Shropshire Community Health NHS
NHS Trust

Policies, Procedures, Guidelines and Protocols

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Local Ref (optional)	
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Who is the document aimed at?	Community Paediatricians, Paediatric trainees
Owner	Dr Shachi Buch, Consultant Community Paediatrician Dr Shona Brothwell, Paediatric Speciality Registrar
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Who has been consulted in the development of this policy ?	Final review by Community Paediatric Doctors at CP meeting on 12 September 2022.
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Other	

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No	Date	Amendment
1	V1 March 2019	New policy
2	V2 May 2023	Review and updated urine metabolic tests and genetic investigations added
3		
4		
5		

Contents

1. Introduction

Global developmental impairment is one of the most common conditions encountered in Paediatrics, affecting 1-3% of the population of children under the age of 5 years. The causes of global developmental impairment can be divided into exogenous, genetic (non-metabolic), or genetic (metabolic), with genetic and structural brain abnormalities being the most frequent cause. Advances in biochemical and genetic testing means that the available investigations for children under 5 years are increasing, and are also increasingly sensitive.

Early recognition and diagnosis means clinicians can instigate appropriate management and/ or commence surveillance for known complications, as well as provide holistic family support. This ensures the best overall outcomes for these patients and their families.

2. Purpose

The purpose of this guideline is to provide a standardised and consistent approach to the medical investigation of children with global developmental impairment for Shropshire Community Healthcare Trust, in order that any child with global developmental impairment receives appropriate medical investigations in a timely manner to make the correct diagnosis. This guideline applies to all medical and clinical professionals who are routinely involved in detection / screening and the diagnosis of children with global developmental impairment.

3. Definitions / Glossary

AFLP	Acute fatty liver of pregnancy
CK	Creatine Kinase
CT	Computerised Tomography
EEG	Electroencephalogram
ERG	Electroretinogram
FBC	Full blood count
GAGs	Glycosaminoglycans
HELLP	Haemolysis, elevated liver enzymes and low platelets
HIE	Hypoxic Ischaemic Encephalopathy
IEM	Inborn Error of Metabolism
LFT	Liver Function Test
MRI	Magnetic Resonance Image
TFT	Thyroid Function Tests
U&E	Urea and electrolytes
VEP	Visual evoked potentials

4. Duties

4.1 The Chief Executive

The Chief Executive has ultimate accountability for the strategic and operational management of the Trust, including ensuring there are effective and appropriate processes in place for the medical investigation of children with global developmental impairment.

4.2 Director of Nursing & Medical Director

The Director of Nursing & Medical Director have responsibility for ensuring that children with global developmental impairment are offered appropriate medical investigations as required to support patient safety at all times.

4.3 Service Managers

Service Managers are responsible for the day to day operational management and coordination of the medical investigation of children with global developmental impairment in line with the clinical guideline.

4.4 All Clinical Staff

Clinical and medical staff are key essential members in ensuring that children with global developmental impairment are offered medical investigations appropriately as per national / local guidelines. All clinical and medical staff is required to comply with this guideline and to report any adverse care related issues to their line manager and to complete a Datix incident report in line with the Trust's Incident reporting policy.

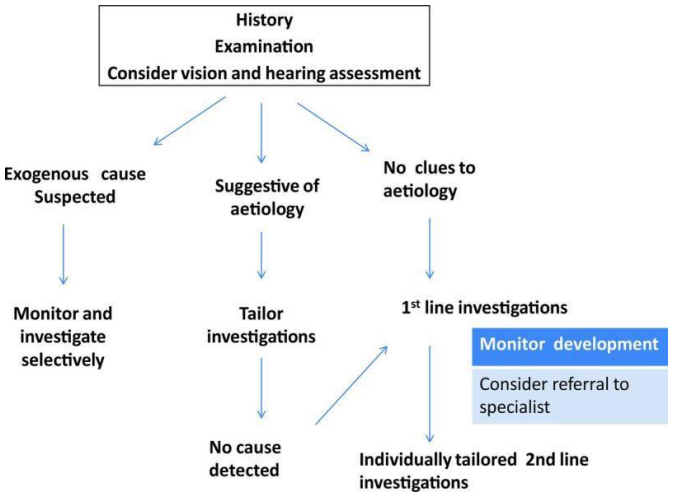
5. Which children require further investigation?

Targeted investigation, following a thorough clinical history (including a family tree, pregnancy and birth history) and a detailed physical examination by a trained specialist, is cost effective and leads to a higher diagnostic yield.

Further investigations should be carried out in children with any of the following:

- Severe developmental impairment (development <50% of expected milestones at that chronological age).
- Global developmental impairment (significant delay affecting 2 or more domains of development).
- Any plateauing or regression of development.

However, it is important to consider investigations in all levels of developmental impairment, including those with persistent "less significant" global developmental impairment, given the variable phenotypic presentations of genetic and metabolic conditions.



Flow chart 1: decision-making for investigations for global developmental impairment in young children (Mithyantha *et al*., 2017)

5.1 History

The medical history (MHx) of the child with developmental impairment should be ascertained in detail. Asking about the following may give additional clues as to the underlying cause (see also section 6.2.4):

Specific features in the history	
Antenatal	- Intrauterine infections - Exposure to teratogens (alcohol/ drugs) - Maternal HELLP syndrome/ AFLP
Birth	- Prematurity - HIE - Birth trauma
Neonatal	- Neonatal infection - Neonatal illness (including neonatal hypoglycaemia) - Abnormal cranial ultrasound scan
MHx	- Developmental regression (red flag) - Faltering growth/ short stature - Seizures - Abnormal movements - Recurrent unexplained episodic illness (vomiting/ encephalopathy) - Prolonged recovery phase from normal childhood illness - Cyclical vomiting - Psychiatric symptoms - Acute life threatening events - Episodes of hypoglycaemia - Protein-avoidant dietary behaviour - Self-injurious behaviour - Recurrent otitis media - Hernias - Sensory impairment (hearing/ vision) - History of possible acquired brain injury (e.g. trauma)
Family	- Parental consanguinity - Previous miscarriages - Unexplained sibling death - Family history of developmental impairment/ learning difficulties
Social	- Concerns regarding neglect - Safeguarding concerns?

However, note that it is important to consider the possibility in the history: for example, perinatal problems/ illness may be caused by an underlying condition (genetic/ due to an antenatal insult) which then causes ongoing impaired development, rather than the perinatal issues being the cause of the developmental impairment.

Identification and correction of sensory deficits are essential, and may provide further clues as to an underlying aetiology.

5.2 Examination

Specific features in the examination	
Inspection	- Dysmorphic features
Growth parameters	- Abnormal head circumference - Rapidly-changing head circumference - Faltering growth/ short stature
Cardiovascular	- Murmur
Abdominal	- Organomegaly - Hernias
Neurological	- Hypotonia - Abnormal movements (ataxia/ dystonia/ other) - Abnormal eye movements - Focal neurological signs
Musculoskeletal	- Scoliosis/ gibbus - Genu valgum
Dermatological	- Neurocutaneous markers - Abnormal subcutaneous fat distribution/ inverted nipples - Ichthyosis/ eczema - Abnormal hair (coarse/ sparse/ kinky)

6. Investigations

Appropriate and individually justified investigations tailored to the individual should be undertaken, providing as much clinical information as possible with each request.

6.1 First Line investigations

First line investigations should be carried out when significant developmental impairment is identified, but there are no specific clinical findings revealed during the history/ examination.

Blood	**Urine**
Microarray	Organic acids (OA)
Fragile X (selected)	Glycosaminoglycans (GAGs)
U&Es	Oligosaccharides
CK	
TFT	
FBC	
Plasma amino acids (AA)	
Homocysteine	
Acylcarnitine profile	
Lead (if pica)	
Ferritin (dietary restriction)	

Consider sending urinary Creatine/ Guanidinoacetate (GAA) as a first line investigation in patients with GLOBAL DEVELOPMENTAL IMPAIRMENT and prominent speech impairment and/ or seizures
(to look for potentially-treatable cerebral creatine deficiency syndromes).

This urine sample needs to be frozen in the local Biochemistry lab at Princess Royal Hospital (PRH) or Royal Shrewsbury Hospital (RSH) in order to prevent deterioration during transport to the Metabolic laboratory at Birmingham Children's Hospital.

The urine sample should be as fresh as possible, and delivered to the PRH or RSH Biochemistry lab immediately (preferably within an hour of the urine being passed).

In order to facilitate this (in relevant patients):

- Provide the family with a universal container
- Advise family to obtain a urine sample on site when the child attends PRH or RSH phlebotomy department for blood tests (or immediately beforehand).
- This sample can then be sent urgently to the local Biochemistry lab from the phlebotomy department, along with the bloods.

If the family are unable to provide the urine sample during their phlebotomy appointment, the family should take the fresh urine sample directly to the Biochemistry lab..

6.2 Second Line Investigations

Second line investigations should be instigated when there are specific factors in the history or examination. Again, these investigations need to be individually tailored to the patient, depending on the specific features identified.

Consider referral/ discussion with the following teams if any specific features present:

- Audiology
- Ophthalmology (Electroretinogram (ERG) / Visual Evoked Potentials (VEP))
- Neurology
- Paediatric Inherited Metabolic Medicine
- Clinical Genetics

Consider congenital infection: in children with intrauterine growth retardation, microcephaly and eye/hearing signs. Requires comparison of maternal booking and current maternal serology. Useful for children up to ~18 months of age.

6.2.1. Genetic tests

Additional genetic testing should be considered when there is global developmental impairment with a clinical phenotype that points towards an underlying genetic diagnosis (for example, dysmorphic features, abnormal growth, specific behaviours or family history).

Clinical syndromes can present with variable phenotypes. Children who have normal first line genetic investigation results (microarray/ Fragile X) may be best assessed by a Clinical Geneticist, to ensure that the most appropriate and cost -effective additional tests are undertaken.

All referrals for testing will be triaged by the local Genomic Laboratory Hub to ensure the most appropriate test is performed.

In instances where testing is requested by the clinical indication, the Genomic Laboratory Hub will review the test request and relevant clinical information and select the most appropriate constituent test(s) to facilitate the test request.

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- Microarray ('molecular karyotype') will not detect conditions where structural changes in the chromosomes result in no loss/ gain of chromosomal material (e.g. balanced translocations). A standard chromosomal karyotype is therefore required if such a disorder is suspected.

- Syndromes caused by methylation defects (Angelman syndrome, Beckwith-Wiedemann syndrome) or mutations in single genes require specific testing and will not be diagnosed with microarray.

- Next-generation sequencing options are increasingly available. Find up-to-date information about available tests on the Genomics England NHS Test Directory: https://www.england.nhs.uk/publication/national-genomic-test-directories/
  To access the request form for whole genome sequencing:
  download.cfm (bwc.nhs.uk)

- 'Intellectual Disability panel' can now be requested directly in children and young persons with a Learning Disability. This should be done when microarray results are normal. There needs to be an NHS Genomics Record of Discussion form signed by person with parental responsibility and the request form is downloadable online. Both are sent to genetics.

Within the West Midlands, there is a monthly regional Developmental Disorders MDT meeting where cases can be presented/ discussed - email bwc.genetics.paedMDT@nhs.net for information.

6.2.2. EEG

Consider EEG (including 24 hour ambulatory EEG where relevant) in patients with:

- Seizures
- Speech regression
- Neurodegeneration/ regression

6.2.3. Neuroimaging

Consider neuroimaging in patients who have global developmental impairment with

additional clinical/ neurological signs (for example: developmental regression, abnormal/ rapidly changing head circumference, focal neurological signs, seizures or abnormal movements).

MRI is a more sensitive test and involves no radiation exposure, making it a preferred choice over CT.

Children under 5 years will need sedation or a general anaesthetic (GA), and some children will need further investigations including a lumbar puncture. Mithyantha *et al*., 2017 suggest, therefore, that children requiring brain imaging should see a specialist (Neurology/ Neurodisability/ Paediatric Inherited Metabolic Medicine) prior to imaging, if a GA is required.

6.2.4. Suspected inborn errors of metabolism (IEM)

IEM are rare causes of developmental impairment in isolation; they more frequently present with developmental impairment associated with other, often progressive, clinical features (for example, regression, neurological signs, organomegaly).

Diagnosing an underlying IEM as the cause of developmental impairment is important - there are increasingly novel treatment options for many IEM (or there may be specific management required in order to reduce the risk of acute decompensation).

Where no treatment exists, diagnosis remains important, to ensure appropriate prognosis, surveillance and genetic counselling is offered, and to enable signposting to appropriate support.

There are often important clues in the history and examination which point towards an underlying IEM. Obtaining a detailed clinical phenotype during a thorough history and examination will therefore guide further investigations (see below).

Table 1 Important history details suggestive of IEM

	Features to suggest an IEM
Pregnancy	Maternal health HELLP, AFLP
Family history	Consanguinity Unexplained neonatal or infantile deaths Three generation pedigree
Past medical history of delayed child	Unexplained hypoglycaemia Encephalopathy Protein aversion Self-injurious behaviour Psychiatric symptoms Seizure disorder
Type of developmental delay	Regression Hypotonia Speech delay

From Cleary & Green, 2005

Table 2 Examination findings

Feature	Disorder(s)
Dysmorphism	Smith-Lemli-Opitz, other cholesterol synthesis disorders Congenital disorders of glycosylation Peroxisomal disorders Lysosomal disorders
Hepato(spleno)megaly	Lysosomal storage disorders, glycogen storage disorders
Cardiomyopathy	Lysosomal storage disorders, fatty acid oxidation defects, mitochondrial disorders
Smell	Organic acid disorders
Neurological signs	
Dystonia	Mitochondrial disorders, organic acidurias, pterin defects
Macrocephaly	Canavan's disease, Tay-Sachs, L-2-hydroxyglutaric aciduria, glutaric aciduria type I
Microcephaly	Sulphite oxidase deficiency, maternal PKU offspring, previous hyperammonaemia, previous hypoglycaemia, GLUT-1 deficiency, neuronal ceroid lipofuscinosis 1
Growth—failure to thrive, short stature	Many IEMs, e.g. organic acid, amino acid, urea cycle disorders
Hair—coarse, "kinky"	Menkes disease, MPS disorders, arginino-succinic aciduria
Skin—coarse, ichthyosis, eczema	LSD, Conradi-Hunermann, biotinidase deficiency, Sjogren-Larsson

From Cleary & Green, 2005

See the MetBioNet guideline (in references below) for further information regarding specific tests.

https://metbio.net/best-practice-guidelines

Discussion with the Inherited Metabolic Medicine Department, Birmingham Children's Hospital is recommended if an IEM is suspected in order to guide further specific investigations.

7. Summary

Global developmental impairment is one of the most common conditions encountered in Paediatrics. There are numerous potential causes; genetic and structural brain abnormalities being the most frequent causes.

Recent advances in biochemical and genetic testing means that the available investigations for children under 5 years are increasing and are more sensitive than previously. In addition, novel therapies for many of the underlying conditions are increasingly available.

Early recognition and diagnosis is essential to ensure the best overall outcomes for these patients and their families. In conjunction with a detailed developmental assessment, a detailed history and examination help to guide individually-tailored investigations which maximise the chance of achieving the correct diagnosis.

In children with significantly disordered development who do not have a specific underlying diagnosis found following initial investigations, ongoing assessment allows further targeted investigations to be considered as the clinical phenotype evolves.

8. Consultation

Members of the Shropshire Community Health NHS Trust Community Medical Team were consulted and contributed towards this guideline

Dr Shachi Buch	Consultant Community Paediatrician
Dr Shona Brothwell	Paediatric Registrar (ST5)
Dr Diane Short	Consultant Community Paediatrician
Dr Saud Ahmad	Paediatric Registrar (ST4)

9. Dissemination and Implementation

The guideline will be disseminated and implemented by the following methods:-

- Directors/Service Leads – to disseminate within their areas
- Staff - via Team Brief process
- Published to the Shropshire Community Healthcare Trust (SCHT) Website.

10. Monitoring Compliance

Compliance will be monitored if medical investigations carried out for global impairment are challenged by another clinician or service users. An audit of the guideline will be considered in the future.

11. References:

Cleary, M.A. & Green, A. Developmental delay: when to suspect and how to investigate for an inborn error of metabolism. Arch Dis Child 2005; 90:1128–1132.

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Horridge, K. Assessment and investigation of the child with disordered development. Archives Diseases in Childhood. Education and Practice Edition. 2011 Feb; 96: 9–20.

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Mithyantha, R., Kneen, R., McCann, E. & Gladstone, M. Current evidence-based recommendations on investigating children with global developmental delay. Arch Dis Child 2017 Nov; 102 (11): 1071-1076.

Van Karnebeek, C.D.M., Shevall, M., Zschocke, J., Moeschler, J.B. & Stockler, S. The metabolic evaluation of the child with an intellectual developmental disorder: Diagnostic algorithm for identification of treatable causes and new digital resource. Mol Genet Metab. 2014 Apr; 111 (4): 428-438.

12. Associated Documents

Shropshire Community Health NHS Trust - Consent to Examination and Treatment Policy