The Importance of Metabolic Testing in the Evaluation of Intellectual Disability

Practice parameters for global developmental delay (GDD) and intellectual disability (ID) have often not recommended comprehensive metabolic evaluations because of the low diagnostic yield. Engbers and colleagues'[1] article in this issue of *Annals* provides data that suggest we revisit this recommendation.

ID and GDD are common and overlapping disorders that impact the patient, family, and society. The estimated prevalence of ID in developed countries is 2 to 3% but varies between different studies from 1 to 10%.[2–7] One study showed that ID was the disease category with the largest healthcare costs, almost equal to the economic impact of stroke, heart disease, and cancer combined.[8] Establishing an accurate diagnosis for ID/GDD patients is essential for proper medical management, for genetic counseling and anticipatory guidance, and for the prevention of unnecessary and costly additional testing. A diagnosis will also allow the patient to access research protocols, and provide better state and federal funding for therapeutic and social services.

To date, there has been a distinct lack of consensus regarding the appropriate clinical and laboratory evaluations for these patients. The expanded newborn screen with tandem mass spectrometry is one of the major advances in screening for potentially treatable diseases. Nevertheless, the number of tested disorders still varies state by state within the United States, as well as in Europe, and ranges anywhere from 2 to 54.[9] In 2006, the American College of Medical Genetics (ACMG) suggested to screen for 29 core conditions and 25 diseases as secondary targets,[10] a recommendation that will hopefully be more widely adopted.

Currently, only three published guidelines for the evaluation of children with ID are available. The first of these, by the ACMG, was published in 1997.[2] Key elements in their recommendations include a three-generation pedigree; prenatal, perinatal, and postnatal history; a complete physical examination with a focus on minor anomalies; neurological examination; assessment of behavioral phenotype; and karyotype testing. Fragile X testing was advised with a positive family history. Neuroimaging and a metabolic workup were recommended only in the presence of suggestive clinical and physical findings. The committee emphasized that repeated clinical evaluation over time is important for diagnostic purposes. The ACMG suggests an extremely low yield for unselected metabolic screening without specific signs of a metabolic disorder.[2] In 2003, the American Academy of Neurology and the Child Neurology Society published their practice parameters. This group also does not recommend routine metabolic testing given 1% diagnostic yields but advises routine cytogenetic testing, neuroimaging, and molecular testing for fragile X with cited yields for these three categories ranging from 3.5 to 65.5%.[11] The published guidelines of the American Academy of Pediatrics are similar to the consensus of the ACMG as outlined earlier.[12] Unfortunately, these recommendations against broad-based metabolic screening are based only on nonuniformly executed cohort studies. Although the diagnostic yields were generally low (ranging from 0.2 to 8.4% with a median of 1%), greater rates were observed in countries in which specific disorders are more common such as in Finland (eg, aspartylglycosaminuria).[13]

Engbers and colleagues'[1] study addresses the yield of targeted metabolic studies during an evaluation at a tertiary care center in children with ID after a prior broad-based evaluation. In their cohort, they find an underlying cause for ID in 14% (59/433 patients) of patients. Among them, 5.1% (22/433) were diagnosed with a genetic cause (nonmetabolic), 5.8% (25/433) with exogenic causes, and 2.8% (12/433) with a metabolic disorder, of which almost 50% were potentially treatable. Before referral, almost all patients (87%) had undergone an extensive metabolic screening (see Engbers and colleagues'[1] study for details), conforming to Dutch guidelines for patients with DD/ID. The extent of the prereferral evaluation is likely responsible for the relatively low diagnostic yield (14%) because other studies that started with unscreened ID/GDD patients reported yields ranging from 41.6 to 63%.[3,14,15] For comparison, it would also have been helpful if the authors had provided data on the number of patients identified with this initial comprehensive metabolic screen.

Importantly, like the ACMG guidelines, Engbers and colleagues[1] directed their workup based on clinical findings and history for each patient. They identified mucopolysaccharidosis and congential disorder of glycosylation in two patients by repeating tests that were initially reported negative, because of convincing phenotypic presentations. Two patients presented with significant language delay and were found to have X-linked creatine transporter deficiency,[16] a test not on

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most clinicians' first-line list, nor is measuring metabolites in cerebrospinal fluid, an approach that diagnosed two patients. Diagnoses for four patients were made because clinical suspicion leads to performing biochemical loading/fasting tests. Importantly, 5 of these 12 diagnosed patients had potentially treatable metabolic disorders.

Where do these findings leave us? Two important points emerge. First, even after broad-based metabolic screening performed by clinicians, further scrutiny identified 14% of the patients with metabolic disorders, many of which were treatable. Second, the diagnosis was made by relying on astute clinical judgment (from a multidisciplinary team of experts) and by ensuring that testing modalities kept up with the newest discoveries (cerebrospinal fluid–based disorders including disruption of creatine transport/metabolism). Although future studies in other cohorts are needed to test the overall applicability of Engbers and colleagues'[1] results, this study cautions us about relying too heavily on practice parameters, particularly if treatable disorders remain undiagnosed.

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The Impact of War-Stress on MS Exacerbations

In the current issue of the *Annals*, Golan and colleagues report on what appears to be markedly increased MS exacerbation rates requiring steroids in 156 relapsing-remitting (RR) MS patients (all residents of northern Israel) during the 33 day Israel-Hezbollah war in the summer of 2006 (1). In this study, 18% of the cohort experienced a relapse of their MS during the war compared to an average of only 3.2 % per month (range 1-6) for this cohort in each of the15 month-periods both before and immediately after of the war-month ($p < 0.02$-0.001). In addition, of those patients who experienced an MS relapse during the war, the percentage who perceived a high level of stress or a life-threat during the war was more than twice as high as in the subgroup of patients who remained relapse-free during the war. On this basis, the authors suggest that the observed increase in MS attacks is related to the stress of the war. Even in the absence of any actual measure of stress, this seems a reasonable hypothesis because, by

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