Pr Nadine Girard, CHU la Timone, Marseille, France

Red Flags in neuroradiology and IEM

The first part will focus on the neuroimaging protocol used in a clinical setting that includes MRI and CT. The different types of MR sequences used in the assessment of metabolic diseases especially in children will be reviewed (T1, T2, susceptibility or T2*, diffusion, spectroscopy, post contrast images) in conjunction with cases examples.

The red flags in term of imaging are not numerous and will be reviewed through cases examples, including the neonatal period.

The last part will illustrate the major diagnoses in infants and older children.

Pr Clara van Karnebeek, AMC Amsterdam, The Netherlands

Red Flags in IEM

Inherited Metabolic Disorders (IMDs) frequently masquerade as common neurological and psychiatric conditions. This presentation provides a clinical roadmap for identifying "red flags" in patients presenting with intellectual disability, cerebral palsy mimics, refractory epilepsy, and multi-organ phenotypes.

We specifically highlight the often-overlooked psychiatric manifestations of IMDs, such as acute psychosis and catatonia, where metabolic correction can be life-changing. To address these complexities, we discuss the role of the United for Metabolic Diseases (UMD) consortium in harmonizing Belgian care and the diagnostic power of multi-omics to resolve variants of uncertain significance. Finally, we demonstrate the utility of IEMbase as a real-time decision-support tool to bridge the gap between complex phenotypes and treatable metabolic diagnoses. Therapies include medical diets and supplements, repurposed and novel drugs, genetic therapies, and regenerative medicine.

By integrating clinical suspicion with collaborative networks and advanced digital tools and -omics and iPSC technologies, we can move from prolonged diagnostic odysseys to precision metabolic medicine.

Dr Cécile Bossaert & Dr Laura Plasse, Adult Emergency Dpt, CHU Lille, France

Metabolic impairements during protoxyde d'azote utilization

Context Nitrous oxide (N_2O) intoxication is a growing public health problem, with an increasing prevalence of clinical complications of this intoxication. These clinical issues are represented by peripheral and central neurological damage, psychiatric conditions and thromboembolic events.

Metabolic issues The underlying pathophysiology is partly related to the oxidation of the cobalt ion in vitamin B12 by N_2O, leading to its inactivation and a subsequent reduction in the activity of vitamin

B12–dependent enzymes methionine synthase and methylmalonyl-CoA mutase. On the one hand, decreased methionine synthase activity impairs the remethylation of homocysteine to methionine, resulting in hyperhomocysteinemia, which is currently used as a marker of recent N_2O exposure according to European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) first diagnostic guidelines. On the other hand, inhibition of methylmalonyl-CoA mutase leads to the accumulation of methylmalonic acid, reflecting the severity of peripheral neurological involvement.

Management of the patients To date, the diagnosis of N_2O intoxication remains challenging, as the substance cannot be routinely measured due to its very short half-life. These metabolic disturbances may also be observed in inherited disorders of cobalamin metabolism or cobalamin deficiency and should not be confused with such conditions. That is why the management of the patients with clinical complications of nitrous oxide intoxication is based on a multidisciplinary approach and on a range of arguments – clinical and biological. The future prospects for addressing the N_2O issue lie in direct measurement and the improvement of clinical management through the use of scores.

Dr Joseph Dewulf, PhD, Metabolic Laboratory, UCL Louvain, Belgium

New Biochemical Red Flags for Newborn Screening of Pyridoxine - Dependent Epilepsy (ALDH7A1)

Pyridoxine-dependent epilepsy (PDE) is a rare developmental epileptic encephalopathy, most often caused by biallelic variants in *ALDH7A1*. Patients have seizures resistant to standard anticonvulsants but responsive to high-dose vitamin B6, making early detection critical. Traditional biomarkers were unstable or nonspecific, limiting newborn screening (NBS). Newly identified stable biomarkers (2-OPP and oxo-PIP) offer improved detection. Integrated into routine FIA-MS/MS workflows, these markers were tested retrospectively in 9 confirmed neonatal cases and 9393 controls. 2-OPP showed highest sensitivity, and combining it with oxo-PIP improved positive predictive value. This approach has led to the implementation of pilot NBS for PDE-ALDH7A1 in Brussels and Southern Belgium in March 2026

Dr Jean-Baptiste Arnoux, Hôpital Necker-Enfants Malades, Paris, France

Arginase deficiency: a new treatable disease

Arginase 1 deficiency (ARG1D) is an ultra-rare disease whose unique pathophysiology distinguishes it from other urea cycle disorders (UCDs). In addition to an inconsistent risk of hyperammonemia, ARG1D is associated with a wide range of symptoms, particularly neurocognitive and motor impairment related to elevated plasma arginine levels, highlighting the dual toxic mechanism of the disease. Consequently, the diagnosis may be mistaken for hereditary spastic diplegia or other progressive neurological disorders.

Until recently, the treatment of ARG1D was similar to that of classical UCDs, except for the more restrictive low-protein diet required to achieve the therapeutic goal of normal plasma arginine levels. In 2023, pegzilarginase enzyme therapy received European market authorization. This new therapeutic approach specifically targets the progressive neurological toxicity of the disease by maintaining consistently normal plasma arginine levels while allowing a less restrictive low-protein diet. Notably, the full potential of any therapeutic strategy can only be achieved when treatment is

initiated presymptomatically, underscoring the importance of diagnosis through newborn screening programs

Dr Jeremie Gras, Medical Director, Institut de Pathologie et de Génétique, Belgium

Will AI shape our future medical practice?

Artificial intelligence (AI) is a disruptive technology and has already an impact on many aspects of human activities. This seems to be also true for medical practice.

At the last ASHG congress held in Boston in October 2025, AI was the main subject. During this congress, the world record for whole genome sequencing was beaten, in 4 hours, with a new platform that incorporates Graphical Processing Units (GPUs) for secondary bioinformatics.

This presentation will address applications of AI for medical practice in genetics, with discussion of innovations like ambient listening and GPU powered genomics.

Europe has taken a strategic delay regarding AI, in comparison to USA and China.

Europe is trying to cope with this delay with the advent of the European Health Data Space (EHDS).

Ethical and legal aspects are key and will also be briefly presented, with a focus on the European situation.

Alice Pierson & Céline Cambron, Glut1 Belgium asbl

The ketogenic diet in GLUT1 DS: daily reality, hidden burden, and how patient associations can help

For a family, the diagnosis of Glut1 Deficiency Syndrome marks a significant turning point. The transition to a strict metabolic therapy is a major shift, requiring a new approach to daily life where food becomes a medical necessity. This often means an abrupt change in feeding habits, especially for a child (such as sharing snacks at school for birthdays), to begin a lifelong medicalized relationship with nutrition.

In this presentation, we would like to bring the perspective of caregivers living with Glut1DS every day. Our aim is to share what exists beyond prescriptions: the invisible work, adaptations, worries, time required for precise meal calculations, financial costs of specialized ingredients, and the social challenges that can accompany a restrictive diet. Families manage a "hidden burden" that creates a constant mental load and affects the entire household. The ketogenic diet is often described as a “diet”, but for families it becomes an around-the-clock medical treatment. Even when the treatment is effective, it can remain socially isolating and mentally demanding for both patients and caregivers. Behind good metabolic control often lies an enormous amount of organisation and energy.

At the same time, families also develop expertise, creativity, and mutual support. Through the experience of Glut1 Belgium, we will illustrate how patient associations offer a support system to help families navigate these daily challenges and reduce isolation. By providing practical tools—such as "keto-packs", an online database of recipes, and peer-to-peer support —the association helps bridge the gap between the hospital and the home. These initiatives, including family days and culinary workshops, aim to turn a solitary struggle into a shared journey. Our hope is to show that while the diet treats the disease, it is the community and the partnership with medical teams that truly support the family.

Selected Communication 1 : Evaluation of the integration of homocysteine remethylation deficiencies into the Belgian newborn screening

Authors : Céline Dufour1, Lionel Marcélis2, Aurélie Empain1, Corinne De Laet1

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2. Université Libre de Bruxelles (ULB), Laboratoire de pédiatrie

Introduction : The aim of this study was to define a screening strategy for homocysteine remethylation deficiencies based on data obtained from neonatal dried blood spot tests (Guthrie tests).

Materiel and methods : A retrospective study was conducted on Guthrie test results from nine patients with confirmed remethylation defects. Methionine, the methionine-to-phenylalanine ratio, propionylcarnitine and propionylcarnitine-to-acetylcarnitine ratio were compared with values from the general population and from patients with vitamin B12 deficiency. The analysis was extended to methionine-to-Xle ratio and a score was developed based on adjusted outlyingness.

Results : Methionine, the methionine-to-phenylalanine ratio and their combination failed to identify all patients with remethylation defect. In contrast, propionylcarnitine, propionylcarnitine-to-acetylcarnitine ratio and their combination successfully identified all patients with the classical form of cobalamin C deficiency. The methionine-to-Xle ratio and the score derived from the weighted mean of the adjusted outlyingness of methionine, methionine-to-phenylalanine and methionine-to-Xle allowed detection of all patients with MTHFR deficiency, as well as those with milder and more difficult to detect clinical phenotypes.

Conclusion : Remethylation defects represent strong candidates for inclusion in newborn screening programs due to the potential for clinical improvement with very ealy treatment. This study demonstrates that the combination of propionylcarnitine and the propionylcarnitine-to-acetylcarnitine ratio enables identification of all patients with a classical cobalamin C deficiency. The methionine-to-Xle ratio and the score based on adjusted outlyingnesses appear to be promising markers for detecting remethylation deficiencies. Larger cohort studies are required to validate these

findings. First-line homocysteine measurement may represent a promising alternative screening strategy.

Selected Communication 2 : Autologous mesoangioblast therapy for mitochondrial myopathy (m.3243A>G): preliminary results from an ongoing phase II study

Florence H.J. van Tienen[1,2], Janneke G.J. Hoeijmakers[2,3], Christiaan van der Leij[4,5], Bart Wagemans[4,5], Laura Differding[6], Chantal Lechanteur[6], Alexandra Briquet[6], Virginie Bettonville[6], Laura Differding[6], Etienne Baudoux[6], Erika Timmer[1,4], Nikki Wanders[1,2], Jen Vanherle[7], Bert O. Eijnde[7], Dimitri Hemelsoet[8], Irenaeus F.M. de Coo[1,2,9], Hubert J.M. Smeets[1,2,4]

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Mitochondrial myopathies caused by a pathogenic mtDNA mutation are characterised by muscle weakness, exercise intolerance, and fatigue, often leading to significant impairment in daily functioning and quality of life. Disease severity is closely related to the mtDNA mutation load in skeletal muscle, with oxidative phosphorylation deficiency occurring above a critical threshold. Currently, no curative treatment is available.

Autologous mesoangioblast transplantation represents a potential regenerative strategy aimed at improving muscle function by reducing mtDNA mutation load in existing muscle fibres and generating new muscle fibres. Following a first-in-human phase I/II study demonstrating the safety of a single intra-arterial administration of autologous mesoangioblasts, we initiated an ongoing phase II clinical study (NCT05962333) in m.3243A>G carriers to evaluate repeated administrations. In this study, autologous mesoangioblasts with a low mtDNA mutation load (<25%) are isolated from muscle biopsies, expanded, and administered intra-arterially into the biceps brachii. Participants receive three infusions at 4–6-week intervals. Outcomes include safety, muscle strength, fatigue, and exploratory analyses of muscle structure and mtDNA mutation load.

Preliminary observations indicate that repeated intra-arterial delivery is safe and feasible. To support completion of this study, we are seeking additional participants and encourage referral of eligible patients.