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Original Article

Diagnostic yield from routine metabolic screening tests in evaluation of global developmental delay and intellectual disability

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Abstract

Global developmental delay and intellectual disability (GDD/ID) affect 3% of the paediatric population. Although inborn errors of metabolism (IEM) are not a common cause of GDD/ID, early therapeutic intervention can improve neurodevelopmental manifestations. In 2012, a first-tier test panel, including specialized metabolic and routine chemistry tests, was piloted to community-based paediatricians in British Columbia with aims to achieve earlier diagnosis of treatable IEM.

Objective: The aim of this retrospective review was to evaluate the diagnostic yield from these first-tier tests in the 7 years before (2006 to 2012) and after (2013 to 2019) implementation at the community paediatrician level.

Results: Prior and postimplementation diagnostic yield of an IEM from first-tier metabolic testing was 9 out of 986 (0.91%) and 11 out of 4,345 children (0.25%), respectively. Disorders of creatine metabolism and organic acidurias were the most frequently established diagnoses in both time periods. No diagnoses were established through acylcarnitine copper/ceruloplasmin, lactate, or ammonia testing. Twenty out of 24 patients had specific neurological or other red flag signs in addition to GDD/ID. Four boys diagnosed with an x-linked creatine transporter defect (CTD) had speech-language delay as the most prominent finding.

Conclusions: The expansion of first-tier metabolic testing to community-based paediatricians in BC did not yield an increase in IEM diagnoses. A modified first-tier test panel should be offered to patients with GDD/ID, neurologic, and/or red flag signs. Urine creatine testing in boys with speech-language delay warrants consideration to detect CTD.

Keywords: *Diagnostic yield; Global developmental delay; Inborn errors of metabolism; Intellectual disability*

Global developmental delay (GDD) and intellectual disability (ID) affect 2% to 3% of the paediatric population (1) and are a frequent reason for referral to paediatricians. Several published guidelines offer various approaches to etiologic evaluation of a child with GDD/ID (1–4). Accurate and timely diagnosis may identify a treatable etiology, provide prognostic information, allow for better access to community services, and resolve the diagnostic odyssey. Early screening may also detect an inborn error of metabolism (IEM) before the phenotype evolves to more severe neurologic and/or systemic symptoms to allow for earlier treatment and improved health outcomes.

The diagnostic yield of routine metabolic tests in evaluation of IEMs in children with GDD/ID has been poorly evaluated. Studies from tertiary care settings, in patients with more severe

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neurological symptomatology, have quoted diagnostic yields up to 10% but were relatively small (<500 subjects) and may not be applicable to a community-based GDD/ID population (5,6). Other studies (7,8) have quoted diagnostic yield between 1% and 2% but were conducted before the expansion of newborn screening. A blood spot test panel of amino acids and acylcarnitines detects several treatable IEM associated with GDD/ID. This advance in newborn screening has decreased the number of children who present with undiagnosed GDD/ID later in life. However, newborn screening cannot detect all treatable IEM associated with GDD/ID and false-negative screens occasionally occur, especially in cases with milder biochemical phenotypes.

In 2012, van Karnebeek et al. published a systematic literature review identifying 81 treatable IEM with ID (9). The potential for improved health outcomes through timely therapeutic intervention has prompted the development of a tiered diagnostic protocol prioritizing treatable conditions (10). Up until that time, there had been no standardized approach to metabolic screening of children with GDD/ID in British Columbia (BC). The Treatable Intellectual Disability Endeavor or 'TIDE protocol' (11) consists of a first tier of metabolic and chemistry tests (Table 1) and access to further assessment by a metabolic specialist for second-tier targeted metabolic and genomic investigations. Beginning in 2012, community-based paediatricians in BC were provided with information on the first-tier TIDE protocol and encouraged to widely screen children with unexplained GDD/ID with or without neurological features and other red flags typically occurring in IEM (Table 2). The rationale was that some IEM may present with GDD/ID as a sole feature for a considerable time before manifestation of neurological features (10). The objective was to facilitate earlier diagnosis of potentially treatable GDD/ID.

The aims of this quality improvement retrospective review were to:

1) Determine the change in ordering practice by general paediatricians in response to the first-tier TIDE protocol
2) Determine the diagnostic yield as a result of first-tier TIDE screening
3) Identify the clinical features of those diagnosed as a consequence of first-tier TIDE screening

Table 1. First-tier metabolic and routine chemistry tests as part of TIDE protocol

Biochemical genetics laboratory metabolic tests	Routine chemistry tests
1. Plasma amino acids	Ammonia
2. Urine organic acids	Copper/ceruloplasmin
3. Dried blood spot acylcarnitines	Homocysteine
4. Urine purine, pyrimidine, creatine metabolites	Lactate

METHODS

The BC TIDE first-tier screen (Table 1) recommends a combination of routine clinical chemistry tests and four specialized metabolic test panels performed exclusively in the Provincial Biochemical Genetics laboratory, BC Children's Hospital. Plasma amino acids were measured by LC-MS/MS and urine organic acids by GC-MS following standard quantitative clinical testing protocols. Acylcarnitines were measured on dried bloodspot cards by the provincial newborn screening program by a flow injection MS/MS method for amino acids and acylcarnitines. Urine purine and pyrimidine analysis was combined with creatine metabolites in a single LC-MS/MS laboratory-developed assay.

Estimation of first-tier TIDE test volume

Metabolic tests may be ordered in the context of GDD/ID or for other clinical indications such as unexplained metabolic acidosis, hyperammonemia, hypoglycemia, liver dysfunction, or nutritional assessment. Clinical information was not required. In order to estimate first-tier TIDE test volume specifically for investigation of GDD/ID, the four Biochemical Genetics lab (BGL) metabolic test panels in combination were selected and searched by year 2006 to 2019. Three of these tests, amino acids, organic acids, and acylcarnitines, may be ordered in other clinical contexts; however, the urine purine, pyrimidine, and creatine panel has limited indications for test ordering and in combination with the other three tests, is almost exclusively ordered for GDD/ID. For this reason, only children who had all four metabolic test panels were included in this review.

Table 2. Neurological features and other red flags suggestive of IEM*

Family history of IEM or unexplained infant death
Consanguinity
Failure to thrive
Head circumference > 2 SD above or 2 SD below mean
Recurrent episodes of vomiting, ataxia, seizures, lethargy, and coma
History of being severely symptomatic and needing longer to recover from inter-current (viral) illness
Unusual dietary preferences
Regression in developmental milestones
Severe hypotonia, dystonia, seizures, and abnormal hypertonia (spasticity)
Neuroimaging abnormalities

IEM Inborn errors of metabolism.
*Adapted from ref. (1).

Urine oligosaccharide and mucopolysaccharide test volumes were selected and searched by year 2006 to 2019 to account for changes in test volume due to other factors such as population growth.

Other routine chemistry tests, included in the first-tier TIDE protocol (serum lactate, ammonia, ceruloplasmin, copper, and homocysteine) were performed in laboratories across the province and were not readily searchable through laboratory information systems. These tests were not included as part of the estimate of the number of children screened.

To determine the diagnostic yield as a result of first-tier TIDE testing, the number of cases detected in the 7 years before the implementation of the first-tier TIDE protocol (2006 to 2012) was compared with the 7 years after the implementation (2013 to 2019). IEM diagnosed by other metabolic or genetic tests were not included in this review.

Statistics

Diagnostic yields in the pre- and postgroups were compared using Pearson's chi-square test.

Retrospective review of test volume

Patients who had all four BGL metabolic tests were searched in the laboratory information system. Field search included test names, collection date range (January 2006 to December 2019), and pathologist comment. Test orders for therapeutic monitoring, based on specific monitor reporting codes, were excluded.

Retrospective review of physician type

The purine/pyrimidine/creatine test, which is almost exclusively ordered in the context of a GDD/ID investigation, was searched in the laboratory information system. The test was sorted by the ordering physician's name at two time points: the year of introduction of the TIDE protocol (2012) and the most recent calendar year (2019). Specialist type for each physician was determined by searching the College of Physicians and Surgeons of BC directory. Specialty type included paediatrician, paediatric neurology, paediatric psychiatry, metabolic specialist, adult neurology, adult psychiatry, and unknown specialty.

Retrospective review of diagnoses

As part of routine practice, new diagnoses were recorded in a secure database in the biochemical genetics laboratory. Inclusion criteria include (1) cases diagnosed between 2006 and 2019 and (2) cases identified by an abnormal finding on one or more first-tier TIDE test with sufficient confirmatory test results. Exclusion criteria include (1) children diagnosed with an IEM from a first-tier metabolic test presenting with acute metabolic decompensation (hyperammonemia and metabolic acidosis) and (2) IEM with insufficient evidence that condition causes GDD/ID, for example, hyperprolinemia. Clinical symptomatology was obtained by review of consult letters from hospital electronic medical record. Wilson disease cases were identified through province-wide subspecialist services (biochemical diseases and paediatric gastroenterology).

RESULTS

Supplementary Appendix 1 shows the number of samples tested for the combined first-tier metabolic screening tests, along with two other tests not included in first-tier testing (urine mucopolysaccharides and oligosaccharides), between 2006 and 2019. While a gradual rise was observed in all sample numbers between 2006 and 2011, there was an inflection point in 2012, where the rate of combined first-tier tests significantly diverges from the baseline, in concert with the roll out of the TIDE protocol.

Test volume for the purine/pyrimidine/creatine test panel ordered by general paediatricians increased between 2012 and 2019 from n=247 to n=710, rising 2.9-fold or almost 300% (Supplementary Appendix 2). In contrast, the number of first-tier tests ordered by subspecialists (metabolic specialists, paediatric neurologists, and medical geneticists) was not appreciably different from the general baseline rise (n=209 in 2012 compared to n=310 in 2019).

Diagnoses

Before TIDE protocol implementation (January 2006 and December 2012), nine children, all with GDD and neurological features, were diagnosed with an IEM from one or more first-tier metabolic test result out of 986 tests (Supplementary Appendix 3). The diagnostic yield was 1:109 (0.91%). After implementation (2013 to 2019), 11 children were diagnosed with an IEM based on one or more abnormal first-tier TIDE metabolic test result out of 4,345 tests. The diagnostic yield was 1:395 (0.25%). Diagnostic yield postimplementation of the TIDE protocol (2013 to 2019) declined significantly in comparison to the pre-TIDE time period (2006 to 2012) (χ^2=9.25, P=0.002).

Eight out of 20 diagnoses were established via the purine, pyrimidine, and creatine test panel 7 of which were disorders of creatine metabolism (n=4 creatine transporter deficiency [CTD]; n=3 GAMT deficiency). Six and three diagnoses were identified from urine organic acid and plasma amino acid panels, respectively and three from total homocysteine measurement (Supplementary Appendix 3).

No diagnoses were established through copper/ceruloplasmin, lactate, and ammonia testing nor the acylcarnitine panel alone.

Sixteen out of 20 patients had specific neurological features including seizures, movement and tone disorders, and/or other red flag signs commonly found in IEM (e.g., neurodevelopmental

regression, lethargy, failure to thrive, and vomiting) in addition to GDD/ID. The remaining four cases, all diagnosed with CTD, had GDD/ID, low muscle mass, and speech-language delay as the most consistent findings (Supplementary Appendix 3).

DISCUSSION

Guidelines uniformly recommend prompt metabolic testing for GDD/ID with red flag signs such as neurological features, neurodevelopmental regression, lethargy, coma, and vomiting (1–4) but lack consensus on recommendations for children without red flag signs. The Canadian Paediatric Society position statement from 2018 (1) recommended first-tier metabolic screening in children with unexplained GDD/ID, even when red flags are absent, and regardless of normal newborn screening results. The diagnostic yield of such an approach is unknown, prompting this retrospective review.

The significant increase in first-tier TIDE testing between 2012 and 2019 and the shift to test ordering by general paediatricians confirms the uptake of the TIDE protocol for the evaluation of children with unexplained GDD/ID. While there was a corresponding decrease in test orders by metabolic specialists, the net effect was a dramatic rise in overall test utilization.

However, the number of diagnoses before and after the implementation of the first-tier TIDE tests for community-based GDD/ID screening did not appreciably change. There was a statistically significant drop in diagnostic yield from 0.91% to 0.25%. The diagnostic yield for children with GDD/ID from this review is significantly lower than published estimates in the literature (5–8). These studies were conducted in tertiary care settings and therefore more likely to include children with more severe GDD/ID. In addition, these studies predate the expansion of newborn screening, which includes a panel of acylcarnitines and amino acids detecting the majority of treatable inborn errors of metabolism by first-tier TIDE tests.

An argument in favour of metabolic screening in GDD/ID is to capture cases missed by newborn screening. Notably, one case of Glutaric aciduria type I (GAI) was detected with urine organic acid analysis in an infant who presented with acute neurological signs. No other false-negative newborn cases were detected through first-tier metabolic testing of children with GDD/ID. To provide some perspective, between 2006 and 2019, 67 infants were identified with phenylketonuria by newborn screening. The false-negative rate for phenylketonuria by tandem mass spectrometry newborn screening is exceedingly low (12).

The diagnostic yield from the chemistry portion of the first-tier TIDE screen revealed some diagnoses from total homocysteine tests. Between 2013 and 2019, three children with GDD and neurological signs had elevated total homocysteine and were diagnosed with a treatable IEM. However, no IEM was detected via the four other chemistry tests (lactate, ammonia, copper, and ceruloplasmin).

The copper and ceruloplasmin tests were aimed to identify Wilson's and Menkes disease (ATP7A and ATP7A deficiency), but no cases with either condition were identified. However, during this period, seven children were diagnosed with Wilson disease (WD) at BC Children's Hospital with isolated liver abnormalities (data not shown). The absence of WD cases detected through first-tier TIDE testing is likely attributable to the timing of testing. WD presenting in childhood is more likely to manifest with liver features, whereas neurological features (dysarthria, drooling, and dysphagia) mostly present in adulthood (13).

Our study protocol did not allow for systematic investigation of false-positive results across all the first-tier test panels. However, a retrospective review of referrals between January 2018 and December 2019 to the metabolic specialist clinic at BC Children's Hospital identified 10 out of 496 for 'abnormal copper or ceruloplasmin results', 6 out of 496 for 'elevated blood lactate and/or ammonia' and 4 out of 496 for 'abnormal creatine results', which all turned out to be false positives. Hence, the number of referrals for abnormal biochemical abnormalities as a result of first-tier TIDE screening was ~4% of total referrals (20/496).

Seizures, developmental regression, and focal neurologic signs were present in 16 of the 20 diagnoses while the remaining four diagnoses presented with less specific signs such as generalized hypotonia, speech-language delay, feeding difficulties, and behavioural issues. X-linked creatine transporter deficiency, the most frequently diagnosed condition, presented with these nonspecific signs and symptoms. These clinical features, with or without seizures, autistic features, and poorly developed musculature, are consistent with descriptions of the disorder in the literature (14,15). Urine creatine testing in boys with speech-language delay and hypotonia may warrant consideration to detect this X-linked disorder.

Overall, this review provides new information for programmatic quality improvement. Despite a dramatic increase in first-tier TIDE testing, there was no concomitant increase in diagnoses in patients. Apart from creatine transporter deficiency, there was no increase in diagnoses presenting without red flag signs typically observed in IEM.

Limitations

This retrospective review precluded access to clinical information to determine the proportion of children with GDD/ID versus GDD/ID with neurological features and other red flags, screened by first-tier metabolic tests. The denominator (the population that had first-tier metabolic testing) is an estimate. The diagnostic yield could be lower if children with GDD/ID

did not have the complete workup (all four metabolic tests). It could be higher if children with other clinical presentations also had these four metabolic tests. Finally, it cannot be assumed that all children who had the four metabolic tests also had the chemistry tests as part of first-tier TIDE. For example, it was not possible to estimate the number of children screened for Wilson disease.

The evidence presented here as well as the considerable costs of first-tier metabolic tests have prompted us to revise the TIDE protocol and its indications. We conclude that metabolic testing should be performed when GDD/ID is associated with additional neurological features and other red flags for IEM. We recommend a modified first-tier TIDE protocol, including plasma amino acids, total homocysteine, urine organic acids, and a test allowing the determination of urine creatine metabolites, while omitting acylcarnitine profile, lactate, ammonia, copper, and ceruloplasmin as originally included in the first-tier TIDE tests.

The clinical availability of whole-exome sequencing for investigation of GDD/ID has increased dramatically with diagnostic yields ranging from 30% to 55% (16) with emerging evidence of clinical utility such as prognostic information, time to diagnosis, pharmacological intervention, and family planning. Therefore, particularly for children with ID/GDD and neurological features, when no etiological diagnosis is identified on first-tier tests, referral to genetics, and/or a metabolic specialist will provide for further tailored metabolic and genetic testing based on specific features, to achieve additional diagnoses.

SUPPLEMENTARY DATA

Supplementary data are available at *Paediatrics & Child Health* Online.

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