A guide to the investigation of children with developmental delay in East Anglia

The guide

These guidelines were produced by an expert group of geneticists and paediatricians in East Anglia as part of a multi-disciplinary project on learning disability undertaken by the Cambridge Genetics Knowledge Park. Further information on the project and supporting documentation is available on the CGKP website.

Definitions

Learning disability is strictly defined as a significant impairment of cognitive and adaptive function with onset before 18 years of age. It is usually described as mild, moderate or severe. Learning disability/developmental delay is a common problem affecting 1-3% of the population.

Overview article on definition and prevalence of learning disability. Gillberg, Lancet. 2003; Sep 6;362(9386):811-21*

Click here for a descriptive summary of the epidemiology and molecular characteristics of learning disability (see sections on definition and prevalence).

Aetiology of learning disability

Delay may be determined by genetic or environmental factors (eg Down syndrome, Fragile X syndrome), antenatal or perinatal problems such as rubella, or prematurity (eg cerebral haemorrhage), early infancy (eg meningitis), or later in childhood (eg head injury). For many children, the cause will not be apparent. In the absence of a family history, there may still be a genetic basis to a child’s developmental delay, which might have important genetic implications for future pregnancies.

Click here for a descriptive summary of the epidemiology and molecular characteristics of learning disability (see sections on aetiology).

Assessment, investigation, diagnosis and beyond - the parent viewpoint

Before proceeding with assessment, investigation and diagnosis take time to consider the parent viewpoint. Why is finding a precise diagnosis and cause of the learning disability important to them, and how can the whole process be undertaken in such a way that it achieves maximum benefit?

This was investigated through an online discussion forum, and through interviews and focus groups by the Project group. Key findings included:

- “Just to know” - to seek an answer to uncertainty, to provide confirmation that there is something wrong, to be reassured that they are not to blame, to have a name for their child's condition.
- To understand the future likely needs of the child, anticipate problems and hope for the best scenarios.
- To understand what the condition means for the rest of the family.
- To provide an end to the diagnostic quest
- To find others affected by the same condition
- To help the child find support and services

These and other benefits and potential problems of a genetic diagnosis are described in detail in the CGKP report.

Click here for parents' guide, which may be helpful in your discussion with parents.

Why is finding a cause important? - a more clinical viewpoint

The clinical benefits of achieving a specific diagnosis include:

**Aetiology**:

- To establish a specific cause and allay concerns about other possible causes such as events during pregnancy.
- To gain an understanding of the condition and possible prognosis:
- To guide optimal management:
- Medical evaluation: it can enhance medical evaluation by enabling the clinician to undertake a targeted evaluation (eg with monosomy 1p36 would include specific evaluation for hearing and visual impairment, palatal abnormalities, and cardiomyopathy or structural cardiac abnormalities in children).
- Surveillance: it can help target a programme of surveillance and vigilance (eg in Down Syndrome would include monitoring for cardiac disease, celiac disease and thyroid function, and vigilance for arthritis, atlantoaxial subluxation, diabetes mellitus, leukaemia, obstructive sleep apnoea and seizures).

Genetic advice Being able to define more precisely the molecular abnormality can also help to give more accurate advice about the possibility of recurrence or risk to the extended family. Thus, for example, a balanced parental translocation substantially increases the risk of an unbalanced event in the family, whereas if the abnormality is found to have arisen de novo and the parental karyotypes are normal, then the risks of recurrence are very low.

Support for family: knowing that a child has a rare disorder can lead to a referral to support organisations where they can meet other parents of children with the same or a similar condition. This is useful for emotional, social and practical support over the years as they care for the child.

**Assessment of developmental delay**

The following consensus documents were used as the baseline from which the East Anglian guidelines were developed:


Following referral for concerns over developmental progress, the paediatrician undertakes a careful history including a detailed family history (FH) and examination of the child with assessment of growth (ht, wt and head circumference) and development and may involve other professionals in this process.

A variety of tools are used in clinical practice. Some of the standard ones used within the United Kingdom are:

- Griffiths Mental Development Scales
- Denver Developmental Screening Test
- Cash's Schedule of Growing Skills

The clinician will exclude the possibility of chronic illness as the cause, both clinically, and through a baseline haematology and biochemical profile. Tests may be offered to try to determine the cause. Testing will be guided by clinical features, but even in the absence of these, investigations can still be useful. Children with significant developmental delay, at whatever age, should be considered for investigation.

Investigations that should be considered initially in all patients

These are usually requested by the paediatrician

Chromosome analysis: this is the investigation with the highest yield for children with unexplained developmental delay


A chromosome analysis is a very broad investigation which can identify problems anywhere in the genome. Specific FISH tests for submicroscopic microdeletions (eg. Williams, 22q11 syndrome) can also be requested.

Papers describing the microdeletion and associated phenotype identified by FISH analysis include:

Fragile X analysis: this is the commonest cause of inherited learning disability, but remains a rare disorder. It has fairly non-specific features and is difficult to diagnose on clinical grounds so it is therefore offered to all children with developmental delay.


Creatine Kinase in boys: some boys with Duchenne muscular dystrophy present with speech delay and delayed motor milestones &/or global delay.


Thyroid function tests: children born in the UK should have been tested for congenital hypothyroidism on the newborn blood spot screen. If this result was normal (need confirmation), unless there are clinical signs suggestive of hypothyroidism, repeat investigation is not required.


Amino and organic acids: inborn errors of metabolism are individually rare, but may present with non-specific features eg. developmental delay &/or failure to thrive. Plasma & urine samples should be arranged if there is developmental regression, episodic decompensation, parental consanguinity, a family history or physical examination findings consistent with a metabolic disorder eg. microcephaly, macrocephaly, hepato-splenomegaly. 'Non-specific' abnormalities are more common than true diagnoses. The diagnostic yield of "metabolic screening" is relatively low in children presenting with developmental delay alone but should be considered in those where the initial evaluation and first line tests have failed to give an answer. These disorders may be very rare but some are amenable to treatment.


Urine glycosaminoglycans (mucopolysaccharidoses): in children with developmental regression, glue ear, coarse features, macrocephaly.

Urine glycosaminoglycans (GAG) quantitation provides a screening test only. False positives are common, especially in young infants. False negatives also occur, particularly in patients with Morquio Disease (MPS IV) and less often in Sanfilippo (MPS III). If there is a strong clinical suspicion of a mucopolysaccharidosis GAG typing should be undertaken.

**Ophthalmological opinion:** especially if there is concern regarding vision, eye signs (eg nystagmus or neurological signs or microcephaly). In addition, examination of the eyes might reveal retinitis pigmentosa (fundus) or structural abnormalities characteristic of certain syndromes eg hypertelorism in Coffin-Lowry syndrome, Opitz G).

**Audiology assessment:** especially if there is speech delay or concern regarding hearing.

**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.

**Further investigations that may be arranged in particular clinical circumstances**

**Telomeres:** where routine chromosome analysis is normal but a chromosome abnormality is suspected.

Large studies suggest a prevalence of about 6.7% in an unselected population with mental retardation.

• Knight SJL, Regan R *et al* Subtle chromosomal rearrangements in children with unexplained mental retardation. *Lancet 1999;354(9191):1676-81* *


**Cranial MRI scan:** MRI scanning in young children with developmental delay requires day case admission to hospital and sedation or anaesthesia. It is indicated in children with microcephaly, macrocephaly, neurological signs (eg hemiplegia, nystagmus, optic atrophy), seizures, unusual facial features (eg spacing of eyes). The diagnostic yield in normally grown children, with no relevant history or neurological signs is very low.

• van Karnebeek CDMD *et al*. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. *European Journal of Human Genetics (2005) 13, 6−25*

The papers listed describe quite high rates of abnormality found on MRI scanning children with LD (up to 60% in one series). However, in many cases the diagnosis would have been apparent from the history, examination or other investigations. In other cases the abnormalities found would not have necessarily caused the LD and might confuse the situation.


Congenital Myotonic Dystrophy (CMD)

Myotonic dystrophy: in children with motor or global delay with floppiness, history of poor suck and poor feeding in infancy or weakness in childhood or a family history of myotonic dystrophy.


Angelman/Prader-Willi Syndrome(PWS): in children with seizures and no/very little speech (AS), infants with floppiness or young children with obesity and a history of poor feeding (PWS).

Excellent review of clinical features and genetic basis of Angelman syndrome


Overview of clinical presentations of PWS


Creatine Kinase in girls (muscle disorders): if significant delay in motor milestones with/without associated global delay.

Excellent compendium of muscle disorders presenting in infancy and childhood including those presenting with developmental delay.


Lactate (mitochondrial disorders): there is usually multisystem involvement. Key features include; growth retardation, visual/hearing impairment, abnormal MRI findings. (Local professional opinion)

Radiographs (X-rays): if there are features suggestive of skeletal involvement. If delay is associated with macrocephaly and tall stature, an X-ray of the left wrist can be helpful to assess bone age.
Specialised investigations that may be arranged in conjunction with specialist services

**MECP2 analysis (Rett syndrome):** only in girls with features consistent with Rett syndrome.

There is a good yield for patients with classical Rett syndrome


MECP2 Mutations are rarely found in children with non-syndromic mental retardation


**7-dehydrocholesterol (Smith-Lemli-Opitz syndrome):** in children with microcephaly, 2,3 syndactyly, cleft palate, congenital heart defect.


**VLCFA’s (peroxisomal disorders):** in children with hypotonia, delayed closure of the anterior fontanelle and multisystem involvement.


**Electrophoresis of transferrin isoforms (congenital disorders of glycosylation):** in children with multisystem involvement (eg lipodystrophy).


**White cell enzymes (lysosomal storage disease):** in children with hepatomegaly, coarse features and/or regression.


**Acyl carnitines (fatty acid oxidation disorders):** in children with a tendency to fasting hypoglycaemia, prolonged failure to thrive, hypotonia or cardiomyopathy.

Indications for referral to a clinical geneticist

The following textbook gives a good general account of the roles of the genetic service and indications of referral


Indications include:

- Abnormal chromosome analysis or other abnormal genetic test result.
- Any child with moderate/severe developmental delay of unknown cause.
- Congenital anomaly, unusual facial features or multisystem problems in addition to developmental delay.
- Unusual growth parameters eg microcephaly or macrocephaly, short or tall stature, failure to thrive or severe obesity.
- Parental consanguinity or a FH of developmental delay or learning disability.
- Parents seek advice about diagnosis or recurrence risks for future pregnancy.

Indications for referral to a paediatric neurologist

- Developmental regression
- Abnormal neurological features on examination or investigation

The paediatric neurologist may help with diagnosis where the above are present. In the absence of these they are unlikely to add information. At present all children should primarily be seen by a local paediatrician with expertise in developmental delay. If they find abnormalities, but are unable to make a diagnosis, then referral may be appropriate.

This guide was written by a multidisciplinary group in East Anglia: Helen Firth & Lucy Raymond (Clinical Genetics), Alasdair Parker (Paediatric Neurology), Moira Pinkney (Community Paediatrics) and Jacqui Calvin (Biochemistry). The work was part of a wider programme supported by the Cambridge Genetics Knowledge Park. For further information, copies of the document and associated reference material see www.addenbrookes.org.uk/genetics/index.html

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