Evidence-based evaluation of patients with intellectual disability for treatable inborn errors of metabolism: TIDE protocol & clinical study

Introduction

Intellectual disability (ID) defined as IQ<70 and termed ‘global developmental delay’ at age <5 years is a debilitating disorder affecting 2.5% of the population. Current recommendations to investigate genetic causes of ID are based on frequencies of single conditions and yield of tests rather than availability of causal therapy. Early recognition of rare but treatable inborn errors of metabolism (IEM) is crucial for preventing / minimizing brain damage, improving health outcomes and reducing of health care costs.

Aim

To implement an evidence-based diagnostic protocol prioritizing treatability for all children with global developmental delay / intellectual disability.

Methods

Our systematic literature review identified 81 IEM which present predominantly with ID and are amenable to causal therapy (Molec Genet Metab 2012).

- Therapeutic modalities are affordable, accessible & safe.
- Evidence level limited (level IV in 62%); therapies often effective.

This knowledge was translated into a diagnostic protocol:

First tier: In all patients: metabolic screening tests in blood & urine > identifies 65% of all treatable IEM.

Second tier: focuses on remaining disorders, requires ‘single test per disease’ approach.

A freely available WebApp (www.treatable-id.org) was designed to support the protocol:

'Treatable Intellectual Disability Endeavor in B.C.': preliminary results

Preliminary results of protocol implementation in BC Children's Hospital as funded study ‘TIDE-BC’ (www.tidebc.org) are reported here:

During the first 6 months:

- Enrollment: 130 ID patients (data & DNA/urine collection)
- 'Diagnostic yield' (preliminary results):
  - confirmed diagnosis in 25%:
    - including 5 treatable IEM (Creatine Transporter Deficiency (n=2), GLUT-1 deficiency, Tyrosine Hydroxylase deficiency, Cobalamin A deficiency)
  - and non treatable genetic conditions (Rett syndrome, Angelman syndrome, chromosomal copy number variants)
  - probable diagnosis in 17% (awaiting molecular confirmation);
    - including 5 treatable IEM (serine deficiency, Niemann Pick Disease Type C, biotinidase deficiency, Creatine Transporter Deficiency)

Future Directions

- Expansion of the TIDE protocol to the province of B.C. & beyond
- Formal (cost-)effectiveness evaluation after 3 years
- International guidelines

Our novel approach may well improve outcomes and convince colleagues and policymakers to change practice and care for individuals with ID.