Developmental Delay – Causes and Investigation

Introduction and definitions

This article provides a systematic approach to the causes of developmental delay and the importance of its rigorous investigation. It particularly highlights practical aspects relevant to adult neurological practice.

Delayed development most commonly follows the usual pattern of development where skills are acquired more slowly (e.g. Down’s syndrome). Less commonly, skill acquisition can be disordered (e.g. autism). ‘Delay’ is a misnomer – children with developmental problems rarely ‘catch up’, and will usually have continuing difficulties with learning later in life.

Developmental delay is common, affecting 1-3% of the population. Developmental delay is defined as significant delay (more than two standard deviations below the mean) in one or more of the following developmental domains:

- Gross motor
- Vision & Fine motor
- Hearing, Speech & Language
- Social, Emotional & Behavioural

Developmental delay can be divided into:

- Global developmental delay – delay in two or more domains (often delayed in all domains)
- Specific developmental delay (e.g. Motor or Speech & Language) – delay in a single domain

The focus of this article is Global Developmental Delay.

Causes of Global Developmental Delay

Global developmental delay can be the presenting feature of a huge number of neurodevelopmental disorders (from learning disability to neuromuscular disorders). It is not possible to provide an exhaustive list; Table 1 gives an approach to aetiology.

Careful evaluation and investigation can reveal a cause in 50-70% of cases. This leaves a large minority where the cause is not determined. It is still useful to investigate globally delayed development whatever the age of the child (occasionally older children with significant disability may not have been investigated adequately).

TABLE 1: Causes of global developmental delay (adapted from Forsyth and Newton 2007).

<table>
<thead>
<tr>
<th>Category</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Genetic or Syndromic</td>
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<tr>
<td>Identified in ~20% of those without neurological signs, dysmorphic features or a family history</td>
<td>• Easily identified syndromes e.g. Down’s syndrome&lt;br&gt;• Genetic causes that are less obvious in early childhood e.g. Fragile X, Velo-cardio-facial syndrome (22q11 deletion), Angelman’s, Sotos, Rett’s, maternal Phenylketonuria, Mucopolysaccharidoses, Duchenne Muscular Dystrophy, Tuberous Sclerosis, Neurofibromatosis Type 1, and subtelomeric deletions</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
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<tr>
<td>Identified in ~1% of those without neurological signs, dysmorphic features or a family history</td>
<td>• Nationwide universal neonatal screening for Phenylketonuria (PKU) and Medium-chain acyl-Co A Dehydrogenase deficiency (MCAD).&lt;br&gt;• e.g. Urea Cycle disorders.</td>
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<tr>
<td>Endocrine</td>
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<tr>
<td>Traumatic</td>
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<td>Environmental Causes</td>
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<td>Cerebral Malformations</td>
<td>e.g. Neuronal Migration Disorders</td>
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<tr>
<td>Cerebral Palsy and Developmental Coordination Disorder (Dyspraxia)</td>
<td>Motor difficulties can prejudice development in general</td>
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<tr>
<td>Infections</td>
<td></td>
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<td>Toxins</td>
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PAEDIATRIC NEUROLOGY
**Why is finding a cause important?**

Establishing a cause has many benefits for the child and family and improves overall quality of life:

- The family gains understanding of the condition, including prognostic information
- Lessens parental blame
- Ameliorates or prevents co-morbidity by identifying factors likely to cause secondary disability that are potentially preventable e.g. surveillance of other systems such as vision and hearing
- Appropriate genetic counselling about recurrence risk for future children and the wider family
- Accessing more support (e.g. within education services and specific syndrome support groups)
- To address concerns about possible causes e.g. events during pregnancy or delivery
- Potential treatment for a few conditions

**Investigation of Global Developmental Delay**

Thorough history and examination are vital to produce a formulation of the child’s problem and target investigations appropriately. The diagnosis may occasionally be immediately obvious from history and examination. More often time is needed to review clinical features, case notes, prior investigations and to consult the literature, dysmorphology and neurogenetic databases.

Transfer of a patient into your clinic from paediatric services is a good opportunity to review the diagnostic process. Most investigations are likely to have been performed early in the child’s life; medical advances especially in genetic investigations and neuroimaging techniques may allow further diagnostic possibilities now. Clinical geneticists are an invaluable source of diagnostic acumen and suggestions for further suitable investigations.

The evidence base for investigation of developmental delay is poor and published work is mainly consensus opinion. There is no one agreed recipe for the investigation of global developmental delay and there is much variation in practice. Historically, there has been patchy introduction of tests as they became available. This means it is well worth reviewing what investigations have actually been done.

A scheme illustrating the investigations considered for global developmental delay is shown in Figure 1. You should expect the first line investigations to have been done, and relevant second line investigations depending on clinical circumstances.

**Practicalities:**

The approach to performing investigations is influenced by:

- identifying treatable conditions
- identifying prevalent serious conditions (e.g. Creatine Kinase for Duchenne Muscular Dystrophy)
- economic considerations (inexpensive, easy to perform tests for less common disorders, e.g. Fragile X)
- the practicalities of performing the investigations on young children

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**Figure 1 Notes:**

- MECP2 = gene for Rett’s
- VLCFA = Very Long Chain Fatty Acids are for Peroxisomal disorders (e.g. Adrenoleukodystrophy)
- GAGs = Glycosaminoglycans are for disorders (e.g. GM1 Gangliosidosis).
- WC enzymes = White cell enzymes. These and oligosaccharides are tests for lysosomal storage disorders (e.g. GM1 Gangliosidosis).
- Transferrins are for congenital disorders of glycosylation (CDG) e.g. type ia
- 7-dehydrocholesterol is for Smith-Lemli-Opitz
- Paired CSF and plasma lactate are to investigate mitochondrial disorders where there are concerns about growth, multi-system involvement, visual and hearing impairments, and abnormal MRI brain.
Simple blood tests can be achieved without too much difficulty. MRI brain may require a general anaesthetic. This may have been delayed if the child was approaching an age (~5yrs or developmental equivalent) where they could manage an MRI without an anaesthetic.

If an anaesthetic is planned, consideration should be given to whether other invasive investigations can be done under the same anaesthetic e.g. blood tests, lumbar puncture, and skin or muscle biopsy.

**Genetics**

Chromosome analysis yields the highest number of abnormalities when investigating global developmental delay, even where there are no clinical features of a genetic problem. Chromosomes and Fragile X testing, some of the line investigations if history and examination do not reveal an obvious aetiology. Fragile X is the commonest cause of inherited learning disability, but remains a rare disorder. Dysmorphisms are difficult to recognise clinically in younger children and girls.

Subtelomeric rearrangements are karyotypically invisible and are traditionally looked for where the karyotype is normal but a genetic abnormality is still suspected. Specific tests for sub-microscopic microdeletions (e.g. for Williams’ or Velo-cardio-facial syndrome) can be requested when clinical index of suspicion is high.

The new advances in Microarray technology offer up to 15% more diagnoses than conventional karyotyping for global developmental delay. They are cost-effective and, although not yet used routinely, are likely to be adopted widely in the future.1

**Neuroimaging**

Cranial MRI in young children (<5-6yrs) requires day case admission to hospital for sedation or general anaesthesia. It is a second line investigation performed in the circumstances outlined in Figure 1, in addition to global developmental delay. Neuroimaging performed in the first two years of life before cerebral myelination has been completed should be repeated after an interval of about a year.

The proportion of neuroimaging abnormalities found in children with delayed development varies widely between studies (9-80%).8 Where high proportions are reported, some of the reported abnormalities are in children where the diagnosis would have been obvious clinically, not contributory to the diagnosis, or of uncertain significance. The yield of useful, diagnostic abnormalities is higher (60%+) using newer imaging techniques and in a population selected for global developmental delay with the clinical features outlined in Figure 1.1,11

CT scanning is only used where cerebral calcification is suspected (e.g. perinatal infection) or to look for an abnormality of skull bones.

**Metabolic**

Individual Inborn Errors of Metabolism (IEM) are a rare cause of global developmental delay (~1%). However, they can present with non-specific developmental delay and some are amenable to treatment. Metabolic investigations are targeted and selective (there is no single test that is a ‘metabolic screen’). Useful metabolic investigations and the clinical circumstances in which they are considered are outlined in Figure 1.11

Biotinidase deficiency uncommonly presents with global developmental delay without other features, but early diagnosis and treatment improves outcome. This is not a universal first line investigation in many parts of the UK, but some authors argue that it should be.1,1 Many countries screen for this disorder as part of universal neonatal screening; the UK does not.

**Biochemistry**

- **CK**
  Boys with Duchenne Muscular Dystrophy can present with delay in more than one domain of their development (e.g. language and motor delay); therefore Creatinine Kinase (CK) is measured as a first line investigation in boys with global developmental delay. CK measurement is considered in girls with severe global (and especially motor) developmental delay.

- **Renal, Bone**
  Electrolytes and Urea are first line investigations, and Calcium measurement can assist in the diagnosis of Velo-cardio-facial and Williams syndromes, and pseudohypoparathyroidism.

- **TFT**
  Thyroid Function tests are easy to perform and have historically been part of investigations for developmental delay. TSH is measured as part of universal neonatal screening. In addition, many chromosomal abnormalities are associated with an increased and ongoing risk of hypothyroidism (e.g. Turner’s, Velo-cardio-facial syndromes). Thyroid function tests are worth repeating periodically in those at risk as the clinical diagnosis of hypothyroidism is more difficult in those with developmental difficulties.

- **Lead**
  Chronic lead toxicity has longstanding developmental effects (developmental delay, behavioural change and poor coordination) and is potentially treatable by chelation. Despite evidence that children with developmental problems have higher blood levels of lead than the general child population,12 interpretation of blood lead levels remains controversial.15

- **FBC**
  A Full Blood Count (FBC) and Ferritin identify iron deficiency which can cause global developmental delay and is easily treated.1

**Neurophysiology**

EEG should not be performed routinely, but reserved for those with seizures, or speech regression (looking for Landau-Kleffner) associated with global developmental delay.

**Other Investigations**

All children with global developmental delay should have Visual and Audiology assessments early on. An Ophthalmology opinion should be sought if there are concerns about visual function, abnormal appearance of the eyes or when looking for clues to the underlying diagnosis.

A TORCH screen for congenital infection is performed in children with Intratuerine Growth Retardation (IUGR), microcephaly or sensory impairments. PCR for infective organisms can be performed retrospectively on the blood spots taken for the neonatal screening programme, even many years later.

Radiographs are performed primarily for suspected skeletal dysplasia, or lead toxicity. Subtle skeletal dysplasia can be difficult to diagnose on radiographs performed when most of the skeleton is not yet ossified and may need to be repeated at a later date.

**Conclusions**

- Global developmental delay is a common problem in paediatric practice and has a wide aetiology.
- Selective investigations are useful in determining the cause, but the cornerstone of the diagnostic process is careful clinical examination.
- Finding a cause confers many medical and social benefits for the child and family.
- Recent technological advances, especially in Genetics and Neuroimaging, make it important to review the need for repeat or updated investigations.
- The transfer of a patient to your practice from paediatrics is an opportunity to review the diagnosis (or lack of one), and to evaluate the need for further investigation.

**REFERENCES**


