Molecular Genetics and Metabolism xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

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

Clara D.M. van Karnebeek [a,b,*], Michael Shevell [c,d], Johannes Zschocke [e], John B. Moeschler [f], Sylvia Stockler [a,b]

[a] Division of Biochemical Diseases, Department of Pediatrics, BC Children's Hospital, Child & Family Research Institute, University of British Columbia, Vancouver, Canada
[b] Treatable Intellectual Disability Endeavor in British Columbia (TIDE-BC (TIDE-BC, www.tidebc.org)), Canada
[c] Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada
[d] Department of Neurology/Neurosurgery, Montreal Children's Hospital, McGill University, Montreal, Canada
[e] Division of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria
[f] Geisel School of Medicine at Dartmouth College, Lebanon, NH, USA

ARTICLE INFO

Article history:
Received 27 November 2013
Received in revised form 19 January 2014
Accepted 19 January 2014
Available online xxxx

Keywords:
Inborn errors of metabolism
Algorithm
Diagnosis
Treatable
App
Cognition

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.

Contents

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.

* Corresponding author at: Division of Biochemical Diseases, Rm K3-201, Department of Pediatrics, BC Children's Hospital, Child and Family Research Institute, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 4480 Oak Street, Vancouver, BC V6H 3V4, Canada. Fax: +1 604 875 2349.
E-mail address: cvankarnebeek@cw.bc.ca (C.D.M. van Karnebeek).

1096-7192/$ – see front matter
http://dx.doi.org/10.1016/j.ymgme.2014.01.011

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 (2012) [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

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

Table 1
Definitions used in systematic literature review and current recommendation.

Global developmental delay (*DD*): applied to age < 5 years; significant delay (defined as performance 2 standard deviations or more below the mean on age-appropriate, standardized norm-referenced testing) in 2 or more of developmental domains including gross/fine motor skills, speech/language, cognition, social/personal, and activities of daily living [2].

Intellectual developmental disorders (*IDD*) [1]: a group of developmental conditions characterized by significant impairment of cognitive functions, which are associated with limitations of learning, adaptive behavior and skills.

Main descriptors

- IDD is characterized by a marked impairment of core cognitive functions necessary for the development of knowledge, reasoning, and symbolic representation of the level expected of one's age peers, and cultural and community environment. Nevertheless, very different patterns of cognitive impairments appear for particular conditions of IDD.
- In general, persons with IDD have difficulties with verbal comprehension, perceptual reasoning, working memory and processing speed.
- The cognitive impairment in persons with IDD is associated with difficulties in different domains of learning, including academic and practical knowledge.
- Persons with IDD typically manifest difficulties in adaptive behavior; that is, meeting the demands of daily life expected for one's age peers, cultural, and community environment. These difficulties include limitations in relevant conceptual, social, and practical skills.
- Persons with IDD often have difficulties in managing their behavior, emotions, and interpersonal relationships, and maintaining motivation in the learning process.
- IDD is a life span condition requiring consideration of developmental stages and life transitions.

Intellectual disability (*ID*): applied to age ≥5 years and manifesting before age 18 years, historically referred to as 'mental retardation'; intellectual functioning level (IQ) less than 70– 75 and significant limitations in two or more adaptive skills [1,5].

Inborn error of metabolism (*IEM*): genetic disease involving a disorder of metabolism with confirmation based on the internationally accepted diagnostic test(s) for that IEM (gene mutations, enzyme deficiency, or specific biochemical marker). This term excludes endocrine disorders such as hypothyroidism and hyperinsulinism.

Causal of IDD: sufficient evidence in literature from bench and/or clinical research to make a pathophysiological relationship between IEMs and ID/DD highly likely.

Treatable IEMs: if a particular therapeutic modality based on pathogenesis is capable of preventing or improving the IDD phenotype, or halting/slowing neurocognitive decline (with acceptable adverse effects) in the IEM, i.e. positively influencing the 'outcome measures'.

Therapeutic modalities: dietary restriction/supplement, co-factor/-enzyme, vitamin, substrate inhibition, (small molecule) substrate reduction, enzyme replacement, bone marrow and hematopoietic stem cell transplant, gene therapy.

Outcome measure/effect: primary = IQ, developmental testing score/performance, survival; secondary = epilepsy, behavior, psychiatric, neurological deficit (e.g. movement disorder), neuro-imaging, systemic symptoms influencing developmental/cognitive performance (e.g. ichthyosis, liver disease).

Levels of evidence: Level 1a = Systematic Review of RCTs, 1b = Individual RCT, 1c = 'All or None' [=(prolongation of) survival with therapy]; Level 2a = Systematic Review of Cohort Studies, 2b = Individual Cohort Study, 2c = 'Outcomes Research' [focussed on end results of therapy for chronic conditions, including functioning and quality of life (http://www.ahrq.gov/clinic.outfact.htm)]; Level 3 = Systematic Review of Case–Control Studies; Level 4 = Individual Case–Control Study or Case-series/report; Level 5 = Expert opinion without critical appraisal; based on physiology, bench research or first principles.

Standard of care: A formal treatment process a physician will follow for a patient with a specific illness, which experts generally accept as 'best clinical practice'.

Individual patient basis: Decision to start specific treatment depends on patient characteristics (i.e. disease stage), physician's opinion, availability of treatment, and potential side-effects.

based on the specific patient presentation remain paramount in this process, especially as the evaluation of usefulness and yield of the algorithm are pending.

2. Systematic literature review for treatable inborn errors of metabolism

The authors (CvK, SS) performed a literature review, following the Cochrane Collaboration methodology (http://www.cochrane.org/training/cochrane-handbook) as closely as possible, to identify all IEMs for which a particular therapeutic modality exists and can prevent or improve the IDD phenotype, or halt/slow neurocognitive decline (with acceptable side-effects), i.e. positively influence 'outcome measures' [23]. Subsequently, the clinical and diagnostic recognition patterns were characterized, as were treatment modalities pertinent to the identified IEMs. An attempt was made to assess the level of available evidence and effect of the various treatments on clinical outcome measures. As this literature review forms the basis of the current recommendations, we provide a summary of the relevant results.

2.1. Treatable IEMs in the year 2011 and updated in the year 2013

Applying the above criteria in 2011, we identified 81 treatable IEMs causing ID, which are listed in Table 2a including MIM number, biochemical deficiency and corresponding gene(s). Since then, 8 novel treatable IEMs have been reported which meet the criteria, and thus were added to the list: dihydrofolate reductase deficiency (oral folinic acid supplements) [24], VMAT2 deficiency (dopamine agonists) [25], SC4MOL deficiency (oral cholesterol supplements) [26], Brown–Vialetto–Van Laere/Fazio Londe (BVVL/FL) syndromes (oral riboflavin) [27], Lesch–Nyhan syndrome (hematopoietic stem cell transplantation) [28], carbonic anhydrase VA deficiency (Carglumic acid, sick day formula) [29], HMPDC (hypermanganesemia with dystonia, polycythemia, and cirrhosis) syndrome (chelation therapy) [30], and MEDNIK (mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratodermia) syndrome (zinc acetate) [31].

These 89 disorders include disorders of amino acids (n = 12); cholesterol and bile acids (n = 3); creatine (n = 3); fatty aldehydes (n = 1); glucose homeostasis and transport (n = 2); hyperhomocysteinemia (n = 7); lysosomes (n = 12); metals (n = 5); mitochondria (n = 2); neurotransmission (n = 8); organic acids (n = 19); peroxisomes (n = 1); purines and pyrimidines (n = 3); urea cycle (n = 8); and vitamins/co-factors (n = 10). Although amenable to treatment, fatty acid oxidation disorders are not included in our list because of their clinical presentation, which is a metabolic crisis with hypoglycemia (and subsequent neurologic sequelae) rather than unexplained IDD. These conditions will not be missed by this protocol however, as the acylcarnitine profile is included as first tier test.

2.2. Clinical features

Nearly all of these conditions are associated with additional neurological and/or non-neurological features. *Neurologic features* include ataxia, behavioral disturbance, dementia, dystonia, encephalopathic crisis, epilepsy, hearing loss, hypotonia/myopathy, neuro-imaging abnormalities (basal ganglia, cerebellum, cerebrum, cysts/dysgenesis, white matter, mixed), neuropathy, ocular movement abnormality, psychiatric disturbance, sensorineural hearing loss, spasticity, stroke, and vision loss. All IEMs except one (Tyrosinemia type II) are associated with at least one additional prominent neurologic feature, of which the most frequent are epilepsy and various types and degrees of movement disorders (e.g. spasticity, dyskinesia and ataxia). However, many of these conditions can present with IDD as sole feature for a considerable time prior to manifestation of the full phenotype (e.g. disorders of creatine synthesis and transport).

The non-neurologic features affect the following anatomic/organ systems: bones and joints; dermatology; endocrinology; eye; facial dysmorphism; growth and stature; heart; gastrointestinal; hematology; immunology; kidney; liver; and odor. For 57 of the 89 (64%) treatable IEMs, a non-neurologic feature is a prominent part of the phenotype.

2.3. Diagnostic testing

54 of the 89 disorders (60%) are identified by metabolic screening tests in blood (plasma amino acids, homocysteine, copper, ceruloplasmin) and urine (creatine metabolites, glycosaminoglycans, oligosaccharides, organic acids, pyrimidines). For the remaining 35 disorders (40%)

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

Table 2a
Overview of the first tier metabolic screening tests denoting all diseases (with OMIM# and gene(s)) potentially identified per individual test.

Diagnostic test	Disease	OMIM#	Gene
Blood tests			
Plasma amino acids	l.o. Argininemia	207800	*ARG1* (*AR*)
Plasma amino acids	l.o. Argininosuccinic aciduria	207900	*ASL* (*AR*)
Plasma amino acids	l.o. Citrullinemia	215700	*ASS1* (*AR*)
Plasma amino acids	Citrullinemia type II	605814	*SLC25A13* (*AR*)
Plasma amino acids	l.o. CPS deficiency	237300	*CPS1* (*AR*)
Plasma amino acids	HHH syndrome (hyperornithinemia, hyperammonemia, homocitrullinuria)	238970	*SLC25A15* (*AR*)
Plasma amino acids	Maple syrup urine disease (variant)	248600	*BCKDHA/BCKDHB/DBT* (*AR*)
Plasma amino acids	l.o. NAGS deficiency	237310	*NAGS* (*AR*)
Plasma amino acids (& UOA incl orotic acid)	l.o. OTC deficiency	311250	*OTC* (*X-linked*)
Plasma amino acids	Phenylketonuria	261600	*PAH* (*AR*)
Plasma amino acids (& UOA)	Tyrosinemia type II	276600	*TAT* (*AR*)
Plasma amino acids (tHcy)	l.o. MTHFR deficiency	236250	*MTHFR* (*AR*)
Plasma total homocysteine	Cobalamin E deficiency	236270	*MTRR* (*AR*)
Plasma total homocysteine	Cobalamin G deficiency	250940	*MTR* (*AR*)
Plasma total homocysteine (& UOA)	Cobalamin F deficiency	277380	*LMBRD1* (*AR*)
Plasma total homocysteine (& OUA)	Cobalamin C deficiency	277400	*MMACHC* (*AR*)
Plasma total homocysteine (& OUA)	Homocystinuria	236200	*CBS* (*AR*)
Plasma total homocysteine (& PAA)	l.o. MTHFR deficiency	236250	*MTHFR* (*AR*)
Plasma total homocysteine (& UOA)	Cobalamin D deficiency	277410	*MMADHC* (*AR*)
Serum ceruloplasmin & copper (& serum iron & ferritin)	Aceruloplasminemia	604290	*CP* (*AR*)
Serum copper & ceruloplasmin (& urine copper)	MEDNIK diseases	609313	*AP1S1* (*AR*)
Serum copper & ceruloplasmin (urine deoxypyridonoline)	Menkes disease/occipital horn syndrome	304150	*ATP7A* (*AR*)
Serum copper & ceruloplasmin (& urine copper)	Wilson disease	277900	*ATP7B* (*AR*)
Urine tests			
Urine creatine metabolites	AGAT deficiency	612718	*GATM* (*AR*)
Urine creatine metabolites	Creatine transporter defect	300352	*SLC6A8* (*X-linked*)
Urine creatine metabolites	GAMT deficiency	612736	*GAMT* (*AR*)
Urine glycosaminoglycans	Hunter syndrome (MPS II)	309900	*IDS* (*X-linked*)
Urine glycosaminoglycans	Hurler syndrome (MPS I)	607014	*IDUA* (*AR*)
Urine glycosaminoglycans	Sanfilippo syndrome A (MPS IIIa)	252900	*SGSH* (*AR*)
Urine glycosaminoglycans	Sanfilippo syndrome B (MPS IIIb)	252920	*NAGLU* (*AR*)
Urine glycosaminoglycans	Sanfilippo syndrome C (MPS IIIc)	252930	*HGSNAT* (*AR*)
Urine glycosaminoglycans	Sanfilippo syndrome D (MPS IIId)	252940	*GNS* (*AR*)
Urine glycosaminoglycans	Sly syndrome (MPS VII)	253220	*GUSB* (*AR*)
Urine oligosaccharides	α-Mannosidosis	248500	*MAN2B1* (*AR*)
Urine oligosaccharides	Aspartylglucosaminuria	208400	*AGA* (*AR*)
Urine organic acids	β-Ketothiolase deficiency	203750	*ACAT1* (*AR*)
Urine organic acids	Cobalamin A deficiency	251100	*MMAA* (*AR*)
Urine organic acids	Cobalamin B deficiency	251110	*MMAB* (*AR*)
Urine organic acids	l.o. Glutaric acidemia I	231670	*GCDH* (*AR*)
Urine organic acids	Glutaric acidemia II	231680	*ETFA, ETFB, ETFDH* (*AR*)
Urine organic acids	HMG-CoA lyase deficiency	246450	*HMGCL* (*AR*)
Urine organic acids	Holocarboxylase synthetase deficiency	253270	*HLCS* (*AR*)
Urine organic acids	3-Methylglutaconic aciduria type I	250950	*AUH* (*AR*)
Urine organic acids	MHBD deficiency	300438	*HSD17B10* (*X-linked recessive*)
Urine organic acids	mHMG-CoA synthase deficiency	605911	*HMGCS2* (*AR*)
Urine organic acids	SCOT deficiency	245050	*OXCT1* (*AR*)
Urine organic acids	SSADH deficiency	271980	*ALDH5A1* (*AR*)
Urine organic acids (& ACP)	Ethylmalonic encephalopathy	602473	*ETHE1* (*AR*)
Urine organic acids (& ACP)	l.o. Isovaleric acidemia	243500	*IVD* (*AR*)
Urine organic acids (& ACP)	3-Methylcrotonylglycinuria	210200	*MCC1/MCC2* (*AR*)
Urine organic acids (& ACP)	l.o. Methylmalonic acidemia	251000	*MUT* (*AR*)
Urine organic acids (& tHcy)	Cobalamin C deficiency	277400	*MMACHC* (*AR*)
Urine organic acids (& tHcy)	Cobalamin D deficiency	277410	*MMADHC* (*AR*)
Urine organic acids (& tHcy)	Homocystinuria	236200	*CBS* (*AR*)
Urine organic acids incl orotic acid (& PAA)	l.o. OTC deficiency	311250	*OTC* (*X-linked*)
Urine organic acids (& PAA)	Tyrosinemia type II	276600	*TAT* (*AR*)
Urine organic acids (& ACP)	l.o. Propionic acidemia	606054	*PCCA/PCCB* (*AR*)
Urine organic acids (tHcy)	Cobalamin F deficiency	277380	*LMBRD1* (*AR*)
Urine purines & pyrimidines	Lesch–Nyhan syndrome	300322	*HPRT* (*AR*)
Urine purines & pyrimidines	Molybdenum cofactor deficiency type A	252150	*MOCS1, MOCS2*, (*AR*)
Urine purines & pyrimidines	Pyrimidine 5-nucleotidase superactivity	606224	*NT5C3* (*AR*)

specific tests are required including primary molecular analysis (Tables 2a and 2b).

2.4. Causal treatments

The therapeutic modalities available for these IEMs include: "sick-day" management; diet; co-factor/vitamin supplements; substrate inhibition; stem cell transplant; and gene therapy. Therapeutic effects include improvement and/or stabilization of psychomotor/cognitive development; behavior/psychiatric disturbances; seizures; and neurologic and systemic manifestations. The levels of available evidence for the effect of various treatments vary from Level 1b, c (n = 5); Level 2a, b, c (n = 14); Level 4 (n = 53), to Levels 4–5 (n = 27) [32]. In clinical practice more than 60% of treatments with evidence Levels 4–5 are internationally accepted as 'standard of care'. This situation, with limited evidence levels guiding clinical practice, is inherent to rare diseases

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

Table 2b
Overview of all diseases (in alphabetical order) requiring second tier biochemical testing, i.e. a specific test per disease approach; for each disease the OMIM# and gene(s) are listed.

Disease	OMIM#	Gene(s)	Diagnostic test
(X-linked) Adrenoleukodystrophy	300100	*ABCD1* (*X-linked*)	Plasma very long chain fatty acids
Biotin responsive basal ganglia disease	607483	*SLC19A3* (*AR*)	Gene analysis
Biotinidase deficiency	253260	*BTD* (*AR*)	Biotinidase enzyme activity
Cerebral folate receptor-α deficiency	613068	*FOLR1* (*AR*)	CSF 5′-methyltetrahydrofolate
Cerebrotendinous xanthomatosis	213700	*CYP27A1* (*AR*)	Plasma cholestanol
Co-enzyme Q10 deficiency	607426	*COQ2*, *APTX*, *PDSS1*, *PDSS2*, *CABC1*, *COQ9* (*most AR*)	Co-enzyme Q (fibroblasts) & gene analysis
Congenital intrinsic factor deficiency	261000	*GIF* (*AR*)	Plasma vitamin B12 & folate
Dihydrofolate reductase deficiency	613893	*DHFR* (*AR*)	CSF 5′-methyltetrahydrofolate
DHPR deficiency (biopterin deficiency)	261630	*QDPR* (*AR*)	CSF neurotransmitters & biopterin loading test
Gaucher disease type III	231000	*GBA* (*AR*)	Glucocerebrosidase enzyme activity (lymphocytes)
GLUT1 deficiency syndrome	606777	*SLC2A1* (*AR*)	CSF: plasma glucose ratio
GTPCH1 deficiency	233910	*GCH1* (*AR*)	CSF neurotransmitters & biopterin loading test
Hypermanganesemia with dystonia, polycythemia, and cirrhosis (HMDPC)	613280	*SLC30A10*	Whole blood manganese
Hyperinsulinism hyperammonemia syndrome	606762	*GLUD1* (*AR*)	Gene analysis (& ammonia, glucose, insulin)
Imerslund Gräsbeck syndrome	261100	*CUBN* & *AMN* (*AR*)	Plasma vitamin B12 & folate
MELAS	540000	*MTTL1*, *MTTQ*, *MTTH*, *MTTK*, *MTTC*, *MTTS1*, *MTND1*, *MTND5*, *MTND6*, *MTTS2* (*Mt*)	Mitochondrial DNA mutation testing
l.o. Metachromatic leukodystrophy	250100	*ARSA* (*AR*)	Arylsulfatase-α enzyme activity
Niemann–Pick disease type C	257220	*NPC1 NPC2* (*AR*)	Filipin staining test (fibroblasts) & gene analyses
l.o. Non-ketotic hyperglycinemia	605899	*AMT/GLDC/GCSH* (*AR*)	CSF amino acids (& PAA)
PCBD deficiency (*biopterin deficiency*)	264070	*PCBD1* (*AR*)	CSF neurotransmitters & biopterin loading test
PDH complex deficiency	OMIM# according to each enzyme subunit deficiency: 312170; 245348; 245349	*PDHA1* (*X-linked*), *DLAT* (*AR*), *PDHX* (*AR*)	Serum & CSF lactate:pyruvate ratio enzyme activity, gene analysis
PHGDH deficiency (*serine deficiency*)	601815	*PHGDH* (*AR*)	CSF amino acids (& PAA)
PSAT deficiency (*serine deficiency*)	610992	*PSAT1* (*AR*)	CSF amino acids (& PAA)
PSPH deficiency (*serine deficiency*)	614023	*PSPH* (*AR*)	CSF amino acids (& PAA)
PTS deficiency (*biopterin deficiency*)	261640	*PTS* (*AR*)	CSF neurotransmitters & biopterin loading test
Pyridoxine dependent epilepsy	266100	*ALDH7A1* (*AR*)	Urine α-aminoadipic semialdehyde & plasma pipecolic acid
Sjögren Larsson syndrome	270200	*ALDH3A2* (*AR*)	Fatty aldehyde dehydrogenase enzyme activity
Smith Lemli Opitz syndrome	270400	*DHCR7* (*AR*)	Plasma 7-dehydrocholesterol:cholesterol ratio
SPR deficiency (*biopterin deficiency*)	612716	*SPR* (*AR*)	CSF neurotransmitters, biopterin & Phe loading test (enzyme activity, gene analysis)
Thiamine responsive encephalopathy	606152	*SLC19A3* (*AR*)	Gene analysis
Tyrosine hydroxylase deficiency	605407	*TH* (*AR*)	CSF neurotransmitters, gene analysis
VMAT2 deficiency	193001	*SLC18A2* (*AR*)	Urine mono-amine metabolites

ACP = acylcarnitine profile; CSF = cerebrospinal fluid; l.o. = late onset form; PAA = plasma amino-acids; Phe: phenylalanine; tHcy = total homocysteine; UOA = urine organic acids.
Mode of inheritance for each gene denoted as: AD = autosomal dominant, AR = autosomal recessive, mt = mitochondrial, X-linked = X-linked.

with small numbers, clinical heterogeneity and outcomes requiring long-term follow-up, which impede clinical trials and generation of solid evidence [23].

3. Diagnostic recommendation for the identification of treatable causes of IDD

Despite the limited evidence for treatment effects of the majority of these rare IEMs, the authors agreed it worthwhile to develop the current recommendation to aid clinicians in the identification of treatable IEMs in children presenting with IDD of unknown cause. In addition to the systematic review of the literature described above, we used the consensus expert opinion generated via meetings with 6 investigators, including experts in the field of treatable IEMs and neurometabolic diseases (SS); evidence-based medicine in rare diseases and IDD (CvK); medical genetics and IEMs (JZ); medical genetics and IDD (JM); and pediatric neurology and global developmental delay/IDD (MS).

3.1. The algorithm

Our recommendation is depicted in Fig. 1, and comprises 2 tiers; it is based on a combination of evidence and clinical expertise and aims to support pediatric specialists by providing a structured approach to the identification of treatable IEMs in IDD of unknown cause.

The categorization of investigations required for reliable diagnosis of the 89 IEMs into the first tier (biochemical only) or second tier (biochemical and/or molecular) was based on availability, affordability, yield and invasiveness. All tests in the first tier are provided by most biochemical genetics laboratories in the academic setting for reasonable prices, and have the potential to identify 3 or more IEMs. Although cerebrospinal (CSF) analyses meet these criteria, these were not included into first tier given the invasiveness of the lumbar puncture (+/− sedation). The second tier is mostly a 'single test per single disease' approach, directed by signs and symptoms and based on a clinical hypothesis.

3.2. First tier investigations

First tier investigations for treatable IDD (Table 2a) include the following, which can be collected at one time to reduce the burden of repeated (invasive) investigations on the patient: serum lactate; serum ammonia; serum copper; serum ceruloplasmin; plasma total homocysteine; plasma amino-acids, and bloodspot quantitative acylcarnitine profile (in blood); and creatine metabolites; purines and pyrimidines; organic acids; oligosaccharides; and glycosaminoglycans (in urine).

As a group, the first tier screening tests can identify 60% of all potentially treatable IEMs. First tier tests are generally accessible and offered by most biochemical genetics laboratories around the world with reasonable turn-around times and affordable prices. Each of these screening tests has the potential to specifically identify treatable IEMs, which is then often confirmed via molecular and/or enzymatic analysis. Some IEMs are diagnosed by a combination of first tier tests, e.g. inborn

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

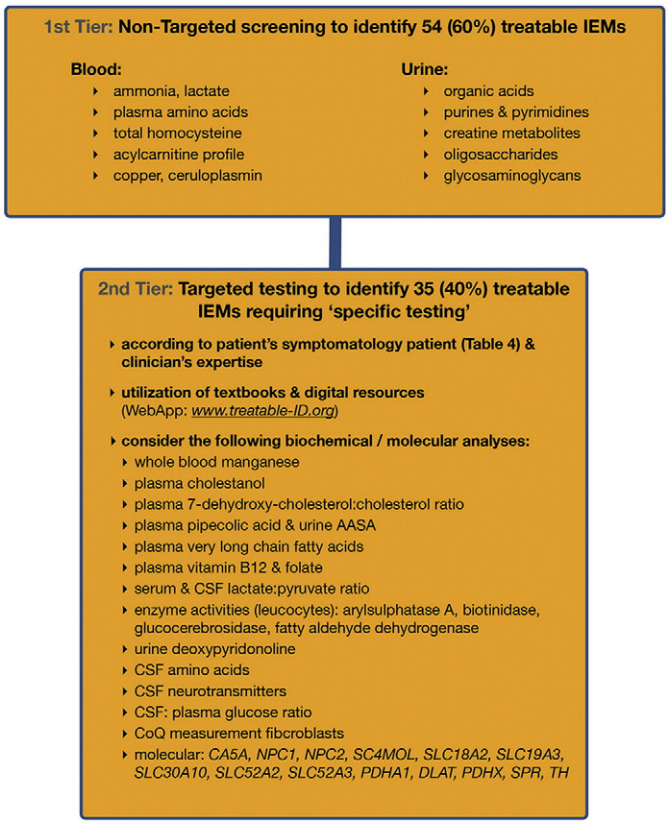

Fig. 1. Two-tiered algorithm for diagnosis of treatable IEMs in IDD. The first tier testing comprises group metabolic tests in urine and blood which should be performed in every patient with IDD of unknown cause. Based on the differential diagnosis generated by the patient's signs and symptoms, the second tier test is ordered individually at a low threshold.

errors of Cobalamin metabolism (urine organic acids, plasma total homocysteine).

Results of the acylcarnitine profile are often supportive rather than primarily indicative of the 89 treatable IEMs on our list. For example, the organic acid profile is the primary indicator for proprionic acidemia (3-OH-proprionic acid), while the acylcarnitine profile further supports this diagnosis showing elevations of C2 and C3, which is also the case in methylmalonic acidemia. In the BVVL/FL syndrome, some but not all patients showed abnormal acylcarnitine profiles (and/or plasma flavin level), thus, on its own, this test is not sufficiently reliable, requiring molecular analysis for diagnosis [27].

3.3. Practical considerations

The set of the first tier tests exceeds usual practice in the clinical setting [19,33]; if the physician wishes to cast as broad a net as possible it is recommended that *all* these tests are done. Performing the urinary tests requires particular attention. Whereas usual screening for IEMs comprise organic acid analysis only, screening for treatable IEMs requires additional tests for urine creatine metabolites (urine creatine: creatinine ratio and guanidine-acetate:creatinine ratio), purines and pyrimidines.

A more focused approach can also be taken with the caveat that milder forms of IEMs can present with unspecific phenotypes and potentially be missed. The tiers can be adapted to local circumstances and/or practice. For example in British Columbia, our hospital laboratory's capacity for the urine oligo- and mucopolysaccharides tests are limited; therefore these are not ordered as first screening tier tests, but rather based on suggestive signs and symptoms only, thus as second tier only.

Samples for plasma amino acids and total homocysteine should not be obtained in the post-prandial period but rather after 4–8 h fasting (e.g. in the morning), and should be processed without delay. When ordering these tests, the clinician should take into account the risks of fasting in the particular patient, especially in the infant and young child. Results should be compared with appropriate age-related control values, taking nutritional status into consideration.

Careful interpretation of results is crucial. Findings might be subtle in attenuated disease variants. For example, females with OTC deficiency do not always have high ammonia; low citrulline and elevated glutamine in plasma along with orotic aciduria would be more consistent findings [34]. Although in the interpretation of laboratory results the focus is mostly on values above the normal range, care should be taken not to miss pathognomonic decreases, e.g. in plasma serine concentrations which may indicate one of the serine deficiency disorders. Low urinary creatinine levels are usually considered to be due to diluted urine, but could also result from inborn errors of creatine synthesis (GAMT and AGAT deficiency).

It must be acknowledged that for the 89 IEMs the sensitivity and specificity of each of the listed first and second tier tests varies; for further information we refer to the "Laboratory Guide to methods in biochemical genetics" [35] and other similar resources.

3.4. Second tier investigations

For the remaining 29 IEMs that are not ruled out with the first tier testing as indicated above, specific investigations are necessary. Mostly this is a 'single test per disease' approach, but some tests such as neurotransmitter analysis in cerebrospinal fluid (CSF) have the potential to identify multiple (up to 7) treatable IDDs. An overview of these specific investigations is provided in Table 2b.

Those conditions for which mutation analysis might serve as the primary specific test, because a biochemical marker is unavailable or unreliable and/or the test requires an invasive procedure, are listed in Table 3.

In practice, the clinician might combine the first tier tests with investigations for those genetic conditions, which do not classify as IEMs (e.g. chromosomal micro-array to detect copy number variants) and one or more specific tests of the second tier, as appropriate, based on the observed clinical phenotype of the patient. The clinical judgment of the medical or biochemical geneticist is particularly important regarding the differential diagnosis and the design of the patient-specific testing strategy. Table 4 provides an overview of symptomatology that could indicate a specific (set of) investigation(s) to test for particular treatable IDD(s) with fitting phenotype(s).

4. Resources

4.1. New online resource

Van Karnebeek et al, have developed a resource App (freely accessible as a digital App via www.treatable-id.org as well as a native App via the App store), accepted by the rare disease community with a publication in a peer-reviewed journal [40]. The App targets the clinical specialist and supports both tiers of the algorithm and also functions as an information portal on these rare diseases and their treatments. It does not replace a careful clinical evaluation but supports the clinician in defining a differential diagnosis focused on treatable conditions.

Treatable IEMs are presented according to biochemical categories; neurologic and non-neurologic signs and symptoms; diagnostic investigations; therapies and effects on primary (IQ/developmental quotient) and secondary outcomes; and available evidence. A 'Disease Page' is provided for each condition with an information portal comprising an overview of all signs and symptoms; a figure showing the effected biochemical pathway; information on available diagnostic tests; and causal therapies. In addition, each page contains numerous linked online

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

Table 3
IEMs for which molecular analysis is the primary specific test.

IEM	OMIM#	*Gene(s)*
AGAT deficiency	612718	*AGAT* (*AR*)
Biotin responsive basal ganglia disease	607483 (same as thiamine responsive encephalopathy)	*SLC19A3*
Brown–Vialetto–Van Laere/Fazio Londe syndromes	211500, 211530	*SLC52A2*, *SLC52A3*
Carbonic anhydrase VA deficiency	114761	*CA5A*
Cerebral glucose transporter deficiency	606777 (GLUT1 deficiency syndrome 1) 612126 (GLUT1 deficiency syndrome 2)	*SLC6A19*
Co-enzyme Q10 deficiency	607426 (primary 1) 614651 (primary 2) 614652 (primary 3) 612016 (primary 4) 614654 (primary 5) 614650 (primary 6)	*COQ2*, *APTX*, *PDSS1*, *PDSS2*, *CABC1*, *COQ9*
l.o. CPS deficiency	608307 (CPS1)	*CPS*
Creatine transporter deficiency	300352	*SLC6A8*
Hyperinsulinism–hyperammonia syndrome	606762	*GDH*
MELAS	540000	*MTTL1*, *MTTQ*, *MTTH*, *MTTK*, *MTTC*, *MTTS1*, *MTND1*, *MTND5*, *MTND6*, *MTTS2*
l.o. NAGS deficiency	237310	*NAGS*
Niemann–Pick disease type C	257220 (NPC1) 607625 (NPC2)	*NPC1* & *NPC2*
Pyruvate dehydrogenase complex deficiency	312170	*PDHA*, *DLAT*, *PDHX*
SC4MOL deficiency	607545	*SC4MOL* (*AR*)
Serine biosynthesis defects	601815, 610992, 614032	*PHGDH*, *PSAT*, *PSPH*
Sjögren–Larssen disease	270200	*FALDH*
Thiamine-responsive encephalopathy	607483 (same as biotin responsive basal ganglia disease)	*SLC19A3*

Direct molecular or gene(s) analysis was deemed the most appropriate diagnostic approach for an IEM if: the biochemical marker is unavailable or unreliable and/or the test requires an invasive procedure and/or the test is difficult to access. This table lists a total of 14 such IEMs with 33 encoding genes.

resources, listed below as well as online abstracts of journal articles, clinical trials, and patient resource websites.

The App provides search capabilities using specific combinations of signs and symptoms, enabling the specialist to refine the differential diagnosis. The App displays a dichotomy: those identifiable by first tier tests (white background) versus those requiring a specific test (green background; second tier). Thus the clinician can immediately discard the IEM with the white background from the differential diagnosis, provided first tier testing was negative. The data on clinical disease features were synthesized based on data extracted from diverse textbooks and online resources [36–39] and combined with the authors' personal experience and expertise, if required. The App lists the main clinical presentation of each disease, i.e. the most characteristic, specific and consistent neurologic signs and symptoms. Cautioned use is required, as the absence or presence of signs and/or symptoms in the App does not in any way rule out the specific disorder in a patient. Further, these data are subject to change as new diagnostic techniques provide novel insights into the spectrum of phenotypic presentations and the natural history of metabolic diseases.

4.2. Other resources

Diverse textbooks and online resources provide valuable information on IEMs, including but not limited to: Scriver et al. [36], Valle et al. [37], Zschocke et al. [38], Fernandes et al. [39], Orphanet (www.orpha.net), OMIM (http://www.ncbi.nlm.nih.gov/omim), Gene Reviews http://www.ncbi.nlm.nih.gov/sites/GeneTests), Online Metabolic and Molecular Bases of Inherited Disease (www.ommbid.org), Gene Cards (www.genecards.org), and Pubmed (www.ncbi.nlm.nih.gov/pubmed).

5. Using this recommendation for metabolic diagnostic evaluation in practice

5.1. General considerations

These recommendations are based on the current best evidence and offer the expert clinician a set of tests to consider when evaluating the child or adolescent with IDD for a treatable IEM. The literature does not address the clinical utility of each individual test discussed in this paper, nor does it address the entire "set" of tests contained in Tier 1. The papers of Engbers et al. and Papavasiliou et al. are cited as two efforts to address the complex problem of identifying treatable IEMs in a series of patients with IDD: however, a larger study systematically implementing the recommended tests for IEMs is necessary to answer the essential questions of clinical utility, costs and treatment outcomes. Such a study is currently in progress in BC Children's Hospital, Vancouver Canada. It might also be noted that not all expert clinicians consulting for children with IDD are trained in biochemical genetics nor consider themselves expert in detecting all clinical signs and symptoms of potential IEMs. This paper offers recommendations for such clinicians, particularly those who might be remotely located. For the approach to treatable IEMs in adults presenting with neurologic symptoms, the reader is referred to the publication by Sirrs et al. [41].

These recommendations are not meant to function in a stand-alone capacity, but rather can be superimposed on the 2011 American Academy of Neurology practice parameters [22], which advises diagnostic tests according to their yield: chromosome micro-array; Fragile X (*FMR1* gene) testing; Rett syndrome; MRI/spectroscopy brain; electroencephalography (EEG) and other neurophysiologic tests; and thyroid function (TSH). Thorough concurrent audiologic and ophthalmologic screening should be used to rule out remediable primary sensory deficits in every patient presenting with IDD.

5.2. Yield

While the incidence of the individual 89 conditions is low in the general population, ranging from 1:10,000 to less than 1:200,000 [42], their collective frequency in the population at risk (i.e. those with IDD) may be higher. Current evidence in the literature suggests low yield of metabolic testing (0.8–2.5%). However in the year 2013 a comprehensive metabolic evaluation as suggested here has not been reported for larger groups of IDD patients [12]. There are several studies which do suggest a higher yield of metabolic testing in the tertiary care setting. For example, Engbers et al. [43], using a multidisciplinary approach, identified IEMs in nearly 3% (n = 12) of 433 individuals with IDD despite 'normal initial metabolic studies before referral'; IEMs comprised 20% of all

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

Table 4
List of specific biochemical tests and the symptoms which could indicate their use.

Specific test	Disease(s) (OMIM#)	Neurologic symptoms	Non-neurologic symptoms
(Whole) Blood manganese (riboflavin?)	Hypermanganesemia with dystonia, polycythemia, and cirrhosis (#673280)	Dystonia	Polycythemia, liver cirrhosis
Plasma cholestanol	Cerebrotendinous xanthomatosis (#213700)	Ataxia, dementia, neuropathy, behavioral/psychiatric disturbances	Bones (osteoporosis), skin (xanthomata), eye (cataract), gastro-intestinal (diarrhea), heart (myocardial infarct), liver (cholestatic icterus)
Plasma 7-dehydroxycholesterol: cholesterol ratio	Smith Lemli Opitz syndrome (#270400)	Hypotonia/myopathy	Bones (congenital anomalies), skin (photosensitivity), facial dysmorphisms, gastro-intestinal (feeding problems), growth/stature, liver (cholestatic icterus)
Plasma pipecolic acid & urine α-amino adipic semi-aldehyde	Pyridoxine dependent epilepsy (#266100)	Epilepsy, brain cysts/dysgenesis, white matter abnormalities	–
Plasma very long chain fatty acids	X-linked Adrenoleukodystrophy (#300100)	Dementia, brain white matter abnormalities, behavioral/psychiatric disturbances, sensorineural hearing loss, vision loss	Endocrinology (adrenal insufficiency)
Plasma vitamin B12 & folate	Congenital intrinsic factor deficiency (#261000), Immerslund Gräsbeck syndrome (#261100)	Ataxia, dystonia, epilepsy	Hematology (macrocytic anemia), immunology, kidney (proteinuria, atypical HUS)
Serum & CSF lactate:pyruvate ratio	PDH complex deficiency (#312170; 245348; 245349)	Brain cysts/dysgenesis, white matter abnormalities, neuropathy	Facial dysmorphisms
Enzyme activity (leucocytes): arylsulphatase A	l.o. Metachromatic leukodystrophy (#250100)	Dementia, brain white matter abnormalities, neuropathy, psychiatric/behavioral disturbances, spasticity	–
Enzyme activity (leucocytes): biotinidase	Biotinidase deficiency (#253260)	Encephalopathic crisis, epilepsy, sensorineural hearing loss	Skin (rash/alopecia)
Enzyme activity (leucocytes): fatty aldehyde dehydrogenase	Sjögren–Larsson syndrome (#270200)	Spasticity	Skin (ichthyosis) & eye (macular dystrophy, retinitis pigmentosa)
Enzyme activity (leucocytes): glucocerebrosidase	Gaucher disease type III (#231000)	Dementia, encephalopathic crisis, epilepsy, ocular movement abnormality	Hepato-/splenomegaly
CSF amino-acids	PHGDH deficiency (#601815), PSAT deficiency (#610992), PSPH deficiency (#614023), l.o. Non-ketotic hyperglycinemia (#605899)	Ataxia, dystonia, epilepsy, cerebral/cerebellar atrophy, brain cysts/dysgenesis, neuropathy, psychiatric/behavioral disturbances	Abnormal growth/stature
CSF neurotransmitters (incl. tetrahydrofolate)	DHFR deficiency (#613893), DHPR deficiency (#261630), GTPCH deficiency (#233910), PTS deficiency (#261640), SPR deficiency (#612716), tyrosine hydroxylase deficiency (#605407)	Dystonia, epilepsy, ocular movement abnormality	Megaloblastic anemia
CSF:plasma glucose ratio	GLUT1 deficiency (#606777)	Epilepsy, cerebral/cerebellar atrophy	–
Urine deoxypyridonoline	Menkes disease, Wilson disease	–	Bones (osteoporosis), skin (pili torti, skin laxicity), facial dysmorphism, gastrointestinal (feeding problems & diarrhea)
Urine mono-amine metabolites	AADC deficiency, VMAT2 deficiency	Dystonia, epilepsy, ocular movement abnormality	–
Co-enzyme Q fibroblasts (+/− molecular analyses *COQ2*, *APTX*, *PDSS1*, *PDSS2*, *CABC1*, *COQ* genes)	Co-enzyme Q10 deficiency (#607426)	Hypotonia/myopathy	Heart (cardiomyopathy), kidney (renal dysfunction)
Molecular analysis *CA5A* gene	Carbonic anhydrase VA deficiency (#114761)	Episodic encephalopathy	–
Molecular analysis *NPC1* & *NPC2* genes	Niemann–Pick disease type C (#257220)	Ataxia, dementia, dystonia, epilepsy, ocular movement abnormality, behavioral/psychiatric disturbance	Liver (hepato-splenomegaly, cholestatic icterus)
Molecular analysis *PDHA1*, *DLAT*, *PDHX* genes	PDH complex deficiency (#312170; 245348; 245349)	Ataxia, dystonia, brain cysts/dysgenesis, white matter abnormalities, neuropathy	–
Molecular analysis *SC4MOL* gene	SC4MOL deficiency (#607545)	Microcephaly	Arthritis, congenital cataracts, psioriasiform dermatitis
Molecular analysis *SLC18A2* gene	VMAT2 deficiency (#193001)	Parkinsonism, non-ambulation, mood disorder, autonomic instability	–
Molecular analysis *SLC19A3* gene	Biotin responsive basal ganglia disease (#607483), thiamine responsive encephalopathy (#606152)	Ataxia, dystonia, encephalopathic crisis, cerebral/cerebellar atrophy, brain cysts/dysgenesis, ocular movement abnormality	–
Molecular analyses *SLC52A2*, *SLC52A3* genes	Brown–Vialetto–Van Laere (#211500)/Fazio Londe syndromes (#211530)	Bulbar palsy, sensorineural hearing loss, facial weakness	Respiratory failure
Molecular analysis *SPR*, *TH* genes	SPR deficiency (#612716), tyrosine hydroxylase deficiency (605407)	Dystonia, ocular movement abnormality	

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

established causes diagnosed, and 4 of these 12 were treatable (a.o. 2 cases with creatine transporter deficiency). Papavasiliou et al. [33] reported the results of individualized investigations based on clinical and neuro-radiologic findings in a highly selected group of children with IDD; IEMs were identified in 13.6% (n = 16).

Several reviews have been published concerning metabolic causes of IDD, most of which reflect expert opinions and individual expertise in the field of IEMs [14,17,18]. The need for multiple tests to exclude a few rare to ultra-rare conditions and the limited availability of laboratories offering comprehensive diagnostic testing, explain why outside highly specialized centers, metabolic work-up of patients with IDD is time-consuming, expensive and often remains incomplete. Because of all these limitations, the diagnostic yield of metabolic testing has been incomplete, varies per publication and is reportedly low in patients presenting with IDD. However, diagnostic standardization through use of the current recommendation could foster greater awareness of otherwise unrecognized causally treatable conditions. While the rate of positive findings may remain relatively lower than, for example CMA testing, the treatment effect is greater with inherent improvement in outcomes.

5.3. Newborn screening

Normal newborn screening results in a patient with IDD of unknown origin should *not* be interpreted such that all treatable IEMs have been ruled out. Newborn screening panels target only a *minority* of treatable IEMs even in countries with a very high number of targets, such as the USA, and some children may have been born in countries that do not perform newborn screening. Even for those IEMs included in many newborn screening programs, such as classic organic acidemias and urea cycle defects, 'late-onset' phenotypic variants constituting treatable IDDs can be missed, as newborn screening may not be sensitive and specific enough to safely detect such disease-variants [44]. Therefore, it is prudent to verify the results whenever possible. The disorders included in the specific regional newborn screening panels are often available online (http://genes-r-us.uthscsa.edu). Thus, although newborn screening is not a substitute for the first tier testing, and completion of all the listed investigations is advised, locally available resources and practices may prioritize certain first tier tests above others. For example, urine creatine metabolites is almost always indicated as these IEMs are not included in panels except for a few scattered pilot studies screening for GAMT deficiency (e.g. ongoing in BC Children's Hospital) [45].

5.4. Treatable IEMs as a cause of unspecific IDD

The majority of the 89 treatable IEMs present with more multiple co-morbidities including epilepsy, neurologic symptoms and signs, and behavioral and psychiatric disturbances. Systemic manifestations occur in 70% of conditions [23]. However, the clinical spectrum of treatable IDD is variable and the absence of co-morbidities does not exclude the presence of a treatable IDD. Rather, the clinical picture is determined by the state of disease progression and by particular disease variants. For example, progressive neurologic decline is characteristic of advanced stages of X-linked adrenoleukodystrophy; subtle loss of cognitive functions accompanied by behavioral disturbances is often the first manifestation. Recognition of the diagnosis at this early disease stage opens a unique window of opportunity for causal treatment with stem cell transplantation, which is not effective at a later stage in the disease course [46]. While clinical co-morbidities are traditionally considered characteristic of metabolic causes of IDD, the absence of such co-morbidities does not exclude them. The same is true for neuro-degeneration, as many of the 89 treatable IEMs present with 'stable IDD', i.e., without a history of regression or plateauing.

5.5. 'Late-onset' or atypical variants of conditions

'Late-onset' or atypical variants of conditions typically presenting as acute metabolic decompensation in the neonatal period deserve special attention. While patients with acute metabolic crisis are diagnosed before they are assessed for IDD, the clinical presentation of the attenuated or 'late-onset' forms of these conditions is often unspecific and chronic in nature. For example, OTC deficiency in males typically manifests with severe neonatal hyperammonemia and outcomes are extremely poor in affected males. However, females with heterozygous OTC deficiency often present with IDD and/or behavioral problems as the only manifestation(s) [34]. Timely recognition of the underlying metabolic defect that enables appropriate treatment to control blood ammonia levels not only helps to prevent acute hyperammonic crises at a later stage of life but also improves cognitive function and behavior.

5.6. Primary gene analysis

Primary gene analysis can enhance the diagnostic yield in conditions with unspecific clinical and biochemical presentation. For example, low urinary excretion of guanidinoacetate is characteristic of AGAT deficiency, a treatable disorder of creatine synthesis, but the detection of low levels continues to pose an analytical challenge in the laboratory, as currently available methods mainly detect extreme elevations of accumulating metabolites. The traditional diagnostic approach to Niemann–Pick Disease Type C (NPC) requires demonstration of free cholesterol via filipin staining in cultivated skin fibroblasts. This test is invasive, time- and cost-consuming, available in a limited number of laboratories worldwide, and is not always sensitive. Recent recommendations added primary *NPC1* and *NPC2* gene sequencing as an alternative diagnostic strategy [47]. High-throughput sequencing technologies may be considered as an alternative diagnostic approach as they facilitate analysis of multiple genes in one sample in a cost-effective manner, although interpretation of previously unreported variants may be challenging. Determination of oxysterols in plasma is a promising, novel approach for low threshold screening for NPC [48].

6. Costs

An overview of the costs of the individual chemistry and metabolic/biochemical tests, based on the costs at one Canadian academic center (Vancouver), is provided in Table 5. The total cost is $527.97 (CAD), which is reasonable in comparison with individual tests (molecular analysis of a single gene often exceeds $500) and future cost-savings, if a child can be treated in a timely way to reach his full potential and participate in society. These costs are likely comparable to those provided by other international academic centers, yet far exceeded by commercial companies.

Table 5
Costs and turn-around time of the individual tests in the first tier screening.

Test	Costs ($CAD)	Turn-around time
Blood		
Bloodspot acylcarnitine	$41.28	3 days
Plasma amino-acids	$78.42	1 week
Plasma total homocysteine	$22.97	1 week
Serum ceruloplasmin	$10.15	1 day
Serum copper	$49.19	1 day
Urine		
Urine creatine metabolites, purines & pyrimidines	$65.01	4–6 weeks
Urine glycosaminoglycans	$59.55	4–6 weeks
Urine oligosaccharides	$32.65	4–6 weeks
Urine organic acids	$105.41	1 week
Urine purines & pyrimidines	$63.34	4–6 weeks
Total	$567.97	

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

7. Metabolic testing for "non-treatable" inborn errors of metabolism

This recommendation is focused on the identification of treatable IEMs, however each of the first tier screening tests also identifies IEMs for which no causal therapy is available or effective, according to the definitions provided here [49]. For example, organic acid analysis also reveals untreatable conditions with major CNS involvement, such as Canavan's disease and 2-hydroxy-glutaric aciduria. Similarly, urine glycosaminoglycans and oligosaccharides analyses can detect conditions such as Schindler disease, MPS IX (Natowicz disease) and sialidosis. Additionally, urine purines and pyrimidines will reveal causally untreatable conditions such as isolated sulfite oxidase deficiency and ureidopriopionase deficiency. Identification of non-treatable causes of IDD is still beneficial to the affected individual and his/her family as it ends the burdensome diagnostic odyssey and allows for reliable genetic counseling.

8. Limitations and future directions

The authors acknowledge the following limitations and suggest strategies to overcome them:

1) As the literature is silent in regard to the effectiveness of this set of recommendations, additional research is necessary to inform our practice in the tertiary care setting. One such effort is a 3-year funded project (www.tidebc.org) initiated in 2011 at B.C. Children's Hospital in Vancouver, Canada where 1200 patients with IDD are evaluated per year by various services including Neurology, Developmental Pediatrics, Psychiatry, Clinical Genetics and Biochemical Diseases. Our one-year pilot study identified treatable IEMs in >5% of 210 IDD patients (*personal communication*). Of note, urine glycosaminoglycans and oligosaccharides were included only as second tier tests due to logistic limitations. Although these results are preliminary and should be interpreted with caution due to potential referral bias, this yield is encouraging and supports this recommendation. IEMs are all rare diseases, so much larger numbers of patients are required to provide reliable data.
2) Access to first and second tier testing may be challenging in practices located remotely from academic laboratories or dependent on commercial laboratories with inherent burden of costs, as well as in regions with significant financial restrictions. The clinician may then choose to select first and/or second tier tests according to feasibility, insights and patient presentation.
3) These recommendations focus on a moving target. As noted, during the period since the literature search was performed for our systematic review in 2011, 8 new 'treatable IDDs' have emerged either through gene discovery and/or generation of evidence for new treatments; the latter is also true for conditions already on the list (e.g. lysine restricted diet as adjunct treatment for pyridoxine dependent epilepsy [50]). To incorporate exciting diagnostic and therapeutic advances such as these, as well as more reliable information on yield, the recommendations should be modified regularly to optimize utility in daily practice.

Funding

This work was supported by funding from the B.C. Children's Hospital Foundation as "1st Collaborative Area of Innovation".

Conflict of interest

CvK and SS developed the content of, and contributed to the design of the freely available App described here (www.treatable-id.org).

Acknowledgments

The authors would like to thank Drs. Graham Sinclair and Hilary Vallance (Biochemical Genetics Lab) for data on cost of first tier testing; Ms. Claire Sowerbutt (medical writer) for text editing; Mrs. Ruth Giesbrecht. Mrs. Maria Boldut and Mrs. Mirafe Lafek for administrative assistance with the tables and manuscript; Dr. Melissa Crenshaw (All Children's Hospital, St. Petersburg, USA) and Wendy Smith (Barbara Bush Children's Hospital, Portland, USA) for their support; Mr. Roderick Houben and Mr. Jeff Joa (Health2Media) for App design and updates.

References

[1] L. Salvador Carulla, G.M. Reed, L.M. Vaez-Azizi, S.A. Cooper, R. Martinez-Leal, M. Bertelli, C. Adnams, S. Cooray, S. Deb, L. Akoury-Dirani, S.C. Girimaji, G. Katz, H. Kwok, R. Luckasson, R. Simeonsson, C. Walsh, K. Munir, S. Saxena, Intellectual developmental disorders: towards a new name, definition and framework for "mental retardation/intellectual disability" in ICD-11, World Psychiatry 10 (2011) 175–180.
[2] R. Luckasson, A. Reeve, Naming, defining, and classifying in mental retardation, Ment. Retard. 39 (2001) 47–52.
[3] M. Shevell, Present conceptualization of early childhood neurodevelopmental disabilities, J. Child Neurol. 25 (2010) 120–126.
[4] M. Shevell, Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation, and etiology, Pediatr. Clin. N. Am. 55 (2008) 1071–1084.
[5] D.E. Jansen, B. Krol, J.W. Groothoff, D. Post, People with intellectual disability and their health problems: a review of comparative studies, J. Intellect. Disabil. Res. 48 (2004) 93–102.
[6] B. Oeseburg, D.E.M.C. Jansen, J.W. Groothoff, G.J. Dijkstra, S.A. Reijneveld, Emotional and behavioural problems in adolescents with intellectual disability with and without chronic diseases, J. Intellect. Disabil. Res. 54 (2010) 81–99.
[7] W.J. Meerding, L. Bonneux, J.J. Polder, M.A. Koopmanschap, P.J. van der Maas, Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study, BMJ 317 (1998) 111–117.
[8] A. Rauch, D. Wieczorek, E. Graf, T. Wieland, S. Endele, T. Schwarzmayr, B. Albrecht, D. Bartholdi, J. Beygo, N. Di Donato, A. Dufke, K. Cremer, M. Hempel, D. Horn, J. Hoyer, P. Joset, A. Röpke, U. Moog, A. Riess, C.T. Thiel, A. Tzschach, A. Wiesener, E. Wohlleber, C. Zweier, A.B. Ekici, A.M. Zink, A. Rump, C. Meisinger, H. Grallert, H. Sticht, A. Schenck, H. Engels, G. Rappold, E. Schröck, P. Wieacker, O. Riess, T. Meitinger, A. Reis, T.M. Strom, Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study, Lancet 380 (2012) 1674–1682.
[9] J. De Ligt, M. Willemsen, B. van Bon, T. Kleefstra, H.G. Yntema, T. Kroes, A.T. Vulto-van Silfhout, D.A. Koolen, P. de Vries, C. Gilissen, M. del Rosario, A. Hoischen, H. Scheffer, B.B. de Vries, H.G. Brunner, J.A. Veltman, L.E. Vissers, Diagnostic exome sequencing in persons with severe intellectual disability, N. Engl. J. Med. 367 (2012) 1921–1929.
[10] J. Moeschler, Genetic evaluation of intellectual disabilities, Semin. Pediatr. Neurol. 15 (2008) 2–9.
[11] C.D.M. van Karnebeek, F.Y. Scheper, N.G. Abeling, M. Alders, P.G. Barth, J.M. Hoovers, C. Koevoets, R.J. Wanders, R.C. Hennekam, Etiology of mental retardation in children referred to a tertiary care center: a prospective study, Am. J. Ment. Retard. 110 (2005) 253–267.
[12] C.D.M. van Karnebeek, M.C.E. Jansweijer, A.G.E. Leenders, M.A. Offringa, R.C.M. Hennekam, Diagnostic investigations in individuals with mental retardation: a systematic literature review, Eur. J. Hum. Genet. 13 (2005) 6–25.
[13] M. Manning, L. Hudgins, Professional Practice and Recommendations Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities, Genet. Med. 12 (2010) 742–745.
[14] D.T. Miller, M.P. Adam, S. Aradhya, L.G. Biesecker, A.R. Brothman, N.P. Carter, D.M. Church, J.A. Crolla, E.E. Eichler, C.J. Epstein, W.A. Faucett, L. Feuk, J.M. Friedman, A. Hamosh, L. Jackson, E.B. Kaminsky, K. Kok, I.D. Krantz, R.M. Kuhn, C. Lee, J.M. Ostell, C. Rosenberg, S.W. Scherer, N.B. Spinner, D.J. Stavropoulos, J.H. Tepperberg, E.C. Thorland, J.R. Vermeesch, D.J. Waggoner, M.S. Watson, C.L. Martin, D.H. Ledbetter, Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies, Am. J. Hum. Genet. 86 (2010) 749–764.
[15] M.E. Coulter, D.T. Miller, D.J. Harris, P. Hawley, J. Picker, A.E. Roberts, M.M. Sobeih, M. Irons, Chromosomal microarray testing influences medical management, Genet. Med. 13 (2011) 770–776.
[16] E. Riggs, K. Wain, D. Riethmaier, B. Smith-Packard, W. Faucett, N. Hoppman, E. Thorland, V. Patel, D. Miller, Chromosomal microarray impacts clinical management, Clin. Genet. (Jan 25 2013), http://dx.doi.org/10.1111/cge.12107.
[17] S.G. Kahler, M.C. Fahey, Metabolic disorders and mental retardation, Am. J. Med. Genet. C: Semin. Med. Genet. 117C (2003) 31–41.
[18] M.A. Kayser, Inherited metabolic diseases in neurodevelopmental and neurobehavioral disorders, Semin. Pediatr. Neurol. 15 (2008) 127–131.
[19] A. Garcia-Cazorla, N.I. Wolf, M. Serrano, U. Moog, B. Pérez-Dueñas, P. Póo, M. Pineda, J. Campistol, G.F. Hoffmann, Mental retardation and inborn errors of metabolism, J. Inherit. Metab. Dis. 32 (2009) 597–608.
[20] C.J. Curry, R.E. Stevenson, D. Aughton, J. Byrne, J.C. Carey, S. Cassidy, C. Cunniff, J.M. Graham Jr., M.C. Jones, M.M. Kaback, J. Moeschler, G.B. Schaefer, S. Schwartz, J. Tarleton, J. Opitz, Evaluation of mental retardation: recommendations of a consensus conference: American College of Medical Genetics, Am. J. Med. Genet. 72 (1997) 468–477.
[21] J. Moeschler, M. Shevell, Clinic genetic evaluation of the child with mental retardation or developmental delay, Pediatrics 117 (2006) 2304–2316.

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011

[22] D.J. Michelson, M.I. Shevell, E.H. Sherr, J.B. Moeschler, A.J. Gropman, S. Ashwal, Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Neurology 77 (2011) 1629–1635.
[23] C.D.M. van Karnebeek, S. Stockler, Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review, Mol. Genet. Metab. 105 (2012) 368–381.
[24] S. Banka, H.J. Blom, J. Walter, M. Aziz, J. Urquhart, C.M. Clouthier, G.I. Rice, A.P. de Brouwer, E. Hilton, G. Vassallo, A. Will, D.E. Smith, Y.M. Smulders, R.A. Wevers, R. Steinfeld, S. Heales, Y.J. Crow, J.N. Pelletier, S. Jones, W.G. Newman, Identification and characterization of an inborn error of metabolism caused by dihydrofolate reductase deficiency, Am. J. Hum. Genet. 88 (2011) 216–225.
[25] J.J. Rilstone, R.A. Alkhater, B.A. Minassian, Braindopamine-serotoninvesiculartrans — port disease and its treatment, N. Engl. J. Med. 368 (2013) 543–550.
[26] M. He, L.E. Kratz, J.J. Michel, A.N. Vallejo, L. Ferris, R.I. Kelley, J.J. Hoover, D. Jukic, K.M. Gibson, L.A. Wolfe, D. Ramachandran, M.E. Zwick, J. Vockley, Mutations in the human SC4MOL gene encoding a methyl sterol oxidase cause psoriasiform dermatitis, microcephaly, and developmental delay, J. Clin. Invest. 121 (2011) 976–984.
[27] A.M. Bosch, K. Stroek, N.G. Abeling, H.R. Waterham, L. Ijlst, R.J. Wanders, The Brown–Vialetto–Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives, Orphanet J. Rare Dis. 7 (2012) 83.
[28] K. Kállay, Z. Liptai, G. Benyó, C. Kassa, V. Goda, J. Sinkó, A. Tóth, G. Kriván, Successful unrelated umbilical cord blood transplantation in Lesch–Nyhan syndrome, Metab. Brain Dis. 27 (2012) 193–196.
[29] C.D. van Karnebeek, W.S. Sly, C.J. Ross, R. Salvarinova, J. Yaplito-Lee, C. Shyr, G. Horvath, et al., Mitochondrial carbonic anhydrase VA deficiency resulting from CA5A alterations presents with hyperammonemia in early childhood, Am. J. Hum. Genet. (2014) in press.
[30] M. Stamelou, K. Tuschl, W.K. Chong, A.K. Burroughs, P.B. Mills, K.P. Bhatia, P.T. Clayton, Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder, Mov. Disord. 27 (2012) 1317–1322.
[31] D. Martinelli, L. Travaglini, C.A. Drouin, I. Ceballos-Picot, T. Rizza, E. Bertini, R. Carrozzo, S. Petrini, P. de Lonlay, M. El Hachem, L. Hubert, A. Montpetit, G. Torre, C. Dionisi-Vici, MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy, Brain 136 (2013) 872–881.
[32] Oxford Centre for Evidence-based Medicine Levels of Evidence, Available at www.cebm.net March 2009.
[33] A.S. Papavasiliou, H. Bazigou, E. Paraskevoulakos, C. Kotsalis, Neurometabolic testing in developmental delay, J. Child Neurol. 15 (2000) 620–622.
[34] M.J. Ahrens, S.A. Berry, C.B. Whitley, D.J. Markowitz, R.J. Plante, M. Tuchman, Clinical and biochemical heterogeneity in females of a large pedigree with ornithine transcarbamylase deficiency due to the R141Q mutation, Am. J. Med. Genet. 66 (1996) 311–315.
[35] N. Blau, M. Duran, M.E. Baskovics, M.K. Gibson, Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases, Second ed. Springer Verlag, Berlin Heidelberg, 2003.
[36] C. Scriver, A. Beaudet, W. Sly, D. Valle, The Metabolic and Molecular Bases of Inherited Disease, McGraw Hill, New York, 2000.
[37] D. Valle, A.L. Beaudet, B. Vogelstein, K.W. Kinzler, S.E. Antonarakis, A. Ballabio, C.R. Scriver, W.S. Sly, The On-line Metabolic and Molecular Bases of Inherited Disease, 2011. (Available at: http://www.ommbid.com).
[38] J. Zschocke, G.F. Hoffmann, Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism, Third ed. Milupa Metabolics, Friedrichsdorf, 2011.
[39] J. Fernandes, J.M. Saudubray, G. van den Berghe, J.H. Walter, Inborn Metabolic Diseases: Diagnosis and Treatment, Fourth ed. Springer, 2006.
[40] C.D.M. van Karnebeek, F.A. Houben, M. Lafek, W. Giannasi, S. Stockler, The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis and care for rare diseases, Orphanet J. Rare Dis. (2010) 47.
[41] S. Sirrs, A. Lehman, S. Stockler, C.D.M. van Karnebeek, Treatable inborn errors of metabolism causing neurological symptoms in adults, Mol. Genet. Metab. 110 (2013) 431–438.
[42] S. Stockler, P.W. Schutz, G.S. Salomons, Cerebral creatine deficiency syndromes: clinical aspects, treatment and pathophysiology, Subcell. Biochem. 46 (2007) 149–166.
[43] H.M. Engbers, R. Berger, P. van Hasselt, T. de Koning, M.G. de Sain-van, H.Y. der Velden, G. Visser Kroes, Yield of additional metabolic studies in neurodevelopmental disorders, Ann. Neurol. 64 (2008) 212–217.
[44] B. Wilcken, Newborn screening: how are we travelling, and where should we be going? J. Inherit. Metab. Dis. 34 (2011) 569–574.
[45] S. Mercimek-Mahmutoglu, G. Sinclair, S.J. van Dooren, W. Kanhai, P. Ashcraft, O.J. Michel, J. Nelson, O.T. Betsalel, L. Sweetman, C. Jakobs, G.S. Salomons, Guanidinoacetate methyltransferase deficiency: first steps to newborn screening for a treatable neurometabolic disease, Mol. Genet. Metab. 107 (2012) 433–437.
[46] S. Kemp, J. Berger, P. Aubourg, X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects, Biochim. Biophys. Acta 1822 (2012) 1465–1474.
[47] M.C. Patterson, C.J. Hendriksz, M. Walterfang, F. Sedel, M.T. Vanier, F. Wijburg, On behalf of the NP-C Recommendations Working Group. Recommendations for the diagnosis and management of Niemann–Pick disease type C: an update, Mol. Genet. Metab. 106 (2012) 330–344.
[48] X. Jiang, R. Sidhu, F.D. Porter, N.M. Yanjanin, A.O. Speak, D.T. te Vruchte, F.M. Platt, H. Fujiwara, D.E. Scherrer, J. Zhang, D.J. Dietzen, J.E. Schaffer, D.S. Ory, A sensitive and specific LC–MS/MS method for rapid diagnosis of Niemann–Pick C1 disease from human plasma, J. Lipid Res. 52 (2011) 1435–1445.
[49] A. Sempere, A. Arias, G. Farré, J. García-Villoria, P. Rodríguez-Pombo, L.R. Desviat, B. Merinero, A. García-Cazorla, M.A. Vilaseca, A. Ribes, R. Artuch, J. Campistol, Study of inborn errors of metabolism in urine from patients with unexplained mental retardation, J. Inherit. Metab. Dis. 33 (2010) 1–7.
[50] C.D. van Karnebeek, H. Hartmann, S. Jaggumantri, L.A. Bok, B. Cheng, M. Connolly, C.R. Coughlin, A.M. Das, S.M. Gospe, C. Jakobs, J.H. van der Lee, S. Mercimek-Mahmutoglu, U. Meyer, E. Struys, G. Sinclair, J. Van Hove, J.P. Collet, B.R. Plecko, S. Stockler, Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials, Mol. Genet. Metab. 107 (2012) 335–344.

Please cite this article as: C.D.M. van Karnebeek, et al., The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable..., Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.01.011