

PERSONAL PRACTICE

Investigation of developmental delay

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The diagnostic process

Paediatricians will often be asked to see children with learning difficulties. They will present at a variety of ages in a number of different ways and it is easy to feel unsure how extensively to investigate the problem and what advice to give. This article will review the common presentations and suggest a rational approach to investigation.

The role of the paediatrician is to help understand the issue of causation, inform the parents of future outlook, deal with any attendant medical problems, and arrange genetic counselling and supportive services. Special investigation plays only a small part in this process. Clinical skills are equally important; a child's appearance, pattern of movement, or mode of presentation may all give important diagnostic clues.

Children with learning difficulties present in relatively few well circumscribed ways: hypotonia in the newborn period, recognised developmental delay later in infancy or in the early toddler age group, language delay, arrest of development, or difficulties at school (see below). In each of these groups the history should detail the pregnancy, including any drug ingestion or early threatened abortion. The presence of fetal distress should lead to careful scrutiny of the obstetric notes, though it is now generally accepted that in order to attribute causation to birth asphyxia the presence of hypoxic-ischaemic encephalopathy must be established. A record of cord or early pH measurements as well as neonatal behaviour are important in this respect as not all early neonatal encephalopathy is due to hypoxic-ischaemic insult.¹⁻³ Parents in their own mind often attribute their child's difficulties to the events of labour and it can be helpful for them to be taken through details of the birth.

A detailed family history is clearly of value especially if supplemented by perusal of the family photograph album. These together with home video recordings can give a surprisingly clear idea of the evolution of a disorder. Many motor disorders such as the spasticity in cerebral palsy or the extrapyramidal involvement in Rett's syndrome may evolve over a period of time, raising the possibility of a neurodegenerative disorder. Careful scrutiny of the history often reveals that whereas things have changed, skills may not actually have been lost.

Presenting symptoms

ABNORMAL BEHAVIOUR IN THE NEONATAL PERIOD

Apart from obvious dysmorphic features, disordered tone, feeding difficulties, irritability, and seizures may all signify continuing neurological abnormality. Hypotonia in the limbs *and* axis raise the possibility of a neuromuscular disorder or the Prader-Willi syndrome. Where hypotonia is confined to the axis, there is usually a central nervous system abnormality including the cerebral dysgeneses, or hypoxic-ischaemic encephalopathy when it may be associated with a full fontanelle due to cerebral oedema, irritability, feeding difficulties, and seizures.

The commonest cause of persisting hypotonia or feeding difficulty is the presence of one of the recognisable forms of learning difficulty of which Down's syndrome is the commonest. Of the metabolic disorders, it should be remembered that the cerebrohepato-renal syndrome of Zellweger (one of the peroxisomal disorders) can mimic Down's syndrome. It is associated with profound hypotonia as well as a craniofacial dysmorphism similar to trisomy 21. The use of one of the computer based databases of dysmorphology can be helpful when attempting to establish a dysmorphic diagnosis.⁴

Arthrogryposis should make one think of a neuromuscular problem or a neuronal migration defect particularly if the hands and arms are held in a 'decorticate' posture. The presence of scoliosis and pooling of secretions with aspiration makes a congenital myopathy and particularly nemaline rod myopathy likely.

DEVELOPMENTAL DELAY

When children attain developmental skills significantly more slowly than the average child they may have continuing difficulties with learning in later life. Many standardised tests are available to back-up an initial impression at the clinical consultation. The Griffiths, Bailey, and Wechsler scales continue to be the most widely used. Lack of stimulation due to social disadvantage or prolonged illness in an infant may result in a transient period of relative delay with subsequent catch-up; on the other hand, assessment in infancy may serve to over estimate the ability of children with more severe learning difficulties, due to an emphasis in the tests on motor skills.

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'FUNNY WALKS'

Many disorders with learning difficulties have an associated gait disturbance. The gait should be observed with particular features in mind. In the absence of a clear heel strike a toe-heel gait may be due to pyramidal or extrapyramidal motor dysfunction, a foot drop due to a lateral popliteal nerve palsy or tight tendo-achilles due to a neuromuscular problem. A wide base seen continuing for some months after children first begin to walk may suggest a cerebellar problem, the general hypotonia of the recognisable forms of learning difficulty or the recently defined carbohydrate deficient glycoprotein syndrome.⁵ Neuromuscular problems leading to proximal weakness often lead to a waddling pattern. The weak gluteal muscles lead the body weight to be transferred outside the weight bearing leg; the resulting mechanical advantage avoids dropping of the pelvis away from the weight bearing side. If one side of the body 'mirrors' movement seen on the other then agenesis of the corpus callosum should be considered.

One third of boys with Duchenne muscular dystrophy have learning difficulties. The average age at which boys with this disorder are taken to doctors with developmental concerns is 2.5 years, whereas the average age of diagnosis is 5.5 years. A large contribution to this delay is a misunderstanding of Gower's sign.⁶ Most people remember the sign as the need to climb up the legs using the hands when rising from a supine to standing position. The most important component, however, is the need to turn prone and in so doing adopting a 'Muslim prayer position' before rising. This overcomes difficulties sustained in attaining a sitting position if the rectus abdominus is weak and furthermore allows the hips to be extended before rising relative to the position of full hip flexion found in the normal squatting position. Most children show a Gower's or modified Gower's manoeuvre before the age of 3 years. If it is seen after the age of 3 then it is highly likely that there is a neuromuscular problem in need of further investigation, or a cause for central nervous system hypotonia leading to poor stabilisation at the hip.

The presence of choreoathetosis naturally would lead to investigations for basal ganglia dysfunction but the erratic movements of Angelman's syndrome may certainly imitate this, particularly in infancy and it may also be an early feature of Friedreich's ataxia.

ABNORMAL HEAD SIZE

The commonest cause of either a small or large head is to have one or both parents with a similar head size. Familial large heads may actually accelerate in growth and cross centiles in the early months of life but usually parallel normal centiles after the age of 6 months or so.

In the presence of neurological abnormality the large head may reflect hydrocephalus, storage disorder, or Canavan's or Alexander's leucodystrophy.

A small head may reflect an underlying

metabolic disorder, neurodegenerative condition, or congenital infection. The retina should be examined for signs of chorioretinitis or pigmentation to reflect a mitochondrial cytopathy or peroxisomal disorder and bone structure and viscera should be examined for signs of abnormal storage.

SYNDROMES OF DEVELOPMENTAL ARREST

A number of conditions lead to similar developmental profiles in that for a while children seem capable of learning; learning then slows, arrests, some skills may actually be lost, and then learning continues at a slower rate. The child with hydranencephaly (think of pyruvate dehydrogenase deficiency) may well return the mother's smile before this skill is lost. Deaf children may babble but then lacking input their language development will subsequently fall into deviancy if the problem is not identified and treated.

Children with autism often make reasonable developmental progress in the first year or so, their problems only becoming evident when there is a greater demand on social contact and language function. Words originally attained may be lost before the depth of communication difficulty is revealed. A very similar profile is seen in the age related epileptic encephalopathies. West's syndrome often begins too early in infancy for much difference with other children to be noticed but in the Lennox-Gastaut syndrome, which often presents in the third or fourth year, there is very often a distinct arrest of developmental progress at the time of onset of the seizure disorder.

In Rett's syndrome, although in retrospect the movement may have had a 'jerky' quality throughout infancy, there is often reasonable early developmental attainment before the process slows and the extrapyramidal features and loss of useful hand function become more evident.

Each of these disorders is determined prenatally. It would appear that the brain is capable of sustaining a certain amount of developmental progress before its association networks malfunction often with the advent of seizures.

Speech, language, and communication disorders

Speech and language disorders are common in childhood, boys being affected twice as often as girls.^{7 8} The history highlights whether the language problem is isolated or seen in the context of a more global developmental delay. As assessment should be made of language opportunity for the child and whether there is any social disadvantage. Children brought up in a bilingual environment tend to develop speech later but then catch up. Left handedness or ambidexterity is associated with speech disorder in half the children involved. Elective mutism, commoner in boys, can usually be recognised in the context of unresolved predicament. Children with elective mutism often talk freely in certain situations and continue to communicate with gesture.

Whenever there is indistinct speech and impaired language development, it is important to rule out deafness and to look for antecedents in the history. Particular attention should be paid to the pattern of speech/language disorder.

Stuttering or stammering is an interruption of the normal rhythm of speech and may involve involuntary repetition, or prolongation or arrest of the sounds. It is very common and present in up to 5% of children at school entry. There is male preponderance with a familial tendency. There are many similarities between stammering and simple tics. As children approach certain sounds in a sentence, anxiety about the approaching sequence rises, a stereotyped stutter follows with a release of tension as the sound is passed over.

Dysphonia is rare and may involve the loudness, tone, pitch, inflection, or vibrato of the sound produced. Most neurological causes are mediated through chest wall weakness or spasticity leading to an abnormal pattern of flow of expired gases over the vocal cords or to a recurrent laryngeal palsy.

Dysarthria or difficulty in articulation is common and persists in one in six children beyond the age of 5 years. It can result from weakness in the bulbar muscles due to a neuromuscular disease, or poor coordination, or abnormal tone due to pyramidal, extrapyramidal, or cerebellar involvement. Dysphagia commonly accompanies the dysarthria. In developmental verbal dyspraxia some children find the sequencing and fluency of bulbar muscles difficult to control as they do any other body musculature. It is rarely an isolated finding and is often seen in association with motor dyspraxia elsewhere, oculomotor dyspraxia, or other forms of learning difficulty.

DEFINITION OF LANGUAGE DISORDER SYNDROME

Neurological and speech therapy assessment will show whether the child's defect represents a developmental problem, determined perhaps by poor hearing or social disadvantage, which will show eventual catch-up or whether language development is deviant in some way. Although many combinations are possible the child's difficulties can be broadly placed within the following groups:

(A) Phonology

Many children in the early months and years of language acquisition demonstrate immature articulation or dyslalia: lispings, rhotism (w for r) and sigmatism ('yeth' for 'yes') are common examples of this. Where speech and language are deviant, initial consonant deletion is more common such as 'oat' for 'boat'.

(B) Lexical syntactic disorders

In the early acquisition of language children commonly make grammatical mistakes such as saying, 'me want ice cream', 'I eated my bread'. Where language is deviant there is

often a word finding difficulty with substitutions and neologisms. Grammatical rules, in particular the complex ones, are often misunderstood.

(C) Semantic disorder

This refers to a difficulty in understanding the meaning of language. In simple immaturity, children initially overextend the meaning of words such as all forms of transport being referred to as 'car'. In deviant semantic language disorder, word finding difficulties are common and the child may be confused by synonyms.

(D) Pragmatic language disorder

This results in the child being confused by everyday use of language in context. The immature child may demonstrate this by using impolite forms when asking for things and may have no insight into the use of sarcasm. In deviant forms of this disorder the child may not have the ability to respond to tone of voice; for example 'the door is open' said sternly may infer that the child should close it. The child merely acknowledges that the door is open and does not respond to the hint to close it.

For each type of language disorder, aetiology should be defined and a treatment plan drawn up. Most children with developmental language problems show catch-up by the time they are 5 or 6 whereas those who showed deviancy in their language development are more likely than not to retain some difficulty.

Trouble at school

Children who present with behaviour problems at school may be having difficulty with balance, coordination, or learning. This may act as a source of frustration when for the first time in their lives children are asked, after school entrance, to perform tasks not previously required of them. The association of poorly set out and untidy work with specific learning difficulties is a common one. Full assessment by an educational psychologist is indicated and remedial therapists may be able to offer useful advice to the child and family. This will include what tasks might usefully be pursued to encourage good proximal girdle muscle fixation and to facilitate the distal execution of fine motor skills; other tasks will improve body image and the sequencing of movement. Tangible success often leads children to feel an improvement in their self esteem which is commonly low in circumstances where they have previously been used to failure.

Physical examination

All children with learning difficulties should be examined for the presence of dysmorphism, signs of a neurocutaneous syndrome, or storage disorder. Dysmorphism probably arises from amplified instability of developmental processes within the fetus when crucial genetic material is either over or under represented.

Often similar features are seen in the general population but a particular pattern may strike the eye and lead to diagnosis. Computerised databases may facilitate this pattern recognition. Particular features may suggest specific brain abnormalities such as hypertelorism with agenesis of the corpus callosum. A relatively large head or one showing accelerating growth may reflect an underlying hydrocephalus, the fragile X syndrome, or a leucodystrophy.

Signs of a storage disorder include coarse facies, frontal bossing or other skeletal abnormality, visceromegaly, and cardiac murmurs. Skin manifestations of the neurocutaneous syndromes are diverse and not confined to the familiar cafe-au-lait patches in neurofibromatosis or the depigmentation, chagrin patches, adenoma sebaceum, and subungual fibromata of tuberose sclerosis. Any unusual skin mark is worthy of note and further reference bearing in mind they are often seen to best advantage under Wood's light.

Examination of the eye may reveal colobomata of the valproate syndrome, the cataracts of Lowe's syndrome, the dislocated lens of homocystinuria or a retinopathy of a mitochondrial cytopathy, peroxisomal disorder, or congenital infection. Small pale optic discs may reflect septo-optic dysplasia.

Critical analysis of the gait and identification of the motor control system dysfunction may lead to a specific line of investigation.

Special investigations

ABNORMAL BEHAVIOUR IN THE NEONATAL PERIOD

The presence of limb and axial hypotonia or arthrogryposis should lead to measurement of serum creatine kinase, electromyography, needle muscle biopsy, and nerve conduction velocity measurement.

Electron microscopy of muscle should be performed particularly when congenital myopathy is suspected. It must be remembered that the Prader-Willi syndrome may lead to persisting hypotonia and a karyotype should always be requested in this group with a particular search being made on chromosome 15q. The presence of dysmorphism should also lead to chromosome analysis.

If a neuronal migration problem is suspected magnetic resonance imaging offers exciting detail of underlying structural abnormalities that in turn will lead to growing understanding of the mechanisms and genetics involved. Our experience is that computed tomography carried out in district general hospitals in this respect often misses important detail either through the quality of the scans or the lack of neuroradiological opinion. Neuronal migration problems should be suspected when early ultrasound either antenatally or postnatally suggests underlying structural abnormality, or when there is a suggestive pattern of arthrogryposis or seizures.

When hypoxic-ischaemic encephalopathy has been ruled out the persistence of encephalopathy should lead to a full metabolic work up looking for the amino or organic

acidopathies and urea cycle defects, after excluding more common derangements of glucose homeostasis; urea and electrolytes and calcium and magnesium concentrations should also be measured.

DEVELOPMENTAL DELAY

Investigation of children with mild to moderate learning difficulty *alone* is rarely rewarding. Very occasionally patients with amino or organic acid abnormalities will be detected, but in retrospect there are often clues to their presence in the past medical history. Some disorders, such as homocystinuria, may present with developmental delay before the onset of more classic features of the disease make the diagnosis obvious. Mucopolysaccharidosis type III (Sanfilippo's syndrome) is associated with only mild somatic abnormalities and the earliest clinical presentation is usually with developmental delay alone, particularly speech delay.⁹ Later the characteristic behavioural abnormality with progressive loss of skills makes the diagnosis easier. Urine screening for amino acids and organic acids as well as glycosaminoglycans is therefore justified in these patients. Detailed lysosomal enzyme studies are not indicated in this group of patients.

Children with severe learning difficulties should certainly have a chromosome analysis and computed tomography and/or magnetic resonance imaging looking for neuronal migration problems as well as the metabolic investigations detailed above. Where clinical suspicion exists a search of the skin for depigmented patches and other signs of tuberose sclerosis is indicated.

'FUNNY WALKS'

A clinical suspicion of weakness should lead to the estimation of serum creatine kinase, electromyography, needle muscle biopsy, and nerve conduction velocity measurement. Pyramidal gait disturbance should lead to computed tomography, looking for abnormalities of white matter for underlying structural abnormality, blood pH and lactate looking for mitochondrial cytopathies, and arylsulphatase A to exclude metachromatic leucodystrophy. If clinical suspicion of a mitochondrial disorder persists despite a normal or near normal blood lactate, the concentration in the cerebrospinal fluid should be checked and a glucose load with serial estimation of lactates is indicated. Confirmed raised concentrations of lactate should be followed by formal measurement of respiratory chain enzyme activity in muscle and a screen for mitochondrial DNA mutations should also be performed on this tissue.

Extrapyramidal signs should lead to a search for a family history of Huntington's disease (spontaneous mutations are exceptionally rare), and copper and ceruloplasmin estimation for Wilson's disease. Mitochondrial cytopathies should be excluded (above) and neuroradiological investigation should search for caudate atrophy reflecting one of the named striatonigral degenerations. Nerve

conduction studies and echocardiography may reveal evidence of Friedreich's ataxia.

Cerebellar signs should lead to a neuro-radiological search for a structural abnormality of the cerebellum and the rare abetalipoproteinaemia. When seen in the presence of an oculomotor dyspraxia, ataxia telangiectasia, a DNA repair disorder should be considered and investigated with an estimation of α fetoprotein (raised in that condition), immunoglobulins (an immune paresis is common) and, if clinical suspicion is sustained, irradiation of white cells and analysis of DNA repair should be performed. Vitamin E deficiency, as a treatable cause should be excluded.

ABNORMAL LANGUAGE DEVELOPMENT

Investigation of this group of patients is rarely rewarding. DNA analysis for fragile X syndrome is justified particularly when the child shows autistic features. Where the language disorder is recently acquired then an electroencephalogram may support the diagnosis of the Landau-Kleffner syndrome.

ABNORMAL HEAD SIZE

A large head requires no investigation where there are no neurological signs and at least one parent has the same condition. It must be remembered that children with familial macrocephaly have the appearance of communicating hydrocephalus on their computed tomogram for the first year or so of life which later becomes normal¹⁰; this observation has led some parents to be given inappropriately gloomy information in the past where scans have been performed (inappropriately!) in this disorder.

In early infancy an ultrasound scan will rule out hydrocephalus and in the absence of other signs it may be worthwhile adopting a 'wait and see' policy and monitoring head growth. Computed tomography may reveal a leucodystrophy which in turn will lead to specific neurometabolic investigation. The phenotype in fragile X syndrome is broad. The investigation should be ordered in particular when there is a relatively large head in a child with below average height who has specific difficulties with language and communication. Macro-orchidism in this condition only occurs after puberty.

Microcephaly can be the end result of many neurometabolic disorders and it is important to remember maternal phenylketonuria as a potential cause. A congenital infection screen and review of the obstetric notes is indicated.

SYNDROMES OF DEVELOPMENTAL ARREST

Autism, Rett's syndrome, and the epileptic encephalopathies of childhood may all carry their own distinctive patterns on electroencephalography. When the clinical picture and electroencephalographic findings are typical of one of these syndromes no further metabolic investigation is warranted. Where neuro-

degeneration is suspected children need a full neurometabolic work-up including urine for oligosaccharide and glycosaminoglycan excretion, amino and organic acid analyses, and a white cell lysosomal enzyme screen. If these are normal and degeneration persists signs of abnormal storage should be sought on a tissue biopsy specimen. Skin, rectum, and conjunctiva have all been used to successfully demonstrate the abnormal process.

TROUBLE AT SCHOOL

It is rarely worthwhile carrying out any specific investigation in the 'clumsy child syndrome', as long as there is no suspicion of clinical deterioration. It is more appropriate to ask the remedial therapists and clinical psychology team for their appraisal of the child's educational strengths and weaknesses as a basis for further remediation. The clinician must be aware of other possibilities, however. The authors have known children with Duchenne muscular dystrophy and ataxia telangiectasia referred at the age of 5 with 'clumsiness' as the main feature.

Giving the news

A word must be said on how to impart investigation results to parents. When tests are complete and thoughts have been formulated on diagnosis a meeting with both parents should be arranged. At least one health authority has, on the basis of comments received, drawn up guidelines for this process.¹¹ Parents wish to receive the facts in a simple and honest way as soon as they are known. The format of this meeting should be to talk about causation, future outlook, and how best people in the child's life might help.

Where investigation has not revealed a cause it is still possible to outline for the parents the likely mechanism in many cases. These tend to be of prenatal origin where clearly some maturational process has fallen short of full development due to the genetic make-up of the child thus creating a brain which is inefficient in all or some of its computing capacity. They should know that genetic is not necessarily inherited genetic and they should receive advice on the relative likelihood of each possibility from the appropriate person.

Parents need to know what the most likely result of the learning difficulty on the child's life is likely to be as soon as possible. This helps their psychological adjustment to the problem and the resolution of their attendant grief. Once they are through that phase they are in a better position to face anything that life brings. It is not helpful to them to hear 'Only time will tell'. Certainly by the age of 10 months or so developmental quotients take on some predictive quality and albeit with very broad confidence intervals it is possible to predict whether a child is likely to have mild to moderate or severe learning difficulties. It is appropriate to state that there is a chance that predictions at that stage may over or

underestimate future ability but at least the parents are being helped to adjust to the most likely outcome.

Parents should be encouraged to have confidence in their own ability as teachers. Research suggests that a few moments each day of good quality play has as much impact on learning as many hours of intensive coaching.¹² It is the role of therapists to suggest to parents and teachers strategies that might be included in play or the curriculum to encourage the next step in the child's development.

A second meeting ought to be called soon after the first in order to answer the many questions that will flood into the parent's minds at this time. Information should be given in a balanced way, being neither too negative nor too positive and for at least part of the consultation the child ought to be present to show how she or he is valued. Failure to follow these guidelines often results in families harbouring resentment towards the messenger and permanent damage to the doctor/patient relationship. The value of the investigations may then be lost forever.

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