Assessment and investigation of the child with disordered development

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ABSTRACT
Every paediatrician, generalist or specialist, at every level and in every setting will come across the child or young person with disordered development and has a duty of care to ensure that appropriate assessment and investigations are undertaken, if each individual is to be given the best possible opportunities to achieve the highest possible level of participation and enjoy the best possible quality of life. Using a structured approach, all paediatricians have the potential to make a significant positive difference and should seek every opportunity to do so, even if seeing the child for an entirely different reason. Key messages of this article include: (1) each child is unique and requires careful, individual, clinical assessment and thought before any investigations are undertaken; (2) there is no single list of appropriate tests to be done for all children with disordered development; (3) the clinical judgement of the experienced clinician (expert triage) is more helpful than ‘guidelines’ in deciding which investigations to do; (4) clinical networking with colleagues in paediatric neurodisability, neurology, clinical genetics, metabolic paediatrics, and so on, is essential to achieve the highest possible yield from investigations and to reduce the number, discomfort and expense of inappropriate investigations; (5) the more effort and thought that goes into formulating differential diagnoses, the more appropriate the investigations are likely to be and the higher the likely diagnostic hit rate. Diagnostic hit rates up to 80% have been reported in the literature for those with severe learning disabilities and this is likely to be even higher once microarray comparative genomic hybridisation becomes more widely available.

INTRODUCTION
Up to 1% of the UK child population have an autism spectrum disorder, 1–2% a mild learning disability (The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) mental retardation, IQ 50–70), 0.3–0.5% a severe learning disability (ICD-10 mental retardation, IQ<50), while 5–10% have a specific learning disability in a single domain.1–4 Disorders of development are common. Baird’s population based study looking for children with less educated parents.4 If we are to move towards greater equity in diagnoses, access to services and outcome opportunities, then in addition to developing expert neurodisability and neurology services for children and young people across the UK, all paediatricians in every setting should be on the alert to indicators of concern in the domain of child development and know when to extend assessment and when to refer on for more expert assessments.

WHY BOTHER?
It is always important to stop and consider the goals and objectives of clinical practice; for the child or young person with disordered development, these include:

Identification of aetiological factors
► If their child is ‘different’, parents are always keen to know why this is so.
► In the absence of any other explanation, parents, especially mothers, blame themselves for their child’s predicament (‘Was it something I did (or didn’t do) when I was pregnant?’ ‘Is it how I am bringing up my child?’).

Making diagnoses, that
► Inform likely functional impact and prognosis.
► Allow accurate genetic counselling about recurrence risks and impact for future generations. Parents of children with disordered development can be too worried to embark on further pregnancies because of uncertainty. Knowledge of definitive diagnoses and the option of prenatal testing can empower them to take informed decisions about having further children.
► Open doors to more appropriate support, early interventions, educational and vocational opportunities.
► Stop further intrusive and possibly painful investigations.

Identification and management of secondary disabilities
► Careful definition of secondary disabilities brings a real chance to make a positive difference, as correct management can alleviate symptoms, for example, epilepsy, gastrooesophageal reflux, drooling, constipation, spasticity, pain, postural deformities, dental problems, behavioural and sleep difficulties, growth and endocrine disorders, and so on.

Offering support and signposting to information and services
► When development is confirmed as disordered, irrespective of whether or not a
specific diagnosis is made, parents want to know: ‘what can be done about it?’ The clinician must arrange a coordinated package of appropriate multidisciplinary support, preferably with an identified key worker or care coordinator, to act as the main link for the family. Once significant developmental difficulties have been identified, timely referrals to colleagues in education, including educational psychology, to maximise opportunities to develop appropriate multidisciplinary care plans in time for transition to nursery and school, as well as to disabled children’s social care teams, to optimise support, should be made.

- It is important to empower parents to ‘remain in charge’ at all times; if multiple on referrals are required, as is often the case in more complex cases, parents need to be given permission to protect some personal time for themselves in the week, to avoid the feeling that their homes turn into highways for professionals or that they come to live ‘in a goldfish bowl’. Although some clinic appointments will need to be on fixed days, regular therapy appointments can be arranged in such a way so as to respect the need for family privacy.

- Parents can be overwhelmed by the wealth of unfiltered information now available on the internet; others may have no computer or internet access. Contact-a-family produce a helpful leaflet for parents about accessing and assessing information available over the internet, available to download free at http://www.cafamily.org.uk/pdfs/about_diagnosis_part9.pdf. Contact-a-Family (http://www.cafamily.org.uk) is an excellent source of information about specific conditions both for parents and professionals and together with the Council for Disabled Children (http://www.ncb.org.uk/cdc) Family Fund (http://www.familyfund.org.uk) and Directgov (http://www.direct.gov.uk/en/DisabledPeople) all offer great signposting facilities for a wide range of resources and benefits that families can avail themselves of. The individual family’s key worker should ensure that they can easily access the information required in a timely and appropriate way.

Prerequisites for paediatric assessment of the child with disordered development

- Competence in detailed clinical assessment.
- A working knowledge of the broadly normal range of child development and common ‘variations’.
- Access to all relevant case notes, reports and assessments that have been done to date; a clinician cannot assess a child fully without these, which may contain vital diagnostic information. For example: the disabled child in special school referred at 3 years for ongoing management’ had a report in the case notes from the Ophthalmologist, documenting ‘upwards dislocated lenses’, which proved to be the vital clue to the diagnosis of molybdenum cofactor deficiency, a rare neurodegenerative disorder, with significant implications for the family in terms of outlook and the potential for future prenatal testing.

- An appropriate, accessible environment in which to assess the child, including standardised equipment and support to accurately weight, measure and assess nutritional status, with a range of growth charts available.

- Access to facilities for investigations, including biochemical, haematological, neurometabolic, immunological, radiological, and so on.

- Knowledge of clinical networks and experts with whom to discuss, or to whom to refer for further assessment and investigation, including neurodisability, neurology, neurophysiology, clinical genetics, metabolic paediatrics, endocrinology, child psychiatry, physiotherapy, speech and language therapy (feeding, swallowing, dysphagia, communication, social communication), occupational therapy, dietetics, specialist teachers, and so on.

A STRUCTURED APPROACH TO THE PAEDIATRIC ASSESSMENT OF THE CHILD WITH DISORDERED DEVELOPMENT

Clinical assessment

For children and young people where development is potentially disordered, this comprises:

- History
- Physical examination
- Developmental assessment
- Assessment for behavioural syndromes or phenotypes
- Differential diagnosis or formulation, including identification of secondary disabilities
- Targeted tests

HISTORY

History taking is the cornerstone of all paediatric assessment, especially so for the child with disordered development, bringing the highest likely yield by way of clues or diagnostic ‘handles’ to inform the process of formulation.

Most mothers know intuitively from very early on if all is not as it should be with their child, but it sometimes takes a while for them to be ‘heard’ by professionals. Some parents are reluctant to accept their child’s differentness or difficulties and need sensitive explanation as to why expert assessment is necessary and the likely benefits for the child.

There is a wealth of published literature to guide history taking and examination where a child or young person has disordered development. The author’s own practice over 17 years of working with children and young people with potential and established disordered
development and disabilities is to use a ‘background information sheet’ to underpin clinical assessment, separate versions being available for preschool and school-aged children (available from http://adc.bmj.com/). This is sent to parents or carers for all new patients, with a request to complete and bring to the consultation, but can also be helpful for opportunistic use by non-specialist clinicians, when it becomes clear during the course of a consultation for a different reason that development may be disordered. Each includes space for basic demographic details, referrer information and reason for referral, with separate sections to record parents’ concerns and their expectations of the assessment; as these are often different from those of the referring professional and knowledge of this can be helpful. Prompts for detailed past history, family and developmental history and profile of current functioning are included. Most parents complete these, even when they have learning difficulties themselves. The quality of information afforded is usually far greater than could be gleaned during a consultation alone; for example, parental observations of the child’s play, functioning and behaviours, information about complex family structure, dynamics or recent bereavements, that can all add value to the clinician’s assessment. Consultation time can then be used more efficiently, noting but moving quickly on where there are no concerns, focusing and expanding as need be where issues are identified.

Key issues in history taking

► Keep a broad view and open mind throughout and beware rushing to conclusions before the breadth and depth of information is available, or potential ‘handles’ to diagnosis may be missed.

► Be mindful that the baby who runs into difficulties at birth may do so because of innate factors that may be genetically determined or due to an insult in utero, rather than perinatal events being the root cause of their developmental difficulties.

► Substantiate parental reporting of neonatal or past history from contemporaneous case notes or discharge summaries where possible.

► Documenting and reflecting upon the child’s medical and developmental journey to date may highlight recognisable patterns of significance.

► In addition to detailed enquiries about the child, it is helpful to learn about parents, siblings and grandparents and any developmental or health issues that have affected them and to maintain broad powers of observation during the consultation. A young woman referred for assessment of a mild hemiplegia, was accompanied by her father, who used a walking stick. On discreter enquiry it came to light that he had a limp since childhood and had never had the benefit of expert neurological assessment. In tandem with investigating his daughter, he was empowered to seek referral to a neurologist. Subsequently assessment in the regional neurogenetics clinic revealed that both had the same, genetically determined, autosomal dominantly inherited developmental brain anomaly, with focal polymicrogyria, clinically manifest as a hemiplegia. Hopefully with foresight, many children the young woman has herself in future will have the best chance of early appropriate intervention and support now that a precise diagnosis has been made.

► Asking if anyone in the family went to special school or needed extra help in school can be more revealing than direct enquiry about a learning disability, which parents may not perceive themselves to have.

► Enquiry about family and other support currently available is essential in gaining a full picture of the resources available for the child and family and may also shed light on the child’s current predicament; the child who has hardly been played with, has no experience of a range of toys or has had no opportunity to date to play with other children in a social setting may suddenly blossom and present quite differently once they have access to a nursery.

► It is vital, no matter how busy the clinic or ward round, to be constantly alert for safeguarding issues and to be quick, in cases of uncertainty, to link with the named or designated paediatrician for advice to inform further expert assessments and multiagency enquiries and avoid scapegoating. Reflection on the predicament of the paediatrician in the case of baby Peter is salutary. There but for the grace of God.

► Enquiries about housing should be sensitive, along the lines of ‘we can sometimes help if there are issues’; a supporting letter from the paediatrician to a housing provider (include parent/s names) can make all the difference in improving the environment for a child and family living in difficult circumstances and have a positive impact on their outcome.

► Open questions about how the child plays can be most revealing, supplemented with more direct enquiries as to exactly what the child does and how they play with their toys, or what their range, or restriction, in interests is. Having a limited range of toys in the clinic room can facilitate direct observation of the child’s spontaneous play while the history is being taken.

► Specific enquiries about a range of developmental domains should then be made, including movements and posture, hand function and personal care, vision, hearing, communication, feeding, social communication and relationships, behaviour, cognition and sleep, recording any concerns and formal assessments done to date in each

domain. Specific enquiries about any rituals, reliance on routines, stereotypies and mannerisms, pointing to share interest and how the child responds if a parent is hurt or upset may reveal clues to a possible autism spectrum disorder.

- It is always important to allow parents to celebrate their child’s positive attributes, strengths and achievements, regardless of their level of functioning and to avoid a long list of all the things they cannot do, which can otherwise be very disempowering.

- Finishing the history with open questions such as ‘is there anything else you think might be important, that I have not asked you about’ may reveal missing vital information about family circumstances, resilience and resources as well as potential clues to diagnoses.

### PHYSICAL EXAMINATION

- Ascertainment of height, weight and head circumference percentiles are essential, with reference to trends over time in the child’s Personal Health Record (ask in the appointment letter for this to be brought to the consultation). Overgrowth, short stature, faltering growth, early or delayed puberty can all be important diagnostic handles, as can very large or very small head size, remembering that head growth reflects brain growth. Those with significant variations in usual growth or pubertal development patterns should be promptly discussed with/referred to a paediatric endocrinologist for further expert assessment and investigation.

- Taking a step back and considering the overall gestalt of the child or young person may facilitate pattern recognition and guide systemic investigations.

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**Box 1 Red flags for important groups of disorders**

- **Metabolic disorders:**
  - Parental consanguinity.
  - Family history of unexplained illness or death in childhood.
  - Unexplained, progressive or intermittent symptoms.
  - Symptom free interval.
  - Slowing of developmental skill acquisition.
  - Loss of skills.
  - Evidence of encephalopathy.
  - Specific phenotype.
  - Coarse facial features.
  - Organomegaly.

As the late Robert Surtees, Professor of Paediatric Neurology at Great Ormond Street Children’s Hospital, taught: ‘there is no such thing as a metabolic screen’; if signs and symptoms suggest a metabolic disorder, discuss with/refer to paediatric neurodisability, neurology, metabolic paediatrics, clinical genetics etc to plan appropriate investigations tailored to the individual child, which may include tests on blood, urine, cerebrospinal fluid, skin, muscle, bone marrow, liver, brain etc.

Support information: http://www.climb.org.uk

- **Neuromuscular disorders:**
  - Reduced foetal movements.
  - Early feeding difficulties.
  - Hypotonia/floppy infant.
  - Late motor milestones (especially if male and not walking by 18 months).
  - ‘Slips through hands’ when picked up.
  - Head lag when pulled to sit.
  - Depressed or absent deep tendon reflexes.
  - Partial or complete Gower’s manoeuvre.
  - Unable to jump by 3 years or hop by 5 years.
  - Waddles when attempting to run.

Check creatine kinase and refer for specialist clinical assessment as per local care pathway (paediatric neurodisability, neurology, muscle team etc).

Support information: http://www.muscular-dystrophy.org

- **Autism spectrum disorders:**
  - Does not point to share interest or attention.
  - Does not initiate interaction.
  - Qualitatively unusual eye contact and/or use of gesture.
  - Does not show appropriate empathy or concern if others hurt or upset.
  - Marked insistence on sameness.
  - Paucity of creative, spontaneous imaginative play.

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Continued
examination; red flags of some patterns are listed in boxes 1 and 2, but these are by no means exhaustive; the more patterns the clinician can learn to recognise, the greater the likely diagnostic accuracy and impact.

Careful surface examination should be made for birthmarks (it saves time to ask parents if they have noticed any), changes in pigmentation (using Woods light in a dark room is most revealing) and dysmorphic features, remembering to take care to ensure that parents understand that the clinician is not being critical or derogatory. Sometimes it can help, while looking at the child, to enquire as to whom in the family the child looks like, but beware the complex family structure that may not be as it first appears...

Detailed systemic examination should include: ears, nose and throat, cardiac, respiratory, abdominal, genitalia (including pubertal status), musculoskeletal, as well as detailed neurological examination (cranial nerves including fundoscopy, eye, face, tongue and palatal movements, visual fields where possible, axial, proximal and distal muscle bulk, tone, power and deep tendon reflexes, planar reflexes, persistence of primitive reflexes, evidence of asymmetry or focal signs, tremor at rest or on reaching etc). The spine should be checked for curvature, dimples or the tell-tale hairy patch with birthmark suggestive of underlying spinal dysraphism; gait, where appropriate, is often best assessed in the corridor where there is adequate space to see how the child moves, their balance and coordination as well as evidence of ataxia.

Getting the child to sit in a space on the floor and show how they get up may reveal a partial or complete Gower’s manoeuvre, which should prompt re-examination for evidence of pseudohypertrophy, weakness and depressed deep tendon reflexes, as well as going back over the history for any pointers that would make exclusion of one of the muscular dystrophies mandatory.

The eyes, often considered to be the ‘window of the nervous system’, warrant special assessment of structure, movements and function, with urgent on referral if indicated to a paediatric ophthalmologist for further detailed assessment and to specialist teaching services for the visually impaired to provide early intervention. Cloudy corneas, cataracts, lens dislocation, presence of Lisch nodules, Kayser-Fleisher rings, retinal pigmentation or retinopathy, pale or hypoplastic optic discs,
<table>
<thead>
<tr>
<th>Box 2</th>
<th>Red flags for patterns of some specific conditions that all paediatricians are likely to come across and therefore need to be able to recognise and conditions that although rare, can be treated</th>
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<tr>
<td><strong>Down’s syndrome (trisomy 21)</strong>&lt;sup&gt;12&lt;/sup&gt;:</td>
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- Hypotonia.  
- Typical facial appearance: upslanting palpebral fissures, epicanthic folds, flat facial profile, brachycephaly with patent posterior fontanelle, short nose with depressed nasal bridge, small ears.  
- Single palmar creases and sandal gap between first and second toes.  
- Congenital heart disease eg, perimembranous ventricular septal defect, patent ductus arteriosus, atrial septal defect, atroventricular septal defect.  
- Cognitive level: mild to severe learning disabilities.  
- Typical behavioural phenotype: relative strengths in visual processing, receptive language and non-verbal social functioning and relative weakness in gross motor and expressive language skills.  
- Typical secondary disabilities and associated conditions: hypothyroidism, Hirschpru̇ng’s syndrome, duodenal atresia, leukaemia, autism spectrum disorder.  
Support information: http://www.downs-syndrome.org.uk |
| **Prader Willi syndrome (chromosome 15 q11–13 deleted or not expressed)**<sup>12</sup>: |  
- Central hypotonia and feeding difficulties (may need early tube feeding) with failure to thrive in infancy.  
- Typical facial appearance: almond shaped eyes, narrow forehead, down turned mouth, triangular shaped upper lip.  
- Cognitive level: low normal to moderate learning disabilities, often with strengths in jigsaws, word finding puzzles, drawing, colouring and sewing.  
- Rapid weight gain between 1 and 6 years: truncal obesity with strikingly fat limbs.  
- Small hands and feet.  
- Short stature.  
- Typical behavioural phenotype: ritualistic behaviours, aspects of autism, temper outbursts, stubbornness, argumentativeness, repeating questions and topics, obsessive compulsive behaviour, skin picking and spot picking, lying and blame shifting, sleep disorders, insatiable appetite with food seeking/hoarding.  
- Typical secondary disabilities: small genitalia in males, prone to diabetes mellitus, hypogonadotrophic hypogonadism in males and females, scoliosis.  
Support information: http://www.pwsa.co.uk |
| **Angelman syndrome (defects in maternally derived imprinting domain on 15q11.13)**<sup>12</sup>: |  
- Severely disordered development with profound speech impairment (most acquire no speech, or 3–4 words at most, receptive and non-verbal skills significantly better than expressive; most use gesture to communicate and some use sign language).  
- Typical facial appearance: wide, smiling mouth, prominent chin, deep set eyes.  
- Movement and balance disorder: ataxic and wide based, stiff legged gait, often with arms held with elbows bent and hands up at shoulder level.  
- Specific behavioural phenotype: excitable personality and inappropriately happy affect, with inappropriate laughter, hand flapping when excited, sociable and inquisitive, love of water and fascination with reflections, sleep disorder.  
- Microcephaly.  
- Hypopigmentation.  
- Typical secondary disabilities: seizures especially atypical absences, tonic and atonic, disordered sleep, behavioural disorders.  
Support information: http://www.angelmanuk.org |
| **22q11 deletion syndrome (has also been called Di George syndrome, Velocardiofacial syndrome, Shprintzen’s syndrome, ‘CATCH-22’)**<sup>12</sup>: |  
- Learning disabilities (range mild to severe; delayed speech milestones, specific difficulties with abstract reasoning and poor problem-solving skills in school aged child.  
- Typical facial appearance: short palpebral fissures with telecanthus, wide and prominent nasal bridge and root, squashed nasal tip, small mouth, ears round in shape with deficient upper helices.  
- Congenital heart disease (eg, especially tetralogy of Fallot, ventricular septal defect, interrupted aortic arch etc).  
- Cleft palate, submucous cleft palate, velopharyngeal insufficiency, bifen uvula, hypernasal speech.  
- Short stature.  
- Pachygryia, polymicrogyria (especially bilateral perisylvian polymicrogyria).  
- Family history of any of the above, marked intrafamilial variability in expression; family history of psychiatric disorder (including bipolar affective disorder and schizophrenia).  
- Typical secondary disabilities and associated medical complications: early feeding difficulties (eg, mild regurgitation through nose); hypocalcaemia, especially neonatal (may be associated with seizures); frequent infections (may have impaired cell-mediated immunity especially under 2 years); mild thrombocytopenia; autoimmune disorder (eg, haemolytic anaemia, type 1 diabetes mellitus, hypothyroidism-Graves disease); chronic serious otitis media; sensorineural hearing loss; structural renal tract anomalies.  
Support information: http://www.maxappeal.org.uk |
Box 2 Continued

- **Williams syndrome (del 7q11.23)**:
  - Variable learning disabilities (range low-average to severe, strengths in language but poor visuospatial skills).
  - Characteristic facial features in young child: periorbital fullness, bulbous nasal tip, long philtrum, flattened nasal bridge, wide mouth, full lips, full cheeks, small, widely spaced teeth,stellate irises.
  - Characteristic appearance in older children and adults: more gaunt appearance with coarser facial features.
  - Congenital heart disease (supravalvar aortic stenosis in 75%, supravalvar pulmonary stenosis in 25%, peripheral pulmonary stenosis in 50–75% that improves with time).
  - Hyperacusis and phonophobia, but may love music and have ‘perfect pitch’.
  - Typical behavioural phenotype: overfriendly personality, ‘cocktail party chatter’, short attention span, high distractibility, anxiety, hyperfocus on eyes of others in social exchanges, obsessional interests, fear of heights, open space and uneven surfaces, emotional immaturity with overreaction to events, exaggerated displays of fear, excitement, sadness, happiness etc.
  - Typical secondary disabilities and medical complications: hypercalcaemia, especially neonatal (15%); renal artery stenosis (40%).

Support information: [http://www.williams-syndrome.org.uk](http://www.williams-syndrome.org.uk)

- **Rett syndrome, MECP2 mutations, deletions or duplications**:
  - **Girls**
    - Relatively normal early development.
    - Normal head circumference at birth with deceleration in head growth.
    - Loss of skills, especially communication and speech.
    - Gait/trunkal apraxia/dyspraxia.
    - Small, cold feet.
    - Stereotyped motor mannerisms eg, hand flapping, complex whole body movements etc.
    - Typical behavioural phenotype: stereotypic hand movements eg, wringing or flapping; social withdrawal during phase of regression, later: alert and interested in the world, but little or no speech; aspects of autism; spontaneous outbursts of laughing or crying, including in sleep; reduced response to pain; disturbed sleep/wake cycle; teeth grinding.
  - **Boys**
    - Neonatal encephalopathy.
    - Early apnoeas.
    - Typical facial appearance (not universal): brachycephaly, midfacial hypoplasia, large ears, flat nasal bridge.
    - Hypotonia.
    - Delayed motor milestones with progressive spasticity predominantly in lower limbs.
    - Learning disability with limited or absent speech, relatively better receptive language, inquisitive.
    - Fall off in head growth.
    - Typical behavioural phenotype: stereotypical movements of hands; aspects of autism; teeth grinding.
    - Typical secondary disabilities and medical complications: recurrent and increasing respiratory infections; ataxia; escalating epileptic encephalopathy and unusual, autonomic attacks (irregularities of breathing, heart rate and temperature with episodic flushing and pale).

Support information: [http://www.rettsyndrome.org.uk](http://www.rettsyndrome.org.uk)

- **Biotinidase deficiency (rare, treatable with biotin)**:
  - Range of learning disabilities, developmental regression.
  - Perioral rash.
  - Alopecia with pale hair.
  - Progressive lethargy with hypotonia and ataxia following intercurrent infections.
  - Lactic acidosis associated with specific organic aciduria.
  - Typical secondary disabilities and medical complications: epilepsy with tonic-clonic or myoclonic seizures refractory to anticonvulsant treatment; retinal impairment, optic atrophy, abnormal visual evoked potentials; sensorineural hearing loss; various acquired neurological deficits (cerebrum, brain stem, cord including progressive spastic paraparesis); respiratory problems with recurrent infections, unexplained episodes of tachypnoea or recurrent stridor can mimic Leigh syndrome.

Support information: [http://www.climb.org.uk](http://www.climb.org.uk)

- **Glucose transporter 1 (GLUT1) deficiency (rare, usually responds to ketogenic diet)**:
  - Learning disability/disordered development often with significantly delayed/disordered speech.
  - Early onset epileptic seizures (generalised tonic or clonic, myoclonic, atypical absences, atonic unclassified): may be resistant to treatment with anticonvulsants.
  - Apnoeas and abnormal eye movements may predate seizures by several months.
  - Hypotonia.
  - Movement disorder, spasticity, ataxia (especially intermittent), dysarthria, paroxysmal exertional dyskinesia.
  - Normal head size at birth, but subsequent slowing of growth, may lead to microcephaly.
  - Lethargy, headaches, myoclonus, involuntary, irregular eye movements, especially before meals.

Check: cerebrospinal fluid (CSF)/blood glucose ratio after a 4–6 h fast. In GLUT1 deficiency the CSF/blood glucose ratio has a mean of 0.35 (range 0.19–0.49) and the lactate is always normal or low.

Support information: [http://www.climb.org.uk](http://www.climb.org.uk)
Best practice

- ‘Walk’ other than on tip toes.
- Sit unsupported by 12 months.
- Lost developmental skills at any age.
- Point at objects to share interest with others by 2 years.
- Hold object placed in hand by 5 months of age (corrected for gestation).
- Head circumference above the 99.6th percentile, below 0.4th percentile.
- Suspected clinical diagnosis of cerebral palsy.
- No speech by 18 months, especially if does not attempt to communicate.
- Complex disabilities.
- Dysconjugate eye movements, vertical gaze palsy, saccade initiation failure, nystagmus, squint, and so on, might each be the vital clue required to clinch a diagnosis, while correct identification of failure to fix and follow or absent optokinetic nystagmus may warn of significant impairment of visual functioning.

Hearing should also be assessed in any child with disordered development, using testing techniques appropriate to developmental level, linking with audiology and Ear, Nose and Throat teams as appropriate.

DEVELOPMENTAL ASSESSMENT

A clinician may make their own eclectic assessment, based on clinical experience and knowledge of the broadly normal range of child development (box 3 contains some ‘red flags’ for significantly disordered development) or choose to use one of the standardised tools for developmental assessment. The author prefers the former, referring on to colleagues in clinical or educational psychology or neuropsychology as need be for more detailed cognitive assessments, as these experts have a far wider range of tools available to them, as well as the competence and time to accurately administer them. The paediatrician should ensure that the clinical aspects of assessment (taking a thorough history and examining the child systematically) are not neglected in order to fit in formal cognitive or other standardised assessments in the time available, otherwise there is the risk of missing important diagnostic clues that might not be picked up by non-medical members of the team. Avoid using the term ‘developmental delay’, which to parents implies that there will be ‘catch up’ in time, unless it is clear that catch up will indeed be achieved. It is clearer for parents and others to speak of ‘disordered development’ and, as soon as appropriate cognitive assessments have been undertaken, ‘learning disability’.

ASSESSMENT OF BEHAVIOURAL SYNDROMES AND PHENOTYPES

Clinicians should be familiar with red flags for common behavioural presentations for which there might not be a ‘test’ and information should be gathered from other expert observers including teachers and therapists about how the child presents in other settings such as school, nursery and home, to augment the clinician’s own observations in clinic. Some examples of behavioural phenotypes are included in box 2.

TIME AND PATTERN RECOGNITION

It is helpful to review the child with significantly disordered development but without a specific underlying diagnosis over time, documenting their progress and emerging phenotype. Some children grow into the typical features of their condition; for example: the child with difficulties with aspects of learning, increasing challenging behaviours who has always been big for age, develops bitemporal balding and the facial gestalt that gives the clues required to make a diagnosis of Sotos syndrome.

Always be alert for the developmental trajectories that might herald neurodegenerative disorders, remembering that in children these are likely to present initially with slowing of developmental skill acquisition, while the more easy to spot loss of skills, as seen in adults, occurs relatively later. The graphs of the late Dr Stuart Green, Paediatric Neurologist in Birmingham, are extremely useful aide memoirs that have prompted diagnosis of numerous neurodegenerative disorders that otherwise might have been missed (see figure 1). Those children who never acquire many developmental skills in the first place need careful consideration also, as neurodegenerative disorders may otherwise be missed in this group (figure 1, purple pathway).

Capturing the child’s gestalt in clinical photographs or videos of patterns of movement of behaviour can speed up the process of seeking further expert opinions, but should always be underpinned by informed consent from those with parental responsibility. Other than in a life and death situation where ‘best interests’ rules apply, seeking consent from whoever has parental

Box 3 Red flags that suggest development is significantly disordered and requires prompt assessment by the most expert clinician available in neurodisability, neurology, clinical genetics etc as appropriate, depending on local networks

- Any child who has:
  - Lost developmental skills at any age.
  - Parental/professional concerns about vision, fixing or following or a confirmed visual impairment at any age (simultaneous referral to Paediatric Ophthalmology).
  - Significant hearing loss at any age (simultaneous referral for expert audiological/ENT assessment).
  - No speech by 18 months, especially if does not attempt to communicate by any other means eg, gesture (simultaneous referral for urgent hearing test).
  - Suspected clinical diagnosis of cerebral palsy.
  - Complex disabilities.
  - Head circumference above the 99.6th percentile, below 0.4th percentile or that has crossed two percentile lines upwards or downwards on the appropriate chart, or is significantly disproportionate to parental head circumference.
  - An assessing clinician who is uncertain about any aspect of assessment, but thinks development may be disordered.

- Or any child who is not able to:
  - Sit unsupported by 12 months.
  - Walk by 18 months (boys) or 2 years (girls) (check creatine kinase urgently).
  - ‘Walk’ other than on tip toes.
  - Run by 2½ years.
  - Hold object placed in hand by 5 months of age (corrected for gestation).
  - Reach for objects by 6 months of age (corrected for gestation).
  - Point at objects to share interest with others by 2 years.

It may be useful to share these red flags with colleagues in primary healthcare, children’s centres, nurseries etc.
The broadly normal range (yellow lines)
Mild learning disability (IQ 50–70)
Severe learning disability (IQ 20–50)
Profound learning disability (IQ<20)

Figure 1 Trajectories of development: acquisition of new skills against age. Neurodegenerative disorders (green, red and purple lines).


http://www.simulconsult.com is a growing tool specific to neurological and developmental disorders and can support and focus the clinician’s thinking, while http://www.childneuro.org.uk signposts to other resources.

If available (they are expensive) the London dysmorphology and neurogenetics databases (http://www.lmdatabases.com) or http://www.possum.net.au can again support thinking, but beware entering too broad a remit, otherwise these tools will turn out a list of 123 possible causes, each with their own specific and expensive test.

Where a child or young person is losing skills, remember in the UK to notify to the British Paediatric Surveillance Unit’s Progressive Intellectual and Neurological Deterioration Study, as each notified case is carefully considered by a ‘think tank’ of international experts in paediatric neurology, from whom feedback with suggestions for further diagnoses and investigation to consider can be extremely useful (http://www.inopsu.com/bpsu/studies/PIND/index.html).

If in doubt, ‘phone a friend’. Do not embark ‘blind’ on a long list of tests. A brief discussion with a colleague in neurodisability, neurology, genetics or metabolic paediatrics can help the diagnostic formulation process no end and saves the child from unnecessary, intrusive and expensive investigations.

In a number of cases, sending the child or young person for a further expert clinical opinion serves them best of all, whether this is to the local expert in neurodisability or a regional or national colleague. No clinician can be an expert in everything and the local expert may not be expert in what is required for the patient in question; sometimes an ‘outside’ view can bring the new perspective required to make a diagnosis or to go down avenues of investigation that have not previously been considered.

If there is already a diagnostic label, seek supporting evidence; undiagnosis can be just as important, although usually much more difficult to manage. For example: the young man in special school with a label of William’s syndrome, when reassessed, had none of the usual expected clinical features to support this diagnosis. His mother was the chair of the regional William’s syndrome support group. She was keen for him to have his diagnosis ‘confirmed’ with the fluorescent in situ hybridisation test, but in fact this achieved the opposite. Moving from the definite to uncertainty was extremely difficult, but it would have been a huge disservice to the young man to have ‘gone along’ with the incorrect diagnosis, as the prognosis and thus the care plan, changed completely.
When considering diagnosis, one should really be considering diagnoses and multi-axial diagnosis. Defining the secondary or associated disabilities that relate to the primary diagnosis can be just as important and actually make more positive difference, if correctly managed, to the participation and quality of life of the individual. For example:

- **Complex disability regardless of primary aetiology**: secondary disabilities can be significant and include the epilepsies, gastro-oesophageal reflux, constipation, postural deformities, spasticity, dystonia, movement disorders, pain, bladder problems, infections, osteopenia leading to fractures, drooling, behavioural and sleep disorders, sensory impairments, growth and endocrine disorders, and so on, all of which need to be carefully looked for, then correctly managed if quality of life is to be improved.

- **Autism spectrum disorders**: it is really important not to stop thinking about other co-existing diagnostic possibilities, because many syndromic and non-syndromic conditions that have a genetic basis may present with aspects of autism that at times are sufficient to meet ICD-10, Diagnostic and Statistical Manual, Fourth Edition or Autism Diagnostic Observation Schedule diagnostic thresholds. Associated secondary disabilities with autism spectrum disorders might include epilepsies, anxiety disorder, catatonia, depression especially in the teenage years, eating disorders, and so on.

### THE TESTS

Rigorous clinical assessment and formulation should precede any investigations. Don’t forget expert assessments of vision and hearing.

**Appropriate and individually justified investigations tailored to the individual** should be undertaken, providing as much clinical information as possible with each request, to maximise diagnostic hit rate. Check with laboratory staff in advance about any unusual investigations, as some need special arrangements for example sample to be transported to lab on ice, special lab arrangements required or sample needs to be sent to distant centre, so needs taking early in the week to ensure arrival in a timely way to still be suitable.

If in any doubt about whether to investigate or which tests to do, discuss with/refer to an expert

### Box 4 Some considerations and red flags for investigations

**First line investigations for children and young people with disordered development ± dysmorphism might include:**

- Full blood count, blood film, ferritin.
- Urea, creatinine, electrolytes, bone chemistry, liver function, creatine kinase.
- Thyroid function (thyroid stimulating hormone, thyroxine (free T4), free T3).
- Uric acid (reduced in the molybdenum cofactor deficiencies, raised in Lesch Nyhan syndrome (boys)), Biotinidase, lead.
- Chromosome karyotype (microarray comparative genomic hybridisation if available, as very much higher detection rates, picking up microdeletions and microduplications in up to 15% of children with learning disability, dysmorphism, growth retardation and microcephaly who were previously undiagnosed).
- DNA for fragile X and to save.
- If phenotype recognised, request appropriate specific test eg, fluorescent in situ hybridisation, specific mutation analysis, irradiation for chromosomal breakages etc.

Further investigations as clinically indicated, depending on diagnostic hypotheses. Discuss with/refer to paediatric neurodisability, neurology, metabolic paediatrics, clinical genetics etc.

**Red flags for consideration of specific investigations:**

- **Neuroimaging (any age).** MRI is more sensitive and specific, unless looking for calcification, in which case CT is preferred.

Check who is reporting the scan; **if in doubt seek expert neuroradiology opinion.**

Undertake neuroimaging of brain ± spine, unless there is a very good reason not to *(if in doubt, discuss with Paediatric Neurologist)*, in all cases of disordered development plus:

- Focal neurological signs.
- Clinical diagnosis of cerebral palsy, including hemiplegia (if imaging NORMAL, refer to Paediatric Neurology to consider alternative diagnosis, eg, one of the dystonias).
- Clinical diagnosis of stroke or suspected vascular malformation.
- Focal seizures (except clinical diagnosis of Rolanic epilepsy with centrotemporal spikes on EEG or other ‘benign’ epilepsy syndromes, as per the National Institute for Clinical Excellence guidance).13
- Infantile spasms or myoclonic seizures in first year of life.
- Persisting, unclassifiable seizures.
- Unexplained seizure relapse after initial good control.
- Endocrinopathy, eg, delayed or precocious puberty, biochemical evidence of pituitary dysfunction etc.
Box 4 Continued

- Significant microcephaly or macrocephaly.
- Head circumference crossing percentiles in either direction.
- Unexplained dysmorphism, comparative genomic hybridisation microarray normal.
- Neurocutaneous stigmata (unless clinical diagnosis of neurofibromatosis type 1 with no neurological signs).
- Arthrogryposis.
- Ataxia.
- Loss of skills.
- Psychosis.
- Catatonia.
- Confusional state without apparent cause (remember to consider drugs/medication).
- Severe visual impairment, acquired nystagmus, optic nerve hypoplasia, optic atrophy, ‘morning glory’ optic disc, acquired gaze palsy, internuclear ophthalmoplegia, ocular motor apraxia, opsoclonus-myoclonus.

Skeletal survey for dysmorphology26 (remember to state this clearly when requesting, or report likely to state ‘no fractures seen’).
- Coarse facial features.
- Organomegaly.
- Significant short stature.
- Disproportionate stature.

Electroencephalography (EEG) and the epilepsies:
- An EEG is not a test for the epilepsies, but may provide helpful information to inform specific epilepsy diagnosis and management, once a clinical diagnosis has been made. A standard EEG is usually interictal (between seizures), although what is most helpful is an ictal recording that captures a typical attack, preferably with simultaneous video (videotelemetry). Specific provocations may be used to try to provoke a typical attack eg, photic and pattern stimulation, eye closure, hyperventilation, sleep. The latter may be induced naturally following sleep deprivation, or require eg, melatonin, which is the least likely ‘sedative’ to interfere with interpretation of the recording. Digital ambulatory EEG allows continuous EEG and ECG recording for longer periods while the child or young person goes about their usual business and may help to capture typical attacks, if these occur frequently enough for this to be practicable. In interpreting the report, it is most important to ascertain whether and when the child had an attack during the recording, so that the appropriate section can be carefully examined.
- Accurate diagnosis of the epilepsies can be complex as can management.
- Intractable seizures with apparent loss or fluctuation of skills may reflect suboptimal seizure control.
- Frequent seizures, especially myoclonus may indicate storage disorders.

In case of uncertainty about diagnosis or management of the epilepsies, discuss with/refer to paediatric neurology.

More information: http://www.nice.org.uk/CG020

Red flags to consider when the child with disordered development presents acutely, including in the resuscitation room, Accident and Emergency department, paediatric assessment unit, ward etc.
- Those with disordered development and disabilities can have the same range of illness as other children and young people, but presentation may be different and it may be harder to elicit clinical signs.
- Children and young people with neuromuscular disorders, whether already diagnosed or presenting for the first time, can quickly slip into respiratory failure without evidence of increased work of breathing; check pCO2 early in this group.
- Those on the autism spectrum and with some specific syndromic diagnoses can have exceptionally high pain thresholds, that can mask usual expected clinical findings eg, fractures, acute abdomen etc.
- Those with metabolic disorders can decompensate with intercurrent illness and require condition-specific treatment.
- Aspiration can be silent, with no outward vomiting in the child or young person with complex disabilities who may have significant gastro-oesophageal reflux.
- Constipation can be severe and cause significant pain. Remember to check for it.
- Other possible causes of pain: hips, teeth, postural deformities, bony fractures, foreign bodies etc.
- Those with difficult epilepsy are likely to have had emergency treatment at home. Check what has been given in all settings, especially how many doses of benzodiazepines, to avoid accumulation and secondary respiratory depression.
- Unless there is a clear individual emergency health plan that states differently, always assess and manage every child, irrespective of apparent level of disability, as per Advanced Paediatric Life Support guidelines and seek senior advice early, to ensure appropriate care at all times.
- Always keep an open mind to potential safeguarding issues.

- Does the child have an emergency healthcare plan27 or personal resuscitation plan? This may contain information about diagnoses, treatment, specific secondary disabilities to look out for, what has been discussed about levels of care, resuscitation, intensive care or not etc.
- If there is no such plan, ask the child’s lead clinician to prepare one, to make communication easier for the next visit, especially clarifying what has been discussed and agreed about appropriate levels of care. (see suggested template online at http://adc.bmj.com).
- If the child has no obvious lead clinician and no evidence of thorough aetiological work up, discuss with/refer to paediatric neurodisability, neurology, metabolic paediatrics, clinical genetics etc as appropriate.
consequences in paediatric neurodisability, neurology, clinical genetics, metabolic paediatrics, and so on.

Some considerations and red flags for investigations in specific situations are listed in box 4. All investigations must test specific diagnostic hypotheses after careful thought.

CONCLUSION

All paediatricians can contribute to the assessment and investigation of children and young people with disordered development, as part of clinical networks. Using a structured approach can increase yield of primary diagnoses and secondary disabilities, with the potential to benefit children, young people and their families. Signposting families to sources of further information and support can be empowering and is appreciated.

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