Best Practice Guidelines for the Biochemical Investigation of Global Developmental Delay for Inherited Metabolic Disorders

Introduction

Global developmental delay (GDD) is defined as delay more than 2 standard deviations below the mean for age in two or more developmental domains (gross and fine motor, speech and language, cognition and/or personal and social development).[1]

GDD contributes to the clinical presentation in a considerable number of inherited metabolic disorders (IMD); however it is very unusual for GDD to be isolated. It is much more common for patients with IMD to have other associated features in addition to GDD. The presence of these associated features can be used to guide investigations. Investigation of isolated GDD is indicated but should be restricted to those disorders where there is evidence that isolated GDD may be presenting sign. General "metabolic screening" is not recommended due to the possibility of non-diagnostic results (e.g. subtle changes in organic acids of uncertain significance) and/or the false assumption that all IMD are excluded by a "metabolic screen".

Investigation of GDD is evolving as the availability of modern genomic sequencing improves. This has the potential to greatly increase the yield of investigation (for example array comparative genomic hybridisation (CGH) has a yield of 10-20%), but has its own limitations. Conversely biochemical investigation has a low yield[1]; investigations should take into account whether any defining features are identified in the clinical assessment. While yield is an important factor, IMD are rare and since many are potentially treatable, it is important that these disorders are identified. A diagnosis of an untreatable IMD is equally significant due to its impact on further unnecessary investigations, family planning choices and access to appropriate supportive care for the child and their family.

Clinical assessment

A detailed history and clinical assessment is essential in GDD. The history should be clearly documented; including pregnancy, perinatal period and early developmental milestones. For older children information from education sources should be included. A family tree should be constructed which includes at least three generations, consanguinity & ethnicity, health status (particularly recurrent miscarriages, developmental delay/intellectual disability, seizures, encephalopathy) as well as age at death (and cause).

Assessment of all developmental domains should be performed and compared against population norms and take into account the trajectory of the developmental delay. Thorough examination of all body systems should be undertaken in order to identify any features to guide investigations.

Biochemical investigation of isolated global developmental delay

The investigations presented below are split into first line and second line investigations with the rationale for each described. However a pragmatic approach is recommended; for example, the paediatrician may opt to do first and second line tests simultaneously, depending on local arrangements, knowing that it would be very difficult to do two rounds of sampling.

First-line investigations

'Routine' biochemical and haematological investigations may be undertaken to exclude systemic disease as a cause of developmental delay (table 1).

First-Line Investigations
Full blood count
U+E, liver function tests & calcium
Plasma amino acids
Thyroid function tests
Creatine kinase (males only)

Table 1: Summary of first-line investigations for isolated GDD

Plasma amino acids may indicate a variety of disorders, for example: raised alanine and proline – lactic acidaemia, raised glutamine – hyperammonaemia / disturbed urea cycle function, raised methionine – classical homocystinuria (more likely vitamin B6 non-responsive type). In boys creatine kinase should also be requested since Duchenne muscular dystrophy may present as isolated GDD.[2] Thyroid function tests should be included. While children born within the UK should have been screened for congenital hypothyroidism, those born outside the UK may not. In addition children may have secondary hypothyroidism (which is not detected in the UK screening programme), or have acquired primary hypothyroidism.

Second-line investigations

Before further investigations are undertaken the history should be reconsidered and the clinical assessment repeated. Where no clinical clues to guide investigations remain, second-line investigations should be initiated.

Many IMD cause developmental delay however this is usually in association with other clinical features. These are described further in the next section. However an increasing number are treatable or have on-going trials and some have been reported to present with isolated GDD and these are described in the table 2.

Test	Disorder(s)	Rationale
Urine and plasma creatine and guanidinoacetate *(Note: urine samples require freezing within 1-2 hours of collection)*	Cerebral creatine deficiency syndromes	• X-linked creatine transporter defect: reported in around 1% of males with intellectual disability • Guanidinoacetate methyltransferase (GAMT)and arginine : glycine amidinotransferase (AGAT) deficiencies can be treated with creatine supplementation and dietary manipulation
Plasma total homocysteine	Classical homocystinuria	May present with isolated GDD, UK screening (since 2015) does not aim to detect pyridoxine-responsive homocystinuria
Urine organic acids	Succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria)	May present with isolated GDD
Urine glycosaminoglycan typing	Mucopolysaccharidosis type III (Sanfilippo syndrome)	May present with isolated GDD, typically after an initial period of normal development.

Table 2: Second-line investigations for isolated GDD

Biotinidase deficiency is mentioned in some reviews[3], however there is a paucity of evidence that it occurs without additional features.[1] Mild forms of adenylosuccinate lyase deficiency may present with isolated developmental delay, but there is no effective treatment at present and the disorder is extremely rare.

Biochemical investigation of global developmental delay with other features

There are a large number of investigations that might be considered where the GDD is associated with other features. These investigations should be guided by the associated features, rather than merely performing an "extended general metabolic screen". Referral to the appropriate paediatric speciality before these specialised investigations are undertaken should be considered. For example an opinion from a paediatric neurologist, metabolic physician or clinical geneticist can assist with test selection in a particular clinical presentation. This input will be advantageous since many of these tests are highly specialised, expensive and have specific caveats. It is therefore particularly important that the results are interpreted in the light of the clinical picture. Table 3 outlines additional biochemical tests to be considered where associated features are present. It is not intended to be an exhaustive list; for example seizures are not included since children with seizures should be investigated against a specific investigation protocol for seizures.

GDD+ Feature(s)	Disorders	Additional Biochemical Tests
Prominent expressive language delay	Creatine synthesis and transport defects	Creatine & guanidinoacetate (urine & plasma)
	Succinic semialdehyde dehydrogenase deficiency	Organic acids
Growth failure	Many IMD – organic acid & amino acid disorders	Glucose, ammonia, lactate, urine organic acids & orotate, acylcarnitines, acid-base
Multisystem involvement	Mitochondrial disorders	Lactate (plasma & CSF), biotinidase, acylcarnitines and organic acids
	Congenital defects of glycosylation	Transferrin glycoforms
Regression	Lysosomal storage disorders (including mucopolysaccharidoses)	White cell enzymes, urine GAG typing
	X-linked adrenoleukodystrophy	Very long chain fatty acids
	Organic acid disorders	Organic acids
	Mitochondrial disorders	Lactate (plasma & CSF), biotinidase, acylcarnitines and organic acids
Epileptic encephalopathy and / or movement disorders	GLUT-1 deficiency	Glucose (paired CSF & plasma)
	Biotinidase deficiency	Biotinidase
	Organic acid disorders	Organic acids
	Mitochondrial disorders	Lactate (plasma & CSF), biotinidase, acylcarnitines and organic acids
	Pterin defects	CSF neurotransmitter metabolites
Acute encephalopathy / ataxia *(Note: results may be normal when asymptomatic)*	Amino acidopathies Organic acid disorders Fatty acid disorders Urea cycle defects	Glucose, ammonia, plasma amino acids, organic acids & orotate, acylcarnitines
Eye signs	Homocystinuria	Plasma total homocysteine
(Note: tests guided by ophthalmology report)	Mitochondrial disease	Lactate (plasma & CSF), biotinidase, acylcarnitines and organic acids
	Lysosomal storage disorders	White cell enzymes, urine GAG typing
Hepato(spleno)-megaly	Lysosomal storage disorders (including mucopolysaccharidoses)	White cell enzymes, urine GAG typing
	Glycogen storage disorders	Glucose, lactate, urate, lipids, erythrocyte & leukocyte glycogen studies
	Niemann Pick Type C	Oxysterols
Dysmorphic features	Lysosomal storage disorders (including mucopolysaccharidoses)	White cell enzymes, urine GAG typing

Table 3: Investigations to consider where other specific clinical features are present

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Disclaimer: These are not evidence based guidelines but reflect expert opinion. The network cannot accept any responsibility for use of these guidelines

References:

[1] Hart AR, Sharma R, Atherton M. et al. Aetiological investigations in early developmental impairment: are they worth it? *Arch Dis Child* 2017;**102**:1004–1013

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[3] McDonald L, Rennie A, Tolmie J, et al. Investigation of global developmental delay. *Arch Dis Child* 2006;**91**:701–5.