

- **MECP2 analysis** - 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 □ 1ml
- **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)** - children with multisystem involvement eg. lipodystrophy □
- **White cell enzymes (lysosomal storage disease)** - in children with hepatomegaly, coarse features and/or regression. Contact lab to discuss □
- **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 genetic test result
- Unusual facial features eg. coarse features
- Unusual growth parameters eg. microcephaly or macrocephaly, short or tall stature, failure to thrive or severe obesity
- Parental consanguinity
- Family history of developmental delay/learning disability
- Congenital anomaly or multisystem problems in addition to developmental delay
- Parents would like advice regarding diagnosis or recurrence risks for a future pregnancy

Indications for referral to a paediatric neurologist

- Developmental regression
- Abnormal neurological features on examination or investigation

Key to samples required:

- 3-5 ml blood in EDTA
- 1-2ml blood in serum tube
- 5-10 ml urine in plain universal container
- 2 ml blood in Li Heparin
- fluoride tube (on ice) for plasma & CSF
- dried blood spot (on Guthrie card)

HF, AP, LR, JC, MP v.6 27.10.04

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

Definition of developmental delay

Delay in any one or more of the following domains:

- Gross/fine motor skills eg. walking, holding a pencil and scribbling
- Speech and language
- Cognition eg. level of understanding
- Social awareness and interaction

Developmental delay is a descriptive term with many different causes.

Assessment of developmental delay

If parents or health care professionals have concern about a child's development, the first step is to discuss this with the health visitor or general practitioner who can then make a referral to a paediatrician with expertise in Child Development. If the paediatrician confirms developmental delay he/she will undertake a careful history, examination of the child and assessment of growth (height, weight and head circumference) and may offer further tests to try to determine the cause.

Causes of developmental delay

Developmental delay is common and affects 1-3% of the population. Delay may be determined by a child's genetic makeup (eg. Down syndrome, Fragile X syndrome), by problems during pregnancy (eg. rubella), around the time of delivery especially if very premature (eg. cerebral haemorrhage), early infancy (eg. meningitis), or later in childhood (eg. head injury). For many children, the cause will not be apparent.

Why is finding a cause important?

Careful evaluation can reveal a cause in about 40% 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
- To identify other systems which may need surveillance eg. hearing/vision

- To alleviate parents' concerns about other possible causes during pregnancy or delivery
- To enable accurate genetic advice for parents about the risk of recurrence in future pregnancies and for other members of the family

Investigations which should be considered initially. These would be 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. New high resolution techniques such as FISH and array-CGH can identify submicroscopic changes in some children where routine G-banded chromosome analysis has yielded a normal result. A telomere screen can identify submicroscopic changes at the chromosome tips. □ & □
- **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 and/or global delay. □
- **Thyroid function tests** - children born in the UK should have been tested for congenital hypothyroidism on the neonatal Guthrie spot. If this result was confirmed normal, repeat investigation is not required unless there are clinical signs suggestive of hypothyroidism. □
- **Amino and organic acids** - inborn errors of metabolism are individually rare, but may present with non-specific features including developmental delay and/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 such as microcephaly, macrocephaly, or hepatosplenomegaly. 'Non-specific' abnormalities are more common than true diagnoses. □ & □
- **Ophthalmological opinion** - especially if there is concern about vision, or eye signs eg. nystagmus or neurological signs eg. microcephaly

- **Audiology assessment** - if there is concern about hearing or speech delay

Further investigations which may be arranged by the paediatrician in particular clinical circumstances

- **Cranial MRI scan** - in young children with developmental delay this requires day case admission to hospital and sedation or anaesthesia. It is indicated in children with: microcephaly (unusually small head size), macrocephaly (unusually large head size), neurological signs eg. hemiplegia, nystagmus, optic atrophy, seizures or unusual facial features eg. spacing of eyes. The diagnostic yield in normally grown children who have no neurological signs is very low.
- **Lactate (mitochondrial disorders)** - there is usually multisystem involvement. Key features include: growth retardation, visual/hearing impairment, abnormal MRI findings. □
- **Consider congenital infection** - in children with intrauterine growth retardation, microcephaly and eye or hearing signs. Testing requires comparison of maternal booking and current maternal serology. Useful for children up to about age 18 months.
- **Urine glycosaminoglycans (mucopolysaccharidoses)** - in children with developmental regression, glue ear, coarse features, and/or macrocephaly □
- **Creatine kinase in girls (muscle disorders)** - if there is significant delay in motor milestones with/without associated global delay. □
- **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 which may be arranged by the paediatrician in conjunction with specialist services

- **Angelman/Prader-Willi syndrome** - children with seizures and no/very little speech (AS), infants with floppiness or young children with obesity (PWS) □
- **Myotonic dystrophy** - in children with motor or global delay with floppiness, history of poor suck and poor feeding in infancy. Family history of myotonic dystrophy. □