EVIDENCE BASED GUIDELINES

Investigation of global developmental delay

L McDonald, A Rennie, J Tolmie, P Galloway, R McWilliam

Arch Dis Child 2006;**91**:701–705. doi: 10.1136/adc.2005.078147

The investigation of global developmental delay in preschool children varies between centres and between paediatricians.¹ Following a literature search and review of the evidence base, guidelines were developed to assist in the assessment and management of such children presenting to secondary level services. Evidence supporting the use of genetic and biochemical investigations on a screening basis was found, but there was no evidence to support the use of metabolic investigations or neuroimaging in the absence of other positive findings on history or examination. Detailed history and examination are paramount in the assessment of children with global developmental delay. Investigations can be a useful adjunct in determining aetiology. Evidence based guidelines have been developed to assist doctors in the selection of appropriate investigations for this group of children.

aetiologies, and independent variables that cannot easily be corrected for. When developing these guidelines to be used locally for the investigation of global developmental delay in preschool children, we searched the evidence base, but ultimately arrived at a protocol based mostly on level IV evidence, i.e. consensus of expert opinion. However, we realised that using an entirely evidence based approach would not fulfil the aims of investigation, which are: to establish causation; to alter management; to predict prognosis or recurrence risks; and to influence prevention strategies.⁵ While investigating children with global developmental delay, it is also vital not to miss conditions which may be exacerbating it, or those rare conditions which are treatable, and this is reflected in the final guidelines which are designed to be a useful working tool for paediatricians. It is hoped that the development of these guidelines on a national scale would present an opportunity to develop a multicentre audit that would contribute further to the evidence base.

A consensus guideline has been produced in North America,⁶ but there are currently no published evidenced based UK guidelines. A comparison between the two papers is presented in the discussion. We are encouraged that our recommendations are broadly similar, indicating a degree of consensus of opinion at international level.

METHODS

A literature search was performed, using Medline, Embase, Cinahl, and PsycINFO. Keywords used in the search included global developmental delay, learning difficulties, mental retardation, guidelines, and investigation. A number of relevant papers were identified. These included retrospective and prospective studies and consensus recommendations, although the majority of papers were review articles or personal practice. Additional articles, for example case reports, were considered important if they contained recommendations relevant to this group of children. The evidence was graded using a standardised system (table 1).⁷ This evidence base was then used in the formulation of our guidelines, the grade of evidence determining the strength of each recommendation (table 2).⁷

The investigations considered in the literature fall into the categories of genetics, neuroimaging, electrophysiology, and biochemical including metabolic. The evidence pertaining to each category will be considered in turn.

Genetics

There is grade III/IV evidence to support the use of chromosome analysis in all cases where

Within the city of Glasgow there are four child development centres, providing secondary level community paediatric care to the population. A variation in practice existed between these centres regarding the use of laboratory investigations in preschool children presenting with global developmental delay. Global delay can be defined as significant delay in two or more developmental domains: gross and fine motor; speech and language; cognition; personal and social development; or activities of daily living.² "Significant" may be defined as performance 2 or more standard deviations below the mean on developmental screening or assessment tests.³ The extent of delay can be classified as mild if functional age is <33% below chronological age, moderate if functional age is 34–66% of chronological age, and severe if functional age is >66% below chronological age.² These definitions will be applied throughout this paper.

Children presenting to secondary level services merit investigation. It is important to assess and investigate all three groups (mild, moderate, and severe), as an aetiological diagnosis may be determined irrespective of the extent of developmental delay.^{3,4} We wanted to standardise investigations by creating a set of evidence based guidelines.

How do you develop evidenced based guidelines when the evidence base is poor? This is the difficulty facing specialities where the subject does not lend itself well to multicentre, randomised controlled trials. Such a subject is neurodisability, with its myriad of presentations,

See end of article for authors' affiliations

Correspondence to:
Dr L McDonald, Achamore
Centre, Drumchapel Health
Centre, 80–90 Kinfauns
Drive, Glasgow G15 7TS,
UK; lmcDonald@doctors.
org.uk

Accepted 13 April 2006

Table 1 Category of evidence

Evidence	
Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports, or opinions or clinical experience of respected authorities, or both

aetiology is not apparent after history and examination.^{2-6 8-14} There was some consensus between papers (grade IV) that a DNA based test for the fragile X gene mutation should be routinely performed,^{4 5 9 10 13 14} since this inherited cause of learning difficulties in boys and girls causes subtle dysmorphism and is difficult to diagnose clinically. Other papers (grade III/IV) suggested that this investigation should be "strongly considered".^{2 6 8 11}

In 1995, researchers from Montreal Children's Hospital performed a retrospective review of all children referred with global developmental delay over a 2.5 year period.² The laboratory test with the highest yield of abnormal results was chromosome analysis. A subsequent prospective study from the same group in 2000 found three cases with a chromosome abnormality in 32 tests performed when the clinician suspected a cytogenetic problem, and a similar abnormality rate (two cases in 38 tests) when the test was performed as a "screen", i.e. without prior clinical suspicion.³ This group also created the guidelines alluded to previously.⁶

- **Recommendation:** High yield, together with the associated implications, make the case for using cytogenetic analysis and the fragile X DNA test on a screening basis (strength of recommendation C/D).

Neuroimaging

A review paper of radiological findings in developmental delay (grade IV) found a wide variation in yield between studies, ranging from 9% to 80%. With newer techniques such as high resolution CT and MRI, positive findings were found in 30–60% of patients with significant developmental delay.¹⁵ This yield is significantly increased if neuroimaging studies are performed for a specific indication, for example abnormalities of head size, presence of seizures, or presence of abnormal findings on neurological examination, in addition to developmental delay.^{3 15}

The radiological findings in this group of children include cerebral injury, cerebral malformations, and cerebral dysgenesis.¹⁵ The cerebral injury group includes periventricular leucomalacia, post-haemorrhagic changes, ventriculomegaly, enlarged extracerebral fluid spaces, and congenital infection

(cerebral injury with or without intracranial calcification). There is some overlap between the cerebral malformation and cerebral dysgenesis categories. Overt malformations may be found, including holoprosencephaly, agenesis of the corpus callosum, septo-optic dysplasia, migrational abnormalities, and abnormalities of white matter development. In addition, subtle markers of cerebral dysgenesis are increasingly found in this population with improved imaging techniques, for example wide or persistent cavum septum pellucidum, hypoplasia of the corpus callosum, and macro cisterna magna.

Should we image all children with global developmental delay, or only those with positive findings on history or examination? Many of the papers reviewed (grade III/IV) advocated the use of neuroimaging for all such children.^{2-6 9 12 14 15} Others suggested that this should be considered when abnormal head size or neurology are present, or when unexpected changes occur in behaviour, occipitofrontal circumference, motor status, cognitive ability, or seizure frequency (grade IV).^{8 10 11}

- **Recommendation:** Neuroimaging should be considered as a second line investigation, when the features described above are found in addition to global developmental delay (strength of recommendation D).

Metabolic investigations

The available evidence does not support the use of metabolic investigations as a screening tool. There was consensus (grade III/IV evidence) that such tests should be selective and targeted.^{2 3 4 5 6 8 9 10 11 14 16} Metabolic tests have the disadvantage of yielding a high frequency of non-specific, non-diagnostic abnormalities. There should, however, be a low threshold for performing these investigations if a metabolic disorder is suspected clinically.

- **Recommendation:** Metabolic tests should be considered as second line investigations (strength of recommendation C/D). History or examination findings that should prompt consideration of these tests will be outlined later in the paper.

Biochemical investigations

There are published case reports (grade IV evidence) of boys with Duchenne muscular dystrophy presenting with global developmental delay.¹⁷

- **Recommendation:** Creatine kinase should be measured at an early stage to prevent late or missed diagnosis (strength of recommendation D).

There is grade III evidence to suggest that children with developmental problems may have significantly higher blood lead concentration than the general childhood population.¹⁸

- **Recommendation:** Lead toxicity should be screened for routinely as this neurotoxin may further contribute to impairment, and is treatable (strength of recommendation C).

Biotinidase deficiency is treatable and may present as global delay with no other signs or symptoms. In many countries, this disorder is screened for routinely in the neonatal period,¹⁹ and it is known that early diagnosis and treatment improves outcome (grade III evidence).^{20 21}

- **Recommendation:** Biotinidase should be measured early in the investigation pathway (strength of recommendation C).

Table 2 Strength of recommendations

Recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

Calcium assay will assist in the diagnosis and management of conditions such as DiGeorge syndrome, Williams syndrome, and pseudohypoparathyroidism (grade IV evidence).²²

- *Recommendation:* Calcium should be measured routinely (strength of recommendation D).

We could not find evidence to support the use of thyroid function tests. This will be discussed in more detail later.

Neurophysiology

There is grade III/IV evidence that EEG is useful in the evaluation of developmental delay, particularly in association with seizures or significant language impairment.^{2 4 6 10 11 14 22 23}

- *Recommendation:* EEG should not be performed routinely, but should be considered if there is a history suggestive of seizures or neurodegenerative disorders; or evidence of speech regression, looking for Landau–Kleffner syndrome (strength of recommendation C/D).

DISCUSSION

History and examination are paramount in the evaluation of children with global developmental delay, and should precede any laboratory investigations. Our completed guidelines are shown in fig 1. These guidelines are not intended for the investigation of children presenting with isolated delay in speech and language or motor development, or with autism.

History

History should be comprehensive, and must include a detailed prenatal, perinatal, and postnatal history. The mother should be asked about drug ingestion during pregnancy and early threatened miscarriage. It is important to note that there must be clear evidence of neonatal encephalopathy and a significant motor disorder before problems are attributed to the perinatal period.^{24 25} It should be ascertained whether the child has developmental delay or regression, and a detailed family history should be sought.

Examination

A complete physical examination must be performed, including:

- Occipitofrontal circumference of child and parents, measured and plotted
- Dysmorphic features
- Neurocutaneous stigmata
- Abdominal examination for visceromegaly
- Spine, reflexes, and gait
- Eyes (may require ophthalmologist).

Serial assessment is important as the phenotype may change with time.⁸

If the diagnosis is not apparent after a full history and physical examination, first line laboratory investigations should be performed as outlined in fig 1. We have included thyroid function tests for two reasons, despite the lack of evidence. Firstly, hypothyroidism is an easily treatable disorder, with significant implications if the diagnosis is missed. Secondly, many chromosomal abnormalities are associated with an increased risk of hypothyroidism, for example trisomy 21, 45X, and 22q11 deletion. Urate is included as this is more stable than both ammonia and lactate, and is an easy way to diagnose purine disorders, which may present as isolated global delay. We also suggest testing for iron deficiency, as this can be associated with developmental delay and is easily measured and treated.²⁶

Second line investigations should be selective, and guided by history and examination findings.

Metabolic investigations should be undertaken when history and examination findings increase clinical suspicion; findings that merit investigation include family history, parental consanguinity, developmental regression, congenital ataxia or dysequilibrium, epilepsy, organomegaly, and coarse facial features. If a metabolic disorder is suspected clinically, blood should be taken for lactate, amino acids, ammonia, very long chain fatty acids, carnitine, homocysteine, and disialotransferrins. Urine should also be tested for organic acids, orotate, glycosaminoglycans, and oligosaccharides.

Neuroimaging is recommended if global delay is found in association with additional features as described earlier in this paper. MRI is the investigation of choice. CT is recommended for visualisation of bony structures or calcification.

EEG should be performed if there is a history of seizures or regression in speech. Twenty four hour EEG recording should be considered.

Referral to the genetics department is particularly useful for the evaluation of dysmorphic features and syndrome diagnosis: clinical clues are abnormal growth (including head size), associated sensory impairment (vision or hearing), unusual behaviour patterns (for example, hyperphagia or onychotillomania), or a family history of a particular condition. Video or photographic documentation is essential. At the genetic clinic, additional genetic investigations may be ordered. For example, chromosome telomere studies may exclude submicroscopic or cryptic chromosome imbalance involving the chromosome ends or telomeres. A telomere abnormality is present in 5% of patients with previously undiagnosed learning difficulties, and such tiny imbalances are not detected by a conventionally stained cytogenetic study.²⁷ The development of new technologies to diagnose hereditary causes of learning difficulties underlines the value of referral to the genetic clinic.

There are some differences between our guidelines and those published in North America.⁶ The North American recommendations suggest that screening for lead toxicity should be targeted to those with risk factors for lead exposure, and that thyroid function tests should be performed only if there are systemic features which suggest thyroid dysfunction. We recommend that both these investigations are performed as first line screening tests, for the reasons outlined above. We also recommend routine measurement of creatine kinase and biotinidase, which are not mentioned in the North American guidelines. Both guidelines contain similar recommendations in relation to cytogenetic testing, fragile X analysis, metabolic screening, EEG, and neuroimaging.

CONCLUSION

Developmental delay is among the commonest problems encountered in community paediatric practice. It is important to investigate such children, primarily in an attempt to identify causation, but also to assist with management and to provide information about prognosis, recurrence risks, and future prevention strategies.

A comprehensive history is essential, as is careful physical examination. Laboratory investigations are not a substitute for history and examination in the evaluation of a child presenting with global developmental delay, but can be a useful adjunct in determining aetiology. Following an extensive review of the literature, evidence based guidelines have been created to assist in the selection of appropriate investigations for this group of children. The guidelines have been approved by all relevant hospital and laboratory departments. It is felt that these will improve service delivery and planning while maintaining fiscal restraint.

Department of Community Child Health Royal Hospital for Sick Children, Glasgow

Global Developmental Delay in Pre School Children

Guidelines for Investigation

Global developmental delay is defined as significant delay in two or more developmental domains.

Investigation should be considered only after a thorough history and examination have been performed.

These guidelines are not intended for isolated speech and language or motor problems, or for children with autism.

- If diagnosis not apparent after history and examination, proceed as follows:-

Figure 1 Guidelines for investigation of global developmental delay in preschool children, Department of Community Child Health, Royal Hospital for Sick Children, Glasgow.

Authors' affiliations

L McDonald, A Rennie, Department of Community Child Health, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK

J Tolmie, Duncan Guthrie Institute of Medical Genetics, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK

P Galloway, Department of Biochemistry, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK

R McWilliam, Fraser of Allander Neurosciences Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK

Competing interests: none declared

REFERENCES

- 1 **Gringras P**. Choice of medical investigations for developmental delay: a questionnaire survey. *Child Care Health Dev* 1998;**24**:267–76.
- 2 **Majnemer A**, Shevell MI. Diagnostic yield of the neurologic assessment of the developmentally delayed child. *J Pediatr* 1995;**127**:193–9.
- 3 **Shevell MI**, Majnemer A, Rosenbaum P, *et al*. Etiologic yield of subspecialists' evaluation of young children with global developmental delay. *J Pediatr* 2000;**136**:593–8.
- 4 **Battaglia A**, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. *Am J Med Genet* 1999;**82**:60–6.
- 5 **Schaefer GB**, Bodensteiner JB. Evaluation of the child with idiopathic mental retardation. *Pediatr Clin North Am* 1992;**39**:929–43.
- 6 **Shevell M**, Ashwal S, Donley D, *et al*. Practice parameter: Evaluation of the child with global developmental delay. Report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology* 2003;**60**:367–80.
- 7 **Shekelle PG**, Woolf SH, Eccles M, *et al*. Clinical guidelines: developing guidelines. *BMJ* 1999;**318**:593–6.
- 8 **Curry CJ**, Stevenson RE, Aughton D, *et al*. Evaluation of mental retardation: recommendations of a consensus conference. *Am J Med Genet* 1997;**72**:468–77.
- 9 **Shevell MI**. The evaluation of a child with a global developmental delay. *Semin Pediatr Neurol* 1998;**5**:21–6.
- 10 **Levy SE**, Hyman SL. Pediatric assessment of the child with developmental delay. *Pediatr Clin North Am* 1993;**40**:465–77.
- 11 **Whiting K**. Investigating the child with learning difficulty. *Curr Paediatr* 2001;**11**:240–7.
- 12 **Newton RW**, Wraith JE. Personal practice: investigation of developmental delay. *Arch Dis Child* 1995;**72**:460–5.
- 13 **FitzPatrick DR**, Pearson P, Halpin S, *et al*. A school based study of children with learning disability indicates poor levels of genetic investigation. *J Med Genet* 2002;**39**:e19.
- 14 **Battaglia A**, Carey JC. Diagnostic evaluation of developmental delay/mental retardation: an overview. *Am J Med Genet C Semin Med Genet* 2003;**117**:3–14.
- 15 **Schaefer GB**, Bodensteiner JB. Radiological findings in developmental delay. *Semin Pediatr Neurol* 1998;**5**:33–8.
- 16 **Papavasiliou AS**, Bazigou H, Paraskevoulakos E, *et al*. Neurometabolic testing in developmental delay. *J Child Neurol* 2000;**15**:620–2.
- 17 **Essex C**, Roper H. Late diagnosis of Duchenne's muscular dystrophy presenting as global developmental delay. *BMJ* 2001;**323**:37–8.
- 18 **Lewendon G**, Kinra S, Nelder R, *et al*. Should children with developmental and behavioural problems be routinely screened for lead? *Arch Dis Child* 2001;**85**:286–8.
- 19 **Elitz C**. 'ABC' of developmental disorders: biotinidase deficiency (BTD): a treatable disorder. *British Academy of Childhood Disability Newsletter* 2004;**10**:4–5.
- 20 **Weber P**, Scholl S, Baumgartner ER. Outcome in patients with profound biotinidase deficiency: relevance of newborn screening. *Dev Med Child Neurol* 2004;**46**:481–4.
- 21 **Grunewald S**, Champion MP, Leonard JV, *et al*. Biotinidase deficiency: a treatable leukoencephalopathy. *Neuropediatrics* 2004;**35**:211–16.
- 22 **Stephenson JBP**, King MD. *Handbook of neurological investigations in children*, revised reprint. Butterworth Heinemann, 1992.
- 23 **Sheth RD**. Electroencephalogram in developmental delay: specific electroclinical syndromes. *Semin Pediatr Neurol* 1998;**5**:45–51.
- 24 **MacLennan A**. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;**319**:1054–9.
- 25 **Aicardi J**. *Diseases of the nervous system in childhood*, 2nd edn. MacKeith Press, 1998:39.
- 26 **Yager JY**, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. *Pediatr Neurol* 2002;**27**:85–92.
- 27 **De Vries BB**, Winter R, Schinzel A, *et al*. Telomeres: a diagnosis at the end of the chromosomes. *J Med Genet* 2003;**40**:385–98.