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Minireview

The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable causes and new digital resource ☆

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ABSTRACT

Intellectual developmental disorders (IDD), characterized by significant impairment of cognitive functions, with limitations of learning, adaptive behavior and skills, are frequent (2.5% of the population affected) and present with significant co-morbidity. The burden of IDD, in terms of emotional suffering and associated health care costs, is significant; prevention and treatment therefore are important. A systematic literature review, updated in 2013, identified 89 inborn errors of metabolism (IEMs), which present with IDD as prominent feature and are amenable to causal therapy. Therapeutic effects include improvement and/or stabilization of psychomotor/cognitive development, behavior/psychiatric disturbances, seizures, neurologic and systemic manifestations. The levels of available evidence for the various treatments range from Level 1b, c (n = 5); Level 2a, b, c (n = 14); Level 4 (n = 53), and Levels 4–5 (n = 27). For a target audience comprising clinical and biochemical geneticists, child neurologists and developmental pediatricians, five experts translated....this data into a 2-tiered diagnostic algorithm: The first tier comprises metabolic "screening" tests in urine and blood, which are relatively accessible, affordable, less invasive, and have the potential to identify 60% of all treatable IEMs. The second tier investigations for the remaining disorders are ordered based on individual clinical signs and symptoms. This algorithm is supported by an App www.treatable-id.org, which comprises up-to-date information on all 89 IEMs, relevant diagnostic tests, therapies and a search function based on signs and symptoms. These recommendations support the clinician in early identification of treatable IEMs in the child with IDD, allowing for timely initiation of therapy with the potential to improve neurodevelopmental outcomes. The need for future studies to determine yield and usefulness of these recommendations, with subsequent updates and improvements to developments in the field, is outlined.

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Abbreviations: CMA, chromosome micro-array; CSF, cerebrospinal fluid; EEG, electro-encephalogram; ICD, international classification of diseases; IDD, intellectual developmental disorder; IEM, inborn error of metabolism; MRI, magnetic resonance imaging; OTC, ornithine transcarbamylase deficiency.

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1. Introduction

1.1. Intellectual developmental disorders (IDD)

In 2011, the World Health Organization International Classification of Diseases (ICD) Working Group on the Classification of Intellectual Disabilities proposed the term intellectual developmental disorders (IDD) to encompass a group of developmental conditions characterized by significant impairment of cognitive functions associated with limitations of learning, adaptive behavior and life skills [1]. IDD comprises both 'Intellectual Disability' (defined as an IQ of <70, at age 5 years or older) [2,3] and 'Global Developmental Delay' (term used at age < 5 years, defined as deficits in 2 or more developmental domains, e.g., fine/gross motor skills, speech and interaction) [4]; IDD is further defined as existing over the course of an individual's life span, requiring consideration of ongoing developmental stages and life transitions. Additionally, it is frequently associated with behavioral problems (autistic features, hyperactivity, aggressive and self-injurious behaviors), as well as neurological symptoms such as epilepsy [5,6]. In the present article we apply the term IDD to both intellectual disability and global developmental delay.

1.2. IDD etiology and diagnostic approach

Affecting 2–3% of children and adults worldwide, IDD is common and associated with the highest life-time health care and economic costs of any disease—nearly equaling the economic impact of stroke, heart disease and cancer combined [7]. The etiology of IDD is diverse and has been conceptualized by the ICD Working Group as a 'meta-syndromic' health condition with infectious, traumatic and toxic origins. However, genetic etiologies represent the most frequent cause of IDD [8,9], and range from numeric and structural chromosomal abnormalities and submicroscopic rearrangements, to methylation abnormalities and single gene defects [10,11].

Presently, recommendations aimed at structuring the evaluation of genetic causes of IDD are based on the frequencies of single conditions and yield of diagnostic methods and procedures [12]. Consequently, karyotyping and array-comparative genomic hybridization are standard practice as part of the first-line investigation and yield a causal diagnosis in up to 20% of cases [13,14]. Such diagnoses provide opportunities for better genetic counseling for the family, modified management strategies and targeted screening for medical complications (e.g. congenital heart disease and tumors) with significant impact on quality and quantity of life in the affected child [15,16]. However, for most of the conditions identified by these investigations, medical intervention *targeting* the underlying defect and/or pathogenesis is not currently available. Therefore, treatment is symptomatic rather than causal and, while essential, in most cases the therapeutic benefits are limited.

1.3. Treatable inborn errors of metabolism and IDD

Inborn errors of metabolism (IEMs) are uniquely amenable to *beneficial causal treatment*, defined as a medical intervention targeting the underlying defect and/or pathogenesis. Treatments include dietary restriction/supplement, co-factor/-enzyme, vitamin, substrate inhibition, (small molecule) substrate reduction, enzyme replacement, bone marrow and hematopoietic stem cell transplant, and gene therapy (see Table 1 for definitions). Several reviews have been published regarding the metabolic causes of IDD, most of which are based on individual expertise in the field of IEMs [17–19]. Further, while technologies for better recognition have been introduced into clinical practice, these have yet to be incorporated into diagnostic practice recommendations or parameters for the evaluation of children with IDD, such as those of the American College of Medical Genetics (1997) [20], the American Academy of Pediatrics (2006) [21], and the American Academy of Neurology (2011) [22].

The target audience of this article includes developmental pediatricians, biochemical and clinical geneticists and neurologists, i.e. all specialists who are faced with the important and often difficult challenge of timely, accurate and expeditious diagnoses of treatable IEMs associated with IDD in children and adolescents. What is especially important in this challenge is that the identification of these conditions is the necessary precondition to the implementation of specific therapeutic interventions known to improve outcomes. The recommendations outlined herein represent an international collaborative effort that integrates available evidence and expert opinion into a two-tiered algorithm supported by a digital application. The recommendations are designed to aid the pediatric specialist in the evaluation of children with IDD. Clinical skills and differential diagnosis