA) due to the role of BCAA transamination in the brain for the regulation of the cerebral glutamate-glutamine pool.[12]

3 | NEUROPSYCHIATRIC OUTCOMES OF PATIENTS WITH IMD IN ADULTHOOD

It seems that most adult patients with IMD present with neurological and/or psychiatric symptoms. These complications are more prevalent than what is usually observed in patients with chronic diseases with childhood onset. This is even true when comparing the neuropsychiatric outcomes of adults with IMD to adults with early onset acquired metabolic diseases like type 1 diabetes (T1D),

for whom, only a subset of patients present learning and memory deficits. In T1D, the strongest effect appears to be the relationship between hyperglycemia, white-matter injury, and reduced information processing, with later-emerging decrements in global cognitive functions.[13] In IMD, the impact on cognition, but also motor and psychiatric outcomes, is likely multifactorial ranging from chronic metabolic derangements affecting cellular homeostasis (dysglycemia, hyperammonemia, hyperhomocysteinemia, ketoacidosis) and causing oxidative damage, to mitochondrial and/or lysosomal dysfunctions. In other words, the multiple metabolic pathways affected in many IMD by a single molecular defect—whereas this defect occurs primarily in the mitochondria, the lysosome, the endoplasmic reticulum, or the Golgi apparatus—is likely to cause cumulative cellular damages affecting altogether energy homeostasis, autophagy-protein recycling, and neuroinflammation. Notably, each of these three processes is associated with brain aging and neurodegeneration.[14] Likewise, pathogenic variants in mitochondrial genes like *PINK1* or *Parkin* are sufficient to cause early onset forms of Parkinson disease (PD), and the accumulation of mitochondrial DNA mutations in the *substantia nigra* with aging may be an important factor in the onset of PD.[15] Furthermore, altered glucocerebrosidase activity, with or without *GBA1* heterozygous variants, is the first risk factor identified to date associated with sporadic PD.[16] Moreover, correcting maladaptive inflammation by restoring myeloid cell metabolism may be sufficient to reverse cognitive decline associated with aging.[17] Therefore, common neuropsychiatric symptoms in adult patients with IMD are likely underlined by the progressive dysfunctions of several organelles and metabolic pathways resulting in neurodegeneration and neuroinflammation.[17]

These observations are critical not only for physicians involved in AMM so that they improve the care of the long-term neuropsychiatric manifestations of their IMD patients, but they also provide essential knowledge to neuroscientists as IMD represent disease models to decipher the various mechanisms associated with brain functions and neurodegeneration. These observations are also relevant to pediatricians involved in the care of patients with IMD. Indeed, even if neurocognitive and psychiatric manifestations may only present in adulthood—for example, disorders of intermediary metabolism, hepatocerebral diseases like cerebrotendinous xanthomatosis (CTX) and Niemann-Pick type C (NPC), peroxisomal disorders like X-linked adrenoleukodystrophy, or mitochondrial diseases—these negative outcomes call for a dedicated and standardized monitoring of cognitive and psychological well-being in children and adolescents. This should encompass neurocognitive evaluations but also patient-reported outcome measures,[18] neuroimaging studies including diffusion tensor imaging to track white matter alterations, and biomarkers that can help identifying children more at risk of developing neuropsychiatric symptoms later in life. Furthermore, besides dedicated treatments targeting primary or secondary metabolic defects, supportive therapies that are known to improve brain functions and slow down neurodegeneration in adults may also be initiated in children and comprise exercise, stress lowering activities, and management of sleep disorders.

4 | CONTRIBUTION OF ADULT MEDICINE TO NEWBORN SCREENING PROGRAMS AND PRESYMPTOMATIC TESTING

While long-term nutritional and neuropsychiatric outcomes in adult patients with IMD diagnosed as children suggest that dedicated research shall be conducted in pediatric metabolic medicine to better understand prognostic factors of poor outcomes and develop early intervention, the observation of attenuated phenotypes in adults of some IMD known to present with severe phenotypes in children calls for caution in the development of newborn screening programs. This is, for example, the case of X-linked adrenoleukodystrophy (ALD). ALD is an X-linked white matter disease caused by mutations in the *ABCD1* gene and the most common leukodystrophy in males. Pathogenic *ABCD1* variants lead to an impairment of peroxisomal beta-oxidation and accumulation of very long-chain fatty acids (VLCFA) in plasma and tissues. Plasma C26:0-lysophosphatidylcholine (C26:0-LPC) has been shown to be even more sensitive than VLCFA for the diagnosis of ALD.[19] All men carrying *ABCD1* pathogenic variants develop a myeloneuropathy, which causes progressive spastic paraparesis, sensory ataxia and neurovegetative dysfunctions. These patients are also at high risk of developing a rapidly progressive leukodystrophy (cerebral ALD, CALD) in which inflammatory demyelinating lesions lead to severe motor and cognitive deficit, bedridden condition, and death.[20] Approximately one third of boys and more than half of men will be affected by CALD, but the individual risk of CALD conversion cannot be predicted by genotype. Hematopoietic stem cell transplantation (HSCT) can halt neuroinflammation and prevent symptoms of CALD to expand/develop when performed at an early disease stage of demyelination.[20] The ABCD1 variant database is a publicly available database that currently catalogs more than 1200 unique *ABCD1* variants, among which about 50% are missense variants. Of these, 20% are classified as a variant of unknown

significance (VUS) and, interestingly, almost all of them have been reported in the last 3 years. Indeed, they were all identified in ongoing newborn screening (NBS) programs in the USA, often with borderline elevated C26:0-LPC concentrations and, in all cases, without a family history of ALD.[21] Overall, a major proportion (62%) of *ABCD1* missense variants identified so far through NBS exhibit uncertainty regarding their pathogenicity.[21] For parents, receiving a result of uncertain clinical significance from NBS is distressing, but this also has consequences on the extended family when this variant is inherited. Functional test in skin fibroblasts can help to classify a VUS as likely benign or likely pathogenic.[22] These tests are performed in newborns referred to specialist centers after their identification by the Dutch NBS program launched in 2023. Moreover, careful clinical and biological evaluation of adult family members carrying *ABCD1* VUS may also help determining that these variants are associated with mild and/or late-onset clinical symptoms.

There are other examples of attenuated phenotypes in adults cautioning the development of NBS program, such as Fabry disease and CTX. Fabry disease is also an X-linked disease for which NBS has, for the majority, identified patients with decreased enzymatic and VUS in the *GLA* gene with many uncertainties regarding the appropriate follow-up and treatment, especially as those are costly, and burdensome.[22] CTX is an autosomal recessive disorder of bile acid synthesis caused by pathogenic variants in the *CYP27A1* gene. Patients can present with neonatal cholestasis, chronic diarrhea, developmental delay followed by bilateral cataracts, tendon xanthomas and various neuropsychiatric symptoms from adolescence onward. As the development of symptoms can be halted or prevented by supplementation with chenodeoxycholic acid,[23] early treatment is essential,[24] making CTX an ideal candidate for NBS. However, milder phenotypes exist and adult patients with CTX may present with tendon xanthomas as the sole or predominant feature, without neurological manifestations,[25] mimicking familial hypercholesterolemia. It is unknow yet whether these attenuated phenotypes will be detected by NBS, but if they are, it does raise concern about the common principle of treating all CTX patients detected by NBS.[26]

Overall, the expansion of NBS programs as well as next-generation sequencing (NGS) techniques requires more and more the development of international and independent registries to collect long-term data about patient outcomes up to adulthood. This also requires close collaboration between geneticists, biochemists and metabolic specialists taking care of both pediatric and adult patients with IMD. The more we will learn from AMM about the outcomes of adult patients diagnosed in infancy, the more we will be able to customize children care and genetic counseling. It is also important to realize that all the experience gathered around presymptomatic testing in adults over the past decades should benefit to presymptomatic testing in children and adolescents. Indeed, when siblings of a child with a treatable IMD are tested presymptomatically, there is often some urgency to render that diagnosis to initiate monitoring and/or treatment at the earliest stages. This is, for example, the case of ALD where the diagnosis of an index case may rapidly lead to presymptomatic testing in several at risk related boys—to treat possible adrenal insufficiency and start brain monitoring of CALD[20]—but also sometimes girls when trying to identify a matched HLA-donor for a boy with CALD requiring urgent HSCT. While a timely diagnosis is mandatory given the medical implications at stake, it is also very important to try preserving a certain time space for these children, providing that they are sufficiently mature to be involved in these procedures. This means giving these children the best tools to apprehend what they are tested for, to offer them psychological support, and, before testing, to include a reflection time (necessarily short in ALD) to process complex information like it is commonly advocated in presymptomatic procedures.[27]

5 | ADULT-ONSET IMD EXPAND OUR UNDERSTANDING OF METABOLISM, INCLUDING IN CHILDREN

While the majority of IMD present both in childhood and adulthood, some IMD manifest exclusively in adults and contribute to a better understanding of cellular metabolism, including for pediatricians. The long-term accumulation of toxic metabolites can underlie some typical adult-onset IMD such as the accumulation of phytanic acid in Refsum disease,[28] or deoxysphingolipids in hereditary sensory neuropathies type I related to *SPTLC1* or *SPTLC2* pathogenic variants.[29] In CTX, while *CYP27A1* pathogenic variants commonly cause neuropsychiatric symptoms in late adolescence and early adulthood, the disease is preceded by non-neurological manifestations in childhood. In another autosomal recessive disease affecting bile acid synthesis and caused by *CYP7B1* pathogenic variants, very few children have been described and essentially in the form of hepatocellular insufficiency. Instead, patients usually manifest in the third or fourth decade of life with a progressive spastic paraplegia called SPG5.[30] These two IMD (CTX and SPG5) underscore that perturbations of cholesterol and oxysterols metabolism can lead to liver manifestations in children but neurodegeneration almost only in

adulthood. This is also partially true for NPC and MEGDEL syndrome due to *NPC1*/*NPC2* and *SERAC1* pathogenic variants, respectively. Ontogenic factors may explain such phenotypic variability as metabolic networks and inter-organ interactions evolve with age.[31]

Another example is glycogen metabolism. Most IMD affecting glycogen metabolism present in childhood with hepatic and/or muscular manifestations. This is also true for glycogen storage disorder type 4 due to *GBE1* pathogenic variants resulting in a deficiency of the glycogen branching enzyme, the last step of glycogen synthesis. Symptoms may even start prenatally with fetal hydrops. Instead, some *GBE1* variants, and especially a recurrent variant in Ashkenazi Jews, cause a milder enzymatic deficiency resulting in an adult-onset neurological form of the disease called adult polyglucosan body disease (APBD). APBD is characterized by a progressive leukodystrophy usually in the fifth or sixth decade causing spastic paraplegia with variable cognitive symptoms and often associated with a peripheral neuropathy.[32] Despite the prominent neuronal loss and observation of polyglucosan bodies in neurons, we showed that the disease does start in astrocytes and that astrocytic pathology is sufficient to cause disease onset.[33] This is consistent with what is known of brain glycogen metabolism. Indeed, glycogen is almost exclusively localized in astrocytes even though neurons have the capacity to synthesize it.[34] Neurons that recover their capacity to synthesize glycogen are driven to apoptosis. The glycogen present in astrocytes is converted into lactate and then transmitted to neurons where it is used as a main substrate, especially during memory formation,[35] when brain energy requirements are increased. Glycogen metabolism may also be a key factor of sleep regulation and altered glycogen metabolism may be associated with sleep disturbances, migraine, and depression.[36] Beyond the understanding of the fundamental role of glycogen in brain metabolism that disease models like APBD can provide, this rare adult-onset IMD has shed the light on the importance of conducting neuroimaging studies and neurocognitive testing in glycogen storage disorders affecting children. Accordingly, neurological observations are now being made in children with Pompe disease,[37] including white matter abnormalities resembling those that we described in APBD.[38]

6 | COMMON MOLECULAR AND CELLULAR MECHANISMS IN NEURODEVELOPMENT AND NEURODEGENERATION

While *GBA1* heterozygous variants are the most important risk factor for developing PD, the odd ratio varies from 10 to 15 for severe variants (e.g., p.L444P) to ≤5 for mild variants (e.g., p.N370S).[39] Importantly, decreased glucocerebrosidase cerebral activity, even in the absence of *GBA1* variants, is also associated with increased PD risk.[40] Indeed, decreased glucocerebrosidase activity leads to increased glucosylceramides and glucosylsphingosines, which impairs the degradation of α-synuclein,[41] a central process in the PD pathophysiology. These findings have opened the way to novel therapies in PD, including metabolic approaches aiming at increasing glucocerebrosidase activity.[39] Moreover, other gene variants involved in lysosomal functions, may further increase the risk to develop PD.[42]

In Alzheimer disease (AD), *APOE4* variants are the first genetic risk factor identified to date with an odd ratio of 8–12 at the homozygous state. Importantly, *APOE4* variants have also been associated with brain microstructural changes and neurocognitive performances in otherwise healthy children. A first study conducted in 162 healthy infants, aged from 2 to 25 months, showed that *APOE4* carriers had lower white matter and gray matter water fractions in brain areas preferentially affected in AD, compared to non-carriers.[43] A subsequent study on 1187 healthy children aged from 3 to 20 years demonstrated that *APOE4* carriers had significantly more hippocampal alterations compared to non-carriers, and poorer performance on attention or working memory.[44] Furthermore, a meta-analysis of 358 children who had a traumatic brain injury showed that *APOE4* carriers had a poorer outcome than non-carriers.[45] Recently, a longitudinal imaging dataset of 15 brain structures collected from 15 640 individuals identified *APOE* as one of the three genes having the most influence on brain structure across lifespan.[46] These various studies underscore the role of APOE and cholesterol metabolism in normal human brain development, but also how early neurodevelopmental alterations may favor neurodegeneration in adulthood. This is also demonstrated in Huntington disease (HD), another model of neurodegeneration, whereby the mutated protein huntingtin alters the earliest stages of in utero neurodevelopment.[47] The fact that these developmental defects could contribute to the onset in adulthood of neurodegenerative diseases like AD or HD change our perspective on these diseases, including the possible timing of therapeutic intervention.

Since metabolic alterations may occur at the earliest stages of neurodevelopment and neurodegeneration, metabolic interventions seem particularly relevant to pursue. In adults, brain metabolism of glucose decreases with age, and hypometabolism of glucose is a very early observation in brain areas preferentially affected in AD.[48–50] In HD, where genetic presymptomatic testing is available for subjects at risks, striatal hypometabolism occurs

many years before symptom onset.[51,52] Conversely, brain metabolism of ketone bodies remains relatively preserved in normal aging brain.[53] Indeed, glucose uptake measured by PET was significantly reduced in several frontal and temporal regions, the cingulate and insula of healthy subjects around 70 years of age compared to subjects around 20 years of age. Instead, acetoacetate uptake was comparable across these two populations.[53] Based on these observations, the group of Stefan Cunnane has developed metabolic strategies based on ketone supplements to improve brain energy metabolism of patients with mild cognitive impairment. In preliminary studies, the ketone supplements led to improved brain connectivity and improvement of processing speed compared to placebo.[54] Therefore, besides the well-known benefit of ketone bodies in IMD like Glut1 deficiency or mitochondrial diseases, metabolic strategies may open new therapeutic perspectives for neurodegenerative diseases.

This may also be the case for anaplerotic compounds like triheptanoin that provides two types of intermediates to the Krebs cycle, acetyl-CoA and propionyl-CoA. In Glut1 deficiency, we showed that triheptanoin decreased dramatically the number of paroxysmal episodes,[55] and that this effect was sustainable over years[56] (Figure 1). Based on the hypothesis of an early brain energy deficiency in HD,[57] and a suspected need for Krebs cycle intermediates reflected by decreased BCAA metabolism in patients,[58] we tested the therapeutic potential of triheptanoin in HD. We first showed that triheptanoin corrected the abnormal brain energy profile of patients measured by ^{31}phosphorus brain spectroscopy[59] (Figure 1). In a randomized controlled trial with 100 patients, triheptanoin led to clinical stability over year and a 50% decrease of the rate of caudate atrophy, a central marker of disease progression[60] (Figure 1). Overall, brain energy rescue may well

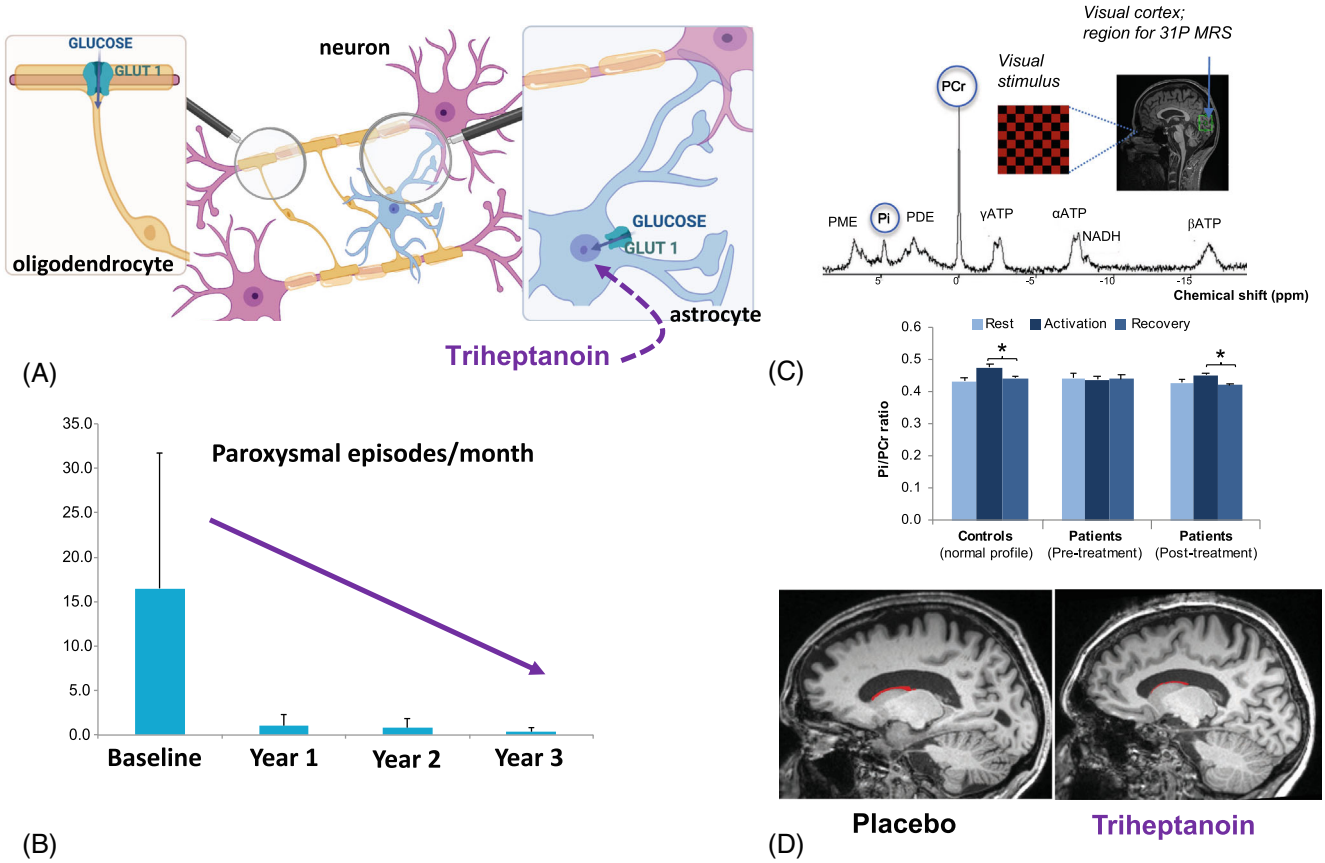

FIGURE 1 Triheptanoin for the treatment of Glut1 deficiency syndrome and Huntington disease. (A) Triheptanoin, an odd-chain triglyceride with anaplerotic properties, bypasses the defective import of glucose in astrocytes to correct brain energy deficiency. (B) Triheptanoin led to >90% decrease of monthly paroxysmal disorders in an open label trial of children and adults with Glut1 deficiency syndrome; this effect was sustainable over years. (C) ^{31}Phosphorus brain NMR spectrum to measure the change in the ratio of inorganic phosphate over phosphocreatine (Pi/PCr) before, during, and after brain stimulation with a flashing checkerboard (top). Unlike healthy individuals, for whom the Pi/PCr ratio increased in the visual cortex when stimulated, the Pi/PCr ratio did not increase in HD patients during visual stimulation; brain energetic response was corrected in HD patients after 1 month of treatment with triheptanoin (bottom). (D) In a randomized trial conducted over 1 year, triheptanoin led a 50% decrease of the rate of caudate atrophy in HD patients.

represent an emerging concept for neurodegenerative disorders of aging.[61]

7 | CONCLUDING REMARKS

The field of IMD has emerged and largely developed in pediatric medicine, even more with the generalization of NBS. Still, today, about half of patients with IMD are adults, with an equal proportion of patients transitioning from pediatric departments and patients diagnosed in adulthood.[62] Monitoring, understanding, and predicting nutritional and neuropsychiatric outcomes of pediatric IMD patients in adulthood can only be achieved if standardized and systematic studies are conducted throughout all ages of life, with a close collaboration between pediatric and adult specialists in IMD. Furthermore, with the continuing expansion of NBS and NGS, it is even more important to strengthen these bridges. Likewise, the interpretation of many VUS will only be possible thanks to phenotypic observations in adults. This will allow for the best care of children, from monitoring to treatment, while diminishing the impact of an unnecessary burden for patients and their families with major implications for long-term quality of life.

For pediatricians, the curiosity for IMD specific to adults is also determinant to the understanding of metabolic pathways and regulations, to benefit from novel therapeutic approaches, and be aware of possible complications not yet evident in children but that should be closely monitored. Overall, the consideration that neurodevelopmental and neurodegenerative processes are intertwined is fundamental. Treatments initially developed for specific molecular targets in children with IMD become novel therapeutic strategies to more common neurodegenerative diseases in adults. Similarly, key actors of neurodegenerative processes, like autophagy, have an increasingly recognized role in neurodevelopment and the physiopathology of IMD,[63] so that synergistic therapeutic developments can be expected that will benefit both fields of pediatric and adult medicine. Nonetheless, these synergies can only strengthen if AMM is supported at national and international levels, with dedicated funding[64] and training[3] of adult specialists in IMD.

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