REVIEW

How to diagnose autism

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Over the past two decades, there has been an explosion of interest in autism and autism spectrum disorders. Knowledge and awareness of the condition has grown exponentially at all levels among the general public, parents, health professionals, the research community and, more recently, at parliamentary level. Alongside the increased understanding of these complex and disabling conditions is the acknowledgment of a broadening of the diagnostic criteria away from a narrow definition of autism to the autism spectrum with less clear diagnostic boundaries. Growing evidence of the importance of early diagnosis and intervention demands knowledge and skills from all professionals working with young children and in particular those involved in recognising early concerns about a child's development. This article outlines current clinical and research findings in relation to early diagnosis and considers the role of the paediatrician in this process. Reference is also made to the National Autism Plan for Children.

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The term autism spectrum disorders (ASDs) is used to describe the group of pervasive developmental disorders characterised by qualitative abnormalities in reciprocal social interactions and patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative behavioural abnormalities are a pervasive feature of the disorder—and are, usually present across many settings.

The spectrum includes autism (sometimes referred to as core autism) as the prototypical disorder, Asperger's syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS). The *International Classification of Diseases 10th edition*[1] and *Diagnostic and Statistical Manual, 4th edition*[2] do not recognise the term ASD but refer to pervasive developmental disorders.

Autism, with its difficulties in the three main domains outlined above, was previously mainly recognised in those individuals with severe levels of impairment, often with intellectual disability. It is now understood that these core difficulties can manifest in individuals with varying degrees of behavioural severity, and language and intellectual abilities. The spectrum runs from individuals, of all ages, who are severely impaired to those considered ''high functioning''. The term ''high functioning'' can be misleading in that an individual of ''high'' intellectual ability may still be significantly impaired in terms of social skills.

HOW BROAD IS THE AUTISM SPECTRUM?

Recognition of this unique pattern of skills and difficulties extends beyond core autism to include ASDs and to varying degrees in the relatives of individuals with autism, the so-called ''broader phenotype''.[3] Subthreshold social and communication difficulties may further extend into the general population.[4]

It seems difficult to define where the threshold lies for ASD versus non-ASD. It is the role of clinicians, including paediatricians, to use their judgement to ascertain the problems for the child and family and to what extent adaptive functioning is impaired.

IS AUTISM/ASDS ON THE INCREASE?

Changes in diagnostic criteria and classification systems may at least in part have contributed to the reported increased rates of ASDs in epidemiological research. Fombonne reviewed 34 surveys conducted in 14 countries over the past 40 years.[5 6] The reported current conservative estimate was 13 per 10 000. Extending the definition from core autism to include all disorders under the umbrella term ''autism spectrum disorders'' yielded a prevalence of around 60 or 65 per 10 000. This figure has been replicated in studies by Chakrabarti and Fombonne.[7] However, Baird *et al*,[8] studying a large cohort of 9–10-year-old children, estimated the total prevalence of ASDs to be 116.1 per 10 000—that is, approximately 1% of the child population.

At first glance, results from epidemiological studies across time suggest that rates of autism have risen dramatically from the original estimate 40 years ago of 4 per 10 000. This apparent increase does seem largely to be as a result of improved ascertainment and a considerable broadening of the diagnostic concept.[9] However, as yet unidentified environmental factors cannot be ruled out.

Much interest has focused on the hypothesised link between measles–mumps–rubella vaccination and autism. However, several systematic studies in the UK and further afield have consistently failed to confirm this link. Case–control comparisons of children from Danish national register records showed no difference in the risk of an ASD in vaccinated children as compared with unvaccinated children.[10] Similarly, findings from a Japanese study of trends over time showed no association between ASD rates and vaccine usage.[11 12]

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; GFCF, gluten-free casein-free; MAA, multiagency assessment; NAPC, National Autism Plan for Children; PDD-NOS, pervasive developmental disorder not otherwise specified

Rates of learning disability in children with core autism have been estimated at 60–70%. However, with the increasing recognition of children with ASD, the proportion of those within the normal ability range increases. Baird *et al*[13] reported that 60% of the children screened for ASD as part of a longitudinal study had IQs within the normal ability range.

EARLY IDENTIFICATION

Increased awareness and knowledge in those with contact with young children—that is, parents, health visitors, play group leaders, etc—is resulting in younger children being presented to professionals, such as paediatricians, for advice and diagnostic clarification. More often, this will include young children with subtle difficulties and with a range of abilities.

Early identification has many advantages for the child and family. These include:

- earlier diagnosis where appropriate;
- early information about education and support;
- earlier access to targeted social, communication and behavioural interventions; and
- identification of comorbid medical, developmental and psychiatric conditions.

Early identification of a child's profile of strengths and difficulties, with opportunities to take up appropriate and targeted interventions, is likely to reduce the risk of additional secondary behavioural difficulties and so help a child maximise his or her future potential.[14]

Several studies reviewed by Charman and Baird[15] have assessed the stability of diagnosis from the second year of life. The consensus from these studies is that diagnosis of childhood autism (core autism) is stable in the third and even second year of life. Diagnosis of the broader range of ASD is less reliable, suggesting that, although early diagnosis is important, a period of continued monitoring and observation may be appropriate. Diagnostic uncertainty should not, however, exclude a child from early social/communication intervention programmes.

It is recognised that access to assessment and targeted interventions is not consistent between local areas or across the UK. In response to this, the National Autism Plan for Children (NAPC)[16] was published to provide a template for professionals. The document addresses identification, assessment, diagnosis and access to early interventions for preschool and primary school aged children with suspected ASD, and provides clear and structured recommendations, with detailed and useable appendices to support each step of the process.

GENERAL DEVELOPMENTAL ASSESSMENT

It is now generally recognised that parents are considerably skilled in detecting early abnormalities in their child's development. They are likely to raise these concerns with their health visitor or general practitioner. This should then trigger referral for a general developmental assessment, referred to as stage 1 within the NAPC. Most often this initial referral is made to a general and/or community paediatrician, although in some areas the referral may go direct to speech and language therapy. These cases should be routed to child health as the single entry point.

The paediatrician is likely to be involved in taking the general developmental history, performing a physical examination of the child and arranging appropriate medical investigations depending on clinical presentation. If at any stage of this initial assessment an ASD is suspected, then a more extensive, multidisciplinary multiagency assessment (MAA) is likely to be needed. This is described in the NAPC as the transition from stage 1, the general developmental assessment, to stage 2, an MAA.

DIFFERENTIAL DIAGNOSES

Differential diagnoses at this stage may include global developmental delay, hearing problems or specific language disorders.

Impairments in early social communicative behaviours at age 2 years (box 1) can help distinguish between the above. It is important to note that isolated examples of pretend play, gaze switching and imitative behaviour cannot rule out an ASD diagnosis.

MULTIAGENCY ASSESSMENT

The key objectives of the MAA (box 2) are to undertake a thorough assessment of the child and family's functioning.

The choice of components of the MAA will depend on clinical presentation. It is important that no one component is used in isolation to reach a diagnosis. Assessments are likely to involve

Box 1 Early signs and symptoms—adapted from the NAPC

- Qualitative abnormalities in communication
  - Delay or lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime
  - A lack of babbling
  - A lack of pointing to express interest or a lack of spontaneous pointing
  - Odd speech patterns, words or phrases, echolalia, unusual tone and pitch
- Qualitative abnormalities in social interaction
  - Poor eye contact
  - Failure to follow gaze
  - Limited social smiling—does the child spontaneously smile in greeting?
  - Limited imitation of others (also seen in play)—for example, pretends to mow lawn
  - Poor use of gestures—for example, shakes head, nods, waves and claps
  - Failure to show an interest
  - Does the child show things of interest?—for example, brings toys to parent?
  - Does the child respond to others' emotions?
  - Limited pretend and imaginative play
  - Limited social play—for example, peekaboo, pat a cake
- Restricted and repetitive interests and behaviours
  - Repetitive play—for example, lining up cars
  - Unusual interests, interest in non-functional elements of play material
  - Oversensitivity to household noises
  - Extreme adverse reaction to change in routine
  - Motor mannerisms or stereotyped behaviour—for example, hand flapping
  - Sensory hypo/hypersensitivity

Box 2 Components of MAA—adapted from the NAPC

- ASD-specific developmental history by an experienced member of the team with recognised ASD training
- Observational assessments includes focused observations taken across more than one setting (such as home, nursery, etc)
- Cognitive assessment, including an individual's unique profile of skills/difficulties on subscales
- Communication, speech and language assessment
- Behaviour and mental health assessment in comorbid neurodevelopmental disorders and psychiatric disorders
- Family assessment, undertaken by the key worker (in some localities, allocation of a key worker during assessment and before diagnosis may provide support for families at this crucial time) to identify strengths and needs using the Framework for the Assessment of Children in Need and their Families[16a]
- A physical examination and medical investigations as guided by clinical presentation
- Other assessments, including physiotherapy and occupational therapy, should be available to identify sensory needs and problems, motor planning and coordination difficulties, and self-care problems

a series of appointments with more than one professional across several settings. These contributions will need to be coordinated, discussed, and the proposed diagnostic formulation and treatment plan agreed with the parents/family.

The paediatrician may have a number of roles in the MAA, depending on the composition of the team. The physical examination and investigations will clearly be the responsibility of the paediatrician (see later). He or she may also be involved in taking an ASD-specific developmental history building on the general developmental assessment. This information will guide further assessments and investigations. The paediatrician may also undertake a coordinating role, such as collating information from assessments and liaising with parents.

Finally, he or she may be involved in undertaking or coordinating standardised assessments (see below). This will be determined by the individual skills of the paediatrician and other team members.

STANDARDISED ASD ASSESSMENTS

The NAPC recommends that at least one member of the team is trained in using standardised assessment tools. The advantage of such training is that it will bring a broader understanding of autism/ASD to the team rather than an expectation that every child should have a standardised assessment. In the clinical setting, standardised instruments may facilitate diagnosis in the context of a comprehensive assessment[17] but may also lead to increased waiting times (with the risk of delaying the child and family's access to early intervention) if used with all referred children.

Two examples of history-based diagnostic tools are the Autism Diagnostic Interview Revised[18] and the Diagnostic Interview for Social and Communication Disorders.[19] These tools provide the structure for a detailed developmental history, focusing on autism/ASD symptoms, and include diagnostic algorithms. They should not be used in isolation and need to be used with caution with very young children or those with a mental age $<$24 months.[20] The NAPC provides an example of a briefer proforma (aide memoire) as a framework for an ASD-specific developmental history. This is less time consuming compared with the Autism Diagnostic Interview-Revised or Diagnostic Interview for Social and Communication Disorders.

One example of an ASD-specific observation tool is the Autism Diagnostic Observation Schedule.[21] This is a semistructured standardised play- and activity-based assessment that can be applied across the age and ability range from young preverbal children through to verbally fluent adolescents.

Such tools were originally developed for research purposes but may be most useful in clinical settings for children with more complex and/or less clear-cut developmental difficulties.

DIAGNOSIS OF SCHOOL-AGED CHILDREN

A child may present after the preschool period for a number of reasons. It may be that the child did not come to the attention of child health professionals and/or the family has managed his or her difficulties. However, as the social world becomes more complex and academic demands increase, the child may experience more problems. Particular risk periods seem to be times of transition, such as nursery to primary, or primary to secondary school. School-aged children and their families will also require an MAA and coordinated care plans that encompass health, social and education services, and the voluntary sector. Close liaison with teachers and educational support staff will be of particular importance.

For children over 5 years (without a learning disability), a single referral point is more difficult to achieve as referral may be made to a number of different agencies such as the local child and adolescent mental health service or education psychology service, rather than directly to the (community) child health team. In these cases, the paediatrician may well be asked to supplement the developmental history, carry out a physical examination, and advise about appropriate investigations, and use of particular interventions including biomedical treatments and medication.

ASSOCIATED MEDICAL CONDITIONS AND SPECIFIC INVESTIGATIONS

The purpose of medical investigations is to identify the underlying conditions that may be associated with autism/ASD, in particular those that are treatable or have genetic implications. The paediatrician therefore needs an understanding of the evidence base for which physical investigations are appropriate. However, reported rates of children with autism with a recognised medical condition vary between studies depending on diagnostic criteria, the population studied and how extensively the children were investigated. Rates range between 8% and 37%, with the consistent finding that the yield of investigations is higher in those with lower IQ.[22 23]

Associated conditions include fragile X, tuberous sclerosis, cerebral palsy, untreated phenylketonuria, neurofibromatosis and congenital rubella. Hearing and visual impairments should also be considered.

The NAPC and other recently published reviews recommend a minimum of routine investigations and indicate that it is helpful for parents to be given an explanation about why a particular test is or, more often, is not indicated for their child.

Evidence supports the recommendation of a general physical examination, including Wood's light, identification of dysmorphic features, and routine hearing and vision testing. Chromosomal analysis and specific DNA testing for fragile X is indicated in case of evidence of significant language or learning difficulty, phenotypic features or family history. Further investigations should be guided by clinical presentation. Cass *et al* support this recommendation in their recent paper considering the evidence and rationale for medical investigation of children with ASD. They conclude that the yield from

investigations is generally low, but factors modifying the pretest probability, such as family history or phenotypic features, of each condition should be evaluated for the child in question.[24]

Epilepsy is known to be significantly associated with autism. Fombonne reviewed 11 studies that reported rates of epilepsy.[6] The median rate was 16.8% (range 0–26.4), with the likelihood of epilepsy increasing with increased severity of mental retardation and with two peaks in the preschool period and adolescence.

Ten per cent of children with autism have an abnormal EEG in the absence of clinical seizures,[25] yet there is no conclusive evidence that epileptiform discharges ''cause'' autism, or that it can be improved with anticonvulsant drugs.[26] Use of anticonvulsants should therefore be restricted to the treatment of clinical epilepsy.

Parents or care givers may enquire about neuroimaging. Routine MRI brain scan and EEG are not indicated unless there are seizures or evidence of a focal abnormality on examination.[27 28] An EEG may be indicated in children with a fluctuating clinical picture or other unusual features.

Rates of regression, or a period of developmental stasis in children with ASD, vary between 10% and 50%, most often occurring between 18 and 24 months of age.[29] Loss of speech before or within the 10-word stage is the most common loss of skill and does not warrant routine EEG. Developmental regression with onset of autism after normal development to ⩾24 months is less frequent and would warrant more extensive neurological investigation. Indications pointing to inborn errors of metabolism are mental retardation, encephalopathy, recurrent vomiting and dysmorphic features.[30]

Recently, Challman *et al* undertook a retrospective case note study of 182 children diagnosed with either autism or PDD-NOS, as defined in the *Diagnostic and Statistical Manual of Mental Disorders IV* criteria.[31] PDD-NOS, although not directly transferable, can be considered to represent those disorders on the autism spectrum excluding core autism. Aetiologically relevant conditions were found in 5.1% of the PDD-NOS group and in 3.1% of the autism group; these figures did not differ statistically. Abnormalities on MRI brain scanning showed abnormalities in both groups but rarely yielded clinically useful information. This study suggests that overall the yield of medical investigations is low but is similar for autism and ASD, suggesting that medical investigation should not be limited to only those children with ''core autism''. These findings, however, need replication in a UK sample. Although much progress has been made in understanding the role of genetics in the aetiology of autism, the picture is far from clear. Genetic factors are important for both core autism (heritability of approximately 90%) and for the broader ASD phenotype. This means that, for a family with a child with autism, an approximately 6% risk of autism for siblings and an increased risk for a broader autism phenotype of 20% are observed. These rates are significantly greater than the risk in the general population of 0.5%.[32]

It is likely that multiple genes contribute to autism and ASD susceptibility. Susceptibility loci on chromosomes 2, 7 and 16 have been the most consistently replicated findings to date.[33] However, no specific candidate genes have as yet been identified. Further, how particular genes interact to produce the clinically heterogeneous spectrum of ASD remains unclear (see Shastry[34] for a recent review).

COMORBID NEURODEVELOPMENTAL AND MENTAL HEALTH DISORDERS

Alongside the increased acceptance of the autism spectrum, there is an increased recognition of the overlap with other neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD),[35] and more specific developmental disorders such as specific language impairment, dyspraxia and dyslexia. A young child may therefore present a complex clinical picture. For instance, the identification of symptoms of ADHD may overshadow parental and professional awareness and/or recognition of difficulties in social communication and interaction such that the neurodevelopmental complexity may not be apparent until ADHD symptoms are controlled. Similarly, children at the more ''able'' end of the spectrum with less severe difficulties and without significant language delay may also experience other behavioural/mental health problems but not trigger an ASD assessment. For the pediatrician with expertise in ASD and other developmental disorders, working with colleagues in mental health is crucial for the identification of comorbid mental health disorders such as depression, anxiety and obsessive compulsive disorder. A recent study by Leyfer *et al* reported that a large proportion of children with autism in their sample met the criteria for a comorbid psychiatric disorder, including about one third with ADHD.[36]

Some complex cases, where there might be uncertainty about diagnosis and/or comorbidity, might be referred for a specialised regional tertiary assessment (a stage 3 referral) according to the NAPC.

CARE PATHWAYS

Many local districts have developed care pathways for children with suspected ASD. Achievable time frames for such multiagency pathways vary between different local areas. The NAPC recommends that time from first concern to completion of multidisciplinary ASD assessment should take no longer than 30 weeks. Preece and Mott[37] recently published a case note audit. Only 19.2% of cases had all assessments been carried out within 30 weeks, although 80% were completed within 45 weeks. The main reasons for delay were long waiting times to see professionals, parental/child reasons and complex problems requiring multiple assessments.

Coordinated multiagency work is resource intensive, time consuming and a challenge as child health professionals are often based in different organisations. Increased awareness and early recognition of difficulties also place increased demands on local resources. However, few services have successfully attracted additional resources or dedicated new funding for this increased workload.

Paediatricians have the knowledge and experience to differentiate deviance from delay in the child's patterns of development. Indeed children with suspected ASD and significant general developmental delay are more likely to receive a diagnosis in the early preschool period than more intellectually able children. Many children with ASD have a learning disability, so it is important that local pathways include children's learning disability services where available.

How each area coordinates and audits the local ASD care pathways and implements newly emerging evidence-based practice is a further resource pressure. The NAPC recommends a local area ASD coordinating group with representation from parents/users of the services, professionals from the multiagency partnerships and strategic planners/managers with particular responsibility to highlight the resource, training and academic needs of each local area.

Coordinating services and developing new resources within the local area may be strengthened by links to regional projects. The West Midlands Special Educational Needs Regional Partnership is an example of a regionally coordinated project with the aim to establish consistency and joint protocols for multiagency provision and services for children with ASD. In addition, such partnerships provide an opportunity for

members to meet, share best practice, provide coordinated training and engage in research.

INTERVENTIONS

The purpose of detailed assessment and diagnostic formulation is to inform the intervention plan for both the child and his or her family. Families require information about local multi-agency services, ASD-specific support groups and national agencies such as the National Autistic Society and Contact a Family. Although a child diagnosed with autism or ASD is unlikely to have particular acute medical needs, the paediatrician will be responsible for the medical review of developmental progress, reassessment of needs, and for the management of any additional medical problems such as epilepsy or referral to paediatric dietetics service. The paediatrician will therefore need to be aware of what general and ASD-specific interventions are appropriate and available in the local area and how they can be accessed.

Although the evidence base for most therapeutic interventions is limited, there is emerging evidence for the positive benefits of early (usually preschool) intervention programmes, especially specific targeted, skills-based educational and behavioural programmes—for example, *More than Words*[38] and *EarlyBird*.[39] However, it is difficult to provide evidence-based information given the lack of well-conducted intervention evaluation studies and the clinical heterogeneity of children on the ASD spectrum. Many unanswered questions remain as to which intervention programmes may be most effective for a particular child and family. Paediatricians will be approached by parents for advice about the best treatments and for their support for funding and access to specific ASD treatments. These may include biomedical interventions such as the use of special restrictive diets or nutritional additives—for example, fish oils. There has been much attention and contention surrounding the hypothesis that peptides derived from gluten and casein have an aetiological role, the so-called opioid theory of autism. Advocates of this approach recommend a gluten-free casein-free (GFCF) diet. Millward *et al* conducted a systematic review of GFCF diets.[40] They reported only one small-scale single-blind trial involving children with autism. Ten children were placed on a GFCF diet for a period of 12 months. Linguistic ability, cognitive skills and motor ability did not differ significantly between treatment and control groups after the 12-month period. However, reduction in parent-reported ''autistic traits'' was found to be significant in the GFCF diet group. Although this result supports anecdotal evidence, larger scientifically rigorous multisite trials with adequate power are required to provide an evidence base to help paediatricians and other child health professionals give advice about the role of a range of biomedical interventions in ASD.

CONCLUSIONS

Better knowledge of and interest in ASDs has resulted in children presenting at an increasingly young age. Evidence suggests that core autism and ASD can be reliably diagnosed earlier in the preschool period than was previously thought. This poses new and exciting clinical challenges. Paediatricians provide a key role in the general developmental and multidisciplinary assessment/MAA of a child with suspected autism/ASD, usually taking responsibility for the developmental history, differential diagnosis, decisions about physical and medical investigations, and the identification of comorbidity especially in the preschool period. Parents and members of the team may also turn to the paediatrician for advice about local provision and for opinion on both medical and non-medical interventions, despite the limited evidence base.

In neurodevelopmental disorders such as ASD, where the complex pattern of skills and difficulties may show a variable pattern across settings and over time, the paediatrician's role within the care pathway is crucial, especially at the time of initial diagnosis and at review of developmental progress and in contributing with colleagues to the identification of onset of new disorders.

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ARCHIVIST

Effectiveness of neonatal screening for MCAD deficiency in Australia

The use of tandem-mass spectrometry for neonatal screening has increased greatly in the last 10 years. In Australia all infants are screened in this way and the disorders most frequently diagnosed are medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and phenylketonuria. There are few reports of outcomes after screening for rare disorders, but a nationwide Australian study of the effectiveness of screening by tandem-mass spectrometry for MCAD deficiency has now been reported (Bridget Wilcken and colleagues. *The Lancet* 2007;**369**:37–42; see also Comment, ibid: 5–6).

The study included 2 495 000 infants born between April 1994 and March 2004, of whom 810 000 were screened. The main cohort consisted of 1 995 000 infants (460 000 screened) born between 1994 and March 2002 and followed up for at least 4 years. In addition, data were available for 500 000 infants (350 000 screened) born between April 2002 and March 2004. In the main cohort, MCAD deficiency was diagnosed in 2.3 per 100 000 infants in the unscreened population and in 5.2 per 100 000 in the screened population. The median age at diagnosis was 16 months in unscreened and 0.5 months in screened infants. Up to the age of 4 years among the unscreened population there were five deaths and 18 children had an episode of non-fatal severe decompensation. Among the screened population there was one death and two children had non-fatal severe decompensation. Conservative estimates of the relative risks of an adverse event (screened vs unscreened infants) were 0.44 in the main cohort by the age of 4 years and 0.26 in the whole cohort of 2 495 000 infants by the age of 2 years. Neuropsychological testing of 19 screened and 19 unscreened patients showed no significant differences between the two groups. There were no known false negative screening tests and screening gave an overall false positive rate of 0.01% and a positive predictive value of 42%.

Neonatal screening for MCAD deficiency is effective in that with appropriate management the risks of death or severe adverse events up to the age of 4 years are reduced.