

## Specialised investigations that may be arranged in conjunction with specialist services

- **MECP2 analysis (Rett syndrome):** only in girls with features consistent with Rett syndrome. ♦
- **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. ♦ 1ml
- **Electrophoresis of transferrin isoforms (congenital disorders of glycosylation):** in children with multisystem involvement (eg lipodystrophy). Δ
- **White cell enzymes (lysosomal storage disease):** in children with hepatomegaly, coarse features and/or regression. Contact lab to discuss. ♦ 5-10mls
- **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

- 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.

**Note:** this is not a comprehensive list of investigations. Some rare disorders require highly specialised investigation eg. mutation analysis of specific genes, skin biopsy for mosaicism etc., but these will usually be initiated by a clinical geneticist.

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

Developmental delay is a common problem affecting 1-3% of the population. 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.

### Why is finding a cause important?

Careful evaluation can reveal a cause in approximately 50% of children. This can be very helpful for many reasons:

- To gain an understanding of the condition and possible prognosis.
- To guide optimal management for the child and identify other systems which need surveillance (eg hearing / vision).
- To address concerns about events during pregnancy or delivery.
- To enable accurate genetic advice for parents and other family members about the risk of recurrence in future pregnancies.

### Assessment of developmental delay

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. He/she 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. ■ & ◇
- **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. Δ
- **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. Δ
- **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. ■, Δ & ▼
- **Urine glycosaminoglycans (mucopolysaccharidoses):** in children with developmental regression, glue ear, coarse features, macrocephaly. ▼
- **Ophthalmological opinion:** especially if there is concern regarding vision, eye signs (eg nystagmus or neurological signs or microcephaly).
- **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. Δ

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

- **Telomeres:** where routine chromosome analysis is normal but a chromosome abnormality is suspected. ■ & ◇
- **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 who have no neurological signs is very low.
- **Myotonic dystrophy:** in children with motor or global delay with floppiness, history of poor suck and poor feeding in infancy or weakness and fatigue in childhood or a family history of myotonic dystrophy. ◇
- **Angelman/Prader-Willi syndrome:** 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). ■ & ◇
- **Creatine Kinase in girls (muscle disorders):** if significant delay in motor milestones with/without associated global delay. Δ
- **Lactate (mitochondrial disorders):** there is usually multisystem involvement. Key features include; growth retardation, visual/hearing impairment, abnormal MRI findings. †
- **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 L wrist can be helpful to assess bone age.

### Key to samples required:

- ◇ 3-5 ml blood in EDTA
- 3-5 ml blood in Li Heparin
- Δ 1-2ml blood in serum tube
- † paired plasma & CSF in fluoride tube (on ice)
- ▼ 5-10 ml urine in plain universal container
- ‡ dried blood spot (on newborn blood spot card)