RECORDATI RARE DISEASES CANADA GROUP

Rare, really?

Genetic conditions: individually rare, collectively common

- >10,000 single gene disorders are estimated to affect 1 in 100 individuals at birth on a global basis[1]
- Inborn errors of metabolism (IEMs) are estimated to occur in ~1 of every 2,500 live births[2]
- 80% of IEMs are diagnosed during childhood[2]
- Diagnosis of late onset forms is thought to be underestimated[2]
- A number of IEMs are treatable, and new diagnostic methods and therapies are available[2]
- Clinical studies suggest that some IEM-specific treatments may be more effective during the early stages of disease, when psychiatric symptoms may be evident. Efficient recognition and identification of the underlying organic disease could therefore allow earlier initiation of specific therapy and possibly improve outcomes[2]

Inborn errors of metabolism (IEMs): An important cause of psychiatric disorders in adolescents and adults[2]

Psychiatric presentation of IEMs[3]

- Intellectual disabilities
- Mood disorders
- OCD
- Schizophrenia-like symptoms
  - Auditory and visual hallucinations
  - Delusions
  - Catatonia
  - Course of thought disorders

Psychiatric signs of IEMs may remain isolated for years before other more specific organic signs appear and IEMs that present purely with psychiatric symptoms are very difficult to diagnose.[4]

Suspect a metabolic disorder:[5]

1. When there is significant family history of metabolic or other neurological disorder
2. When psychiatric symptoms occur coincident with neurological, cognitive, or other systemic symptoms
3. When the course is episodic and triggered by specific conditions that result in metabolic stress
4. In presence of the following features:[2]
   - Acute confusion
   - Visual hallucinations and/or auditory hallucinations
   - Catatonia
   - Progressive cognitive decline
   - Early or acute onset
   - Treatment resistance

IEMs with psychiatric presentations

Organic symptoms

Homocystinuria (CBS deficiency)[2]	• Thromboembolism • Skeletal changes • Marfan-like habitus • Lenticular ectopia/severe myopia
Homocystinuria (MTHFR deficiency)[2,6]	• Encephalopathy • Microcephaly • Ataxia
Urea Cycle Disorders (UCDs)[2,7]	• Abdominal pain • Migraine-like headaches • Confusion/lethargy/dizziness • Nausea/vomiting • Protein aversion/self-selected low protein diet • Hepatomegaly/elevated liver enzymes
Porphyria[2,3,5]	• Abdominal pain/constipation • Peripheral neuropathies • Black/red urine • Nausea/vomiting • Confusion • Erythropoietic disturbances • Hepatic disturbances

Triggering events[2,7-9]

- High-protein diet
- Surgery
- Infections/fever
- Chemotherapy
- Drugs (e.g., valproic acid in UCDs, hormonal contraceptives in porphyria)
- Sepsis
- Alcohol
- Crash diet/bariatric surgery

It is important to identify IEMs as early as possible in order to refer patients to specialist centres for appropriate management, disease-specific treatment, possible prevention of irreversible physical and neurological complications, and genetic counselling.[10]

References: 1. WHO. *Genes and human disease.* 2018. Available at: http://www.who.int/genomics/public/geneticdiseases/en/index2.html. Retrieved 18 January, 2018. **2.** Bonnot O, et al. Diagnostic and treatment implications of psychosis secondary to treatable metabolic disorders in adults: a systematic review. *Orphanet J Rare Dis.* 2014;9:65. **3.** Bonnot O, et al. Secondary psychosis induced by metabolic disorders. *Frontiers in Neuroscience.* 2015;9:177. **4.** Demily C, et al. Psychiatric manifestations of treatable hereditary metabolic disorders in adults. *Ann Gen Psychiatr.* 2014;13(1):27. **5.** Walterfang M, et al. The neuropsychiatry of inborn errors of metabolism. *J Inherit Metab Dis.* 2013;36(4):687-702. **6.** Rosenblatt DS. *Disorders of cobalamin and folate transport and metabolism. Inborn Metabolic Diseases:* Springer; 2000:284-298. **7.** Haberle J, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis.* 2012;7:32. **8.** Balwani M, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management. *Hepatology.* 2017;66(4):1314-1322. **9.** Saudubray J-M, et al. *Inborn metabolic diseases: diagnosis and treatment:* Springer; 2016. **10.** Sedel F, et al. Therapy insight: inborn errors of metabolism in adult neurology--a clinical approach focused on treatable diseases. *Nat Clin Pract Neurol.* 2007;3(5):279-290.

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