

Autism

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Autism spectrum disorders are characterised by severe deficits in socialisation, communication, and repetitive or unusual behaviours. Increases over time in the frequency of these disorders (to present rates of about 60 cases per 10 000 children) might be attributable to factors such as new administrative classifications, policy and practice changes, and increased awareness. Surveillance and screening strategies for early identification could enable early treatment and improved outcomes. Autism spectrum disorders are highly genetic and multifactorial, with many risk factors acting together. Genes that affect synaptic maturation are implicated, resulting in neurobiological theories focusing on connectivity and neural effects of gene expression. Several treatments might address core and comorbid symptoms. However, not all treatments have been adequately studied. Improved strategies for early identification with phenotypic characteristics and biological markers (eg, electrophysiological changes) might hopefully improve effectiveness of treatment. Further knowledge about early identification, neurobiology of autism, effective treatments, and the effect of this disorder on families is needed.

Introduction

Autism is a neurodevelopmental disorder in the category of pervasive developmental disorders, and is characterised by severe and pervasive impairment in reciprocal socialisation, qualitative impairment in communication, and repetitive or unusual behaviour. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)¹ and the International Classification of Diseases, 10th edition (ICD-10),² include autistic disorder, Asperger's syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's syndrome, and childhood disintegrative disorder as pervasive developmental disorders. Clinicians and researchers use autism spectrum disorders to include autism, Asperger's syndrome, and PDD-NOS, which we discuss in this Seminar. For children with Rett's disorder or childhood disintegrative disorder, their clinical course, pathophysiology, and the diagnostic strategies used are different and are not addressed in this Seminar.

Search strategy and selection criteria

We searched Medline, Psycinfo, and Cochrane Library databases from January, 1998, to December, 2008, with the search terms "autism", "autistic disorder", "pervasive developmental disorder", "autism spectrum disorder", and "Asperger syndrome" in combination with "evaluation", "diagnosis", "treatment", "therapy", "medication", "pharmacotherapy", "epidemiology", "genetics", "neuroimaging", "behavior therapy", "early identification", "outcome", and "complementary and alternative therapy." We largely selected reports published within the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched references from recent reviews and other reports identified by this search strategy, and selected those we judged relevant. Review articles and book chapters are cited to provide more details and references than are provided in this Seminar. Our reference list was modified on the basis of comments from peer reviewers.

Epidemiology

We focus on prevalence of autism spectrum disorders and possible causes of changes in prevalence. Although estimates vary, prevalence seems to have increased greatly since the 1960s, when rates included only autistic disorder. In the 20 years since, in the USA and Europe prevalence rates ranged from five to 72 cases per 10 000 children.^{3,4} These estimates were affected by screening, case-confirmation strategies, and sample size, with small sample sizes resulting in high estimates. Prevalence of autistic disorder is between ten and 20 per 10 000 children.⁵ Estimates of autism spectrum disorders have been more consistent than have those for autistic disorder—perhaps because they are less sensitive to small differences in case definitions. These estimates are close to 60 per 10 000 children.⁶ However, in a prevalence study⁷ researchers reported a rate of 116 per 10 000 children for all autism spectrum disorders. They used a small sample of children in South Thames, UK, and relied on screening and case-confirmation methods, with a broad definition of these disorders. When the definition of autism was narrowed, they reported a prevalence of 25 per 10 000.

A rise in the number of children identified with autism spectrum disorders in educational systems has resulted in public health concern.⁸ Some of the reported increase is attributable to new administrative classifications in special-education settings and the subsequent reclassification of children from a different category to autism.⁸ Symptoms of these disorders might resemble or arise with intellectual disability, attention deficit-hyperactivity disorder, or obsessive-compulsive disorder.⁹ Policy and practice changes rather than true changes in community prevalence might be responsible for recorded increases. Substantial small-area variation in prevalence could be related to local health-care and education resources,¹⁰ and pressure to obtain intensive services might result in over-diagnosis.

Clinical characteristics and screening

Core symptoms of autism spectrum disorders affect domains of socialisation, communication, and behaviour

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(panel 1). Clinical signs are usually present by age 3 years, but typical language development might delay identification of symptoms. Results of prospective studies¹¹ of infants at risk (ie, younger siblings of affected children) have shown that deficits in social responsiveness, communication, and play can be present in those as young as age 6–12 months. Diagnoses show heterogeneity of clinical phenotype, severity, and type and frequency of symptoms. Autism spectrum disorders

have characteristic diagnostic criteria, ages of symptom recognition, associated medical and developmental features, standard effective treatments, and usual courses of development (table 1).

Early detection enables referral to intervention services and for family support, with the goal of an improved outcome.¹³ Two methods of identification have emerged. The strategy in the UK combines targeted or selective screening with recognition of alerting signals by clinicians and families.¹⁴ The practice endorsed in the USA is routine general developmental surveillance with disorder-specific screening for those who are identified to be at risk during routine screening, or universal autism-specific screening at high-risk ages (eg, 18 and 24 months or 30 months), or both.¹⁵ Few data are available to compare the effectiveness of these approaches. Universal whole-population screening with standardised tests has not been supported in the UK¹⁶ because of poor sensitivity and specificity of tests.¹⁴

Tebruegge and colleagues¹⁴ investigated the effect of targeted checks—more than a third of children with autism spectrum disorder were not identified at age 2 years. These researchers supported routine child health surveillance at age 2·0 years and 3·5 years by health professionals with awareness of typical development. The joint working party on child-health surveillance and the American Academy of Pediatrics (AAP)¹⁶ recommended education of clinicians and families to recognise red flags or alerting signals. Other countries have adopted similar strategies, combining routine child-health surveillance with a standardised method. In Japan, the young autism and other developmental disorders checklist tool (YACHT) is administered by public health nurses to children aged 18 and 24 months.¹⁷ Wong and colleagues¹⁸ have modified the checklist for autism in toddlers (CHAT) for use in China, with a two-stage screening strategy in CHAT-23, incorporating a questionnaire and a direct observation

Panel 1: Core domains of autism¹

Socialisation

- Impaired use of non-verbal behaviours to regulate interactions
- Delayed peer interactions, few or no friendships, and little interaction
- Absence of seeking to share enjoyment and interests
- Delayed initiation of interactions
- Little or no social reciprocity and absence of social judgment

Communication

- Delay in verbal language without non-verbal compensation (eg, gestures)
- Impairment in expressive language and conversation, and disturbance in pragmatic language use
- Stereotyped, repetitive, or idiosyncratic language
- Delayed imaginative and social imitative play

Restricted, stereotyped, and repetitive patterns of behaviour

- Preoccupation with stereotyped or restricted interests or topics
- Adherence to routines, rigidity, and perseverative behaviour
- Stereotyped, repetitive motor mannerisms, and selfstimulatory behaviour
- Preoccupation or fascination with parts of items and unusual visual exploration

	Autism	Asperger's syndrome	Pervasive developmental disorder—not otherwise specified (PDD-NOS)
Age of recognition (diagnosis*)	0–3 years (3–5 years)	>3 years (6–8 years)	Variable
Regression	About 25% (social or communication)	No	Variable
Sex ratio (male:female)	2:1	4:1	Male>female (variable)
Socialisation	Poor; >2 DSM-IV criteria	Poor	Variable
Communication	Delayed, deviant; might be non-verbal	No early delay; qualitative and pragmatic difficulties later	Variable
Behaviour	More impaired than in Asperger's syndrome or PDD-NOS (includes stereotypy)	Variable (circumscribed interests)	Variable
Intellectual disability	>60%	Mild to none	Mild to severe
Cause	More likely to establish genetic or other cause than in Asperger's syndrome or PDD-NOS	Variable	Variable
Seizures	25% over lifespan	Roughly 10%	Roughly 10%
Outcome	Poor to fair	Fair to good	Fair to good

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition. *Average age at diagnosis. Data adapted from Volkmar and Pauls.¹²

Table 1: Differential diagnostic features of autism spectrum disorders

stage that has more sensitivity and specificity than does CHAT.

Assessment

Children identified to be at risk should be referred for comprehensive developmental and diagnostic assessment for autism spectrum disorders. This assessment might be done through community resources (eg, early intervention staff, educators, psychologists, or speech pathologists), educational agencies, or local developmental clinicians. Reviews of early identification and screening are available.^{15,17,19} If concerns that a child has autism spectrum disorder are validated, comprehensive diagnostic assessment is needed (figure 1). These assessments should be multidisciplinary, addressing core symptoms, cognition, language, and adaptive, sensory, and motor skills. The multidisciplinary team should include clinicians skilled in speech and language therapy, occupational therapy, education, psychology, and social work. Ozonoff and colleagues¹⁹ reviewed domains of assessment, including neuropsychological, attention, executive function, and academic functioning.

Diagnostic assessment of autism spectrum disorders includes use of ICD or DSM diagnostic criteria,²¹ and standardised methods to assess core (panel 1) and comorbid symptoms (table 2). This multidisciplinary assessment includes a review of caregiver concerns, descriptions of behaviour, medical history, and questionnaires.²¹ Input from families about their observations and concerns are crucial. Although parents are often aware of developmental problems in their child from age 18 months, a diagnosis is often not made until 2 years after the initial expression of parental concern. In some cases diagnosis has not been confirmed until close to age 6 years,²⁸ which is sometimes associated with delays attributable to access to services and regional variations in diagnosis.

Table 3 shows methods for diagnosis and categorisation of autism spectrum disorders.¹⁹ Standardised questionnaires such as the social responsiveness scale provide data about severity of core deficits of socialisation, and the revised repetitive behaviour scale provides information about stereotyped or repetitive behaviours (figure 1). Use of two research quality, gold-standard assessment methods based on DSM criteria, the autism diagnostic observation schedule (ADOS)⁵⁸ and the revised autism diagnostic interview (ADI-R),⁵⁹ have improved accuracy and reliability of diagnosis.¹⁹ The ADOS is a semistructured standardised assessment for social behaviour, communication, and imaginative play, and is used in research and clinical settings. To diagnose individuals with intellectual disability is difficult because behaviours might not be specific to autism spectrum disorders; the ADOS diagnostic algorithm was revised to address these issues. The time needed for administration of the ADI-R (1–3 h) precludes its use in many clinical settings.

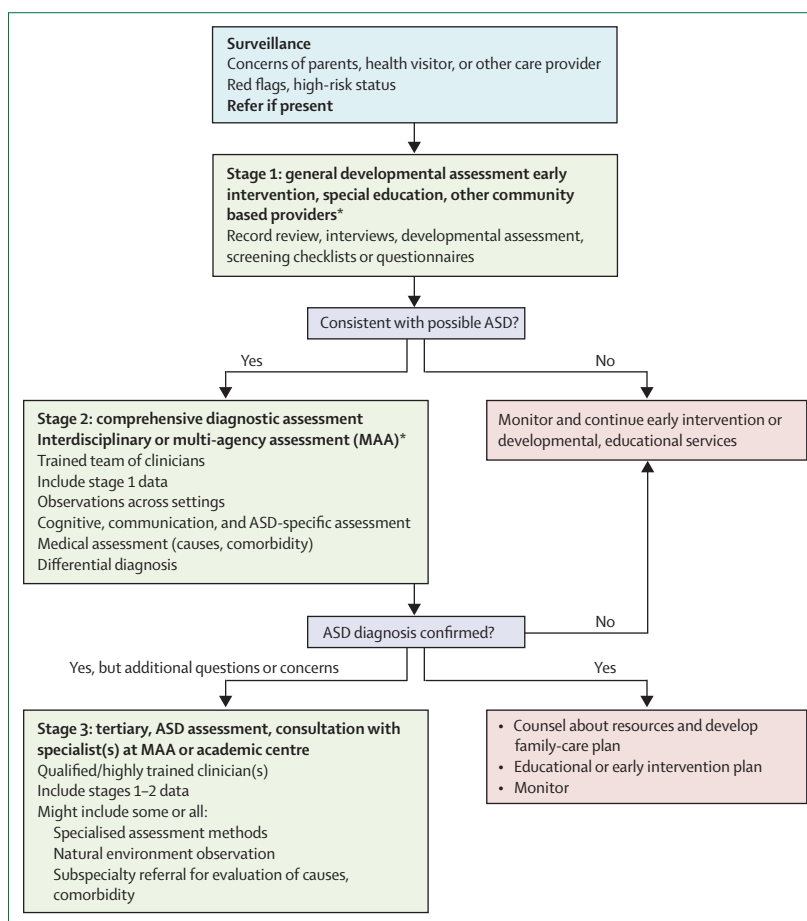


Figure 1: Stages of identification and diagnosis of autism spectrum disorder

ASD=autism spectrum disorder. Adapted from the National Autistic Society and¹⁵ and the Pennsylvania Department of Public Welfare.²⁰

Comorbid disorders are common in children⁶⁰ and families of children with autism spectrum disorders, and might have a greater effect on function and outcome than do core symptoms (table 2). Parents of affected children have increased rates of stress and mental health comorbidity (eg, anxiety and depression), which might be associated with their child's behavioural problems.⁶¹ Comorbid behavioural or developmental disorders include intellectual delays, inattention or other symptoms of attention deficit-hyperactivity disorder, externalising behaviours (such as aggression and disruption), affective difficulties (such as depression or anxiety), sleep disruption, and sensory differences.²² Medical comorbidities, such as gastroesophageal reflux, food selectivity, and neurological disorders (eg, tics and seizures) also have a substantial effect on management and on the family. Some behavioural or affective comorbidities might be targets for pharmacotherapy.

A comprehensive diagnostic assessment should include medical investigation for causes and associated diagnoses.⁶² Results will inform families about related

	Frequency	Treatments
Developmental¹		
Cognitive; intellectual disability	40–80%	Educational
Language deficits	50–63%	Communication training, speech and language therapy
Attentional problems, impulsivity, or hyperactivity	59%	Behavioural intervention, psychopharmacotherapy (eg, stimulants, atomoxetine, or alpha blockers)
Motor delay	9–19%	Physical therapy
Hypotonia	50%	Physical therapy
Psychiatric²²		
Anxiety	43–84%	Behavioural treatment such as relaxation, cognitive behavioural treatment, psychopharmacotherapy (eg, SSRIs or alpha-2 agonists)
Depression	2–30%	Psychotherapy, antidepressants
Obsessive compulsive disorder or interfering repetitive behaviour	37%	Behavioural treatment, SSRIs and other drugs such as atypical antipsychotics
Oppositional defiant disorder	7%	Behavioural treatment
Behavioural problems	3%	Behavioural treatment
Behavioural²³		
Disruptive, irritable, or aggressive behaviour	8–32%	Behavioural intervention, atypical antipsychotics (eg, risperidone or aripiprazole)
Self-injurious behaviour	34%	Behavioural intervention; drugs (eg, risperidone, naltrexone, and others)
Sensory²⁴		
Tactile	80–90%	Occupational therapy, behavioural treatment, and desensitisation
Auditory sensitivity	5–47%	Occupational therapy
Neurological²⁵		
Seizures and epilepsy	5–49%	Anticonvulsants
Tics	8–10%	Alpha-2 agonists (clonidine and guanfacine) and others such as atomoxetine
Gastrointestinal²⁶		
Food selectivity	30–90%	Behavioural treatment, investigation as appropriate for gastrointestinal difficulties
Gastro-oesophageal reflux, constipation	8–59%	Gastrointestinal investigations as appropriate (eg, barium swallow or milk scan for gastroesophageal reflux; flat plate, clean out, stool softener, or cathartic for constipation as clinically indicated)
Sleep²⁷		
Sleep disruption	52–73%	Sleep diary, sleep hygiene, behavioural supports, investigation of possible medical comorbidities as cause, drugs (eg, melatonin and clonidine)

SSRI=selective serotonin reuptake inhibitor.

Table 2: Comorbid symptoms or disorders

genetic, neurological, or medical problems, and risk of recurrence in future siblings. An appropriate medical investigation for causes includes a detailed history and physical examination (with careful examination for dysmorphology). Clinical genetic assessment might include laboratory studies ordered by the primary care practitioner or referral to a clinical geneticist. Genetic laboratory studies can include routine karyotype and molecular DNA testing for fragile X, or comparative genomic hybridisation, or both.⁶³ Associated medical problems such as seizures show a need for electroencephalogram (EEG), substantial regression a need for metabolic investigation, and abnormal head size a need for neuroimaging in some. Routine brain imaging

or EEG is not recommended unless specific clinical features are indicative of an active neurological process needing clinical diagnosis.

Neurobiology

Attempts to identify unified theories explaining core and comorbid deficits have been unsuccessful, which is not surprising in view of the heterogeneous expression of autism spectrum disorders. In studies⁶⁴ of this disorder as a neurodevelopmental disorder of prenatal and postnatal brain development, researchers have attempted to elucidate these theories by examination of brain growth, functional neural networks, neuropathology, electrophysiology, and neurochemistry. Neurocognitive theories include pragmatic language impairment and difficulties in intersubjectivity (theory of mind), executive function and problem-solving mindset, weak central coherence and difficulty with integration of information into meaningful wholes,¹² and deficits in connectivity and processing demands.⁶⁵

Neurobiological findings support different theories. Macrocephaly is noted by age 2–3 years in 20% of children with autism spectrum disorder. Brain growth accelerates at 12 months.⁶⁵ These changes arise in parallel with onset of core symptoms during the first 2 years of life. Results of neuroimaging studies⁶⁶ have shown overgrowth in cortical white matter and abnormal patterns of growth in the frontal lobe, temporal lobes, and limbic structures such as the amygdala. These brain regions are implicated in development of social, communication, and motor abilities that are impaired in autism spectrum disorder. In post-mortem brain studies,⁶⁷ researchers have also noted cytoarchitectural abnormal findings, including reduced number and size of purkinje cells, and abnormal findings in the cortical minicolumn.

Functional MRI has shown differences in patterns of activation and timing of synchronisation across cortical networks, with lowered functional connectivity relating to language, working memory, social cognition or perception, and problem solving. The most reliably replicated functional MRI abnormal finding is hypoactivation of the fusiform face area, associated with deficits in perception of people compared with objects (figure 2).^{64,67} Results of other functional MRI studies⁶⁸ done during imitation tasks have suggested impaired mirror neuron activity in the inferior frontal gyrus (pars opercularis). With diffusion tensor imaging (figure 3), researchers⁶⁵ have shown disruption of white matter in brain regions associated with social functioning.

Magnetoencephalography is a non-invasive measure of magnetic fields generated by neuronal activity, providing spatial and temporal localisation of activity within the brain. This technique has been used to investigate auditory processing deficits with the hope to identify an electrophysiological signature that might enable early detection or monitoring of progress.⁶⁹ Neurochemical investigations with animal models and empirical drug

	Description	0–3 years	3–5 years	SA	Adult	Administration time (min)
Checklist or inventory						
Screening method						
Quantitative checklist for autism in toddlers ²⁹	Parent questionnaire, 25 questions	X	..	..	..	5–10
Modified checklist for autism in toddlers ³⁰	Questionnaire 23 questions	X	..	..	..	10
First year inventory ³¹	Parent report 60 questions	X	..	..	..	NS
Early childhood inventory-4 ³²	Parent rating scale 108 items Teacher rating scale, 87 items	..	X	..	..	<20
Child symptom inventory-4 ³³	Parent rating scale 97 items, teacher rating scale 77 items	..	..	X	..	Variable
Social communication questionnaire ³⁴	Parent interview or questionnaire 40 items	..	X	X	..	10–15
Asperger's syndrome diagnostic scale ³⁵	Parent or teacher rating scale 50 items	..	..	X	..	10–15
Krug Asperger diagnostic index ³⁶	Parent, caregiver, or teacher questionnaire 32 items	..	..	X	..	10–15
Autism spectrum quotient ³⁷	Parent questionnaire, for child, adolescent, and adult 50 questions	..	..	X	X	NS
Autism behaviour checklist ³⁸	Parent or teacher questionnaire 57 items	..	X	X	..	10–20
Pervasive developmental disorder rating scale ³⁹	Rating scale 51 items	X	X	..	..	NS
Pervasive developmental disorder in mental retardation scale ⁴⁰	Clinician and teacher observation instrument 12 items	..	X	X	..	10–20
Dimensional assessment						
Developmental behaviour checklist, ⁴¹ and developmental behaviour checklist—early screen ⁴²	Questionnaire; 96 items and 17 items	X	X	..	..	10–15
Pervasive developmental disorder behaviour inventory ⁴³	Parent, caregiver, or teacher rating scale 8–10 subscales (124–188 items)	X	X	X	..	20–45
Aberrant behaviour checklist ⁴⁴	Parent rating scale 58 items	..	X	X	..	20–30
Child communication checklist ⁴⁵	Parent rating scale 70 items	..	X	X	..	5–15
Social responsiveness scale ⁴⁶	Parent and caregiver questionnaire 65 items	..	X	X	X	15–20
Repetitive behaviour scale—revised ⁴⁷	Parent and caregiver questionnaire 43 items	X	X	X	X	15–20
Social and communication disorders checklist ⁴⁸	Parent and caregiver rating scale 12 items	..	..	X	X	10–15
Structured interview						
Diagnostic method						
Parent interview for autism ⁴⁹	Parent interview 118 items	X	..	..	..	20–30
Diagnosis of social and communication disorder schedule ⁵⁰	Semistructured caregiver interview schedule 2–4 h administration, more than 300 items	..	X	X	..	180
Autism diagnostic interview—revised ⁵¹	Semistructured, investigator-based interview for caregivers	X*	X	X	X	90–180
Diagnostic method, dimensional assessment						
Developmental, dimensional, and diagnostic interview (3di) ⁵²	Caregiver computerised interview 183 items (demographics), 266 items (ASD related), 291 items (current mental state)	X	X	X	X	45–90
Observational measures						
Screening method						
Checklist for autism in toddlers ⁵³	Caregiver rating scale plus observations	X	..	..	..	10
Screening tool for autism in children aged 2 years ⁵⁴	Clinician observation 12 items	X	..	..	..	20†
Diagnostic method, dimensional assessment						
Autism observation schedule for infants ⁵⁵	Clinician observation 18 item	X	..	..	..	20†
Autism diagnostic observation schedule—modules 1–4 ⁵⁶	Standardised observation method	X	X	X	X	40–60†
Diagnostic method						
Childhood autism rating scale ⁵⁷	History and observation 15 items (Likert scale)	X	X	X	X	20–30

SA=school-aged children. NS=not specified. ASD=autistic spectrum disorder. X=appropriate method *Mental age older than 2 years. †Training needed to administer this method.

Table 3: Selected methods for autism diagnosis and categorisation

studies remain inconclusive. Serotonin and genetic differences in serotonin transport seem to have the most empirical evidence for a role in autism spectrum disorder,⁷⁰ whereas data lending support to the roles of dopaminergic and glutaminergic systems are presently less robust, but are evolving. Study of the role of the

dopaminergic and cholinergic system, oxytocin, and aminoacid neurotransmitters shows promise.⁷⁰ Together, results of clinical, neuroimaging, neuropathological, and neurochemical studies⁶⁶ show that autism spectrum disorders are disorders of neuronal-cortical organisation that cause deficits in information processing in the

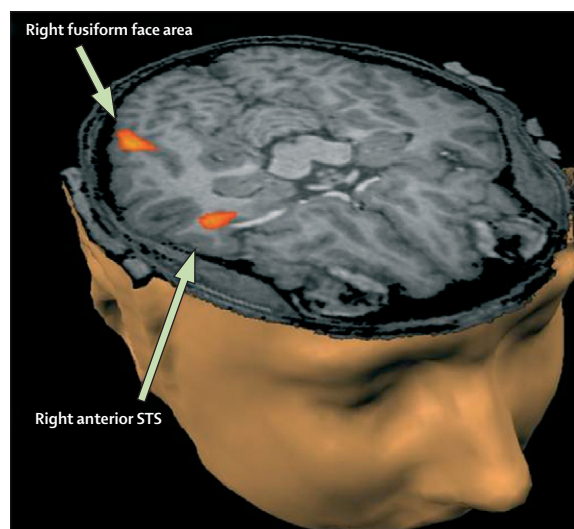


Figure 2: Functional MRI
Functional MRI is used to study activity of the relation of the amygdala to the fusiform face area and superior temporal sulcus (STS), which are responsible for face perception.

nervous system, ranging from synaptic and dendritic organisation to connectivity and brain structure. These changes probably alter developmental trajectory of social communication and seem to be affected by genetic and environmental factors.

Causes

Autism spectrum disorder is highly genetic. The relative risk of a second child having this diagnosis is 20–50 times higher than the population base rate,⁷¹ and thus families should consider genetic counselling. Parents and siblings often show mild, subsyndromal manifestations of autism, the broad autism phenotype,⁷² including delayed language, difficulties with social aspects of language (pragmatics), delayed social development, absence of close friendships, and a perfectionistic or rigid personality style.⁷³ Heritability estimates from family and twin studies⁷¹ suggest that about 90% of variance is attributable to genetic factors, making this disorder the neuropsychiatric disorder most affected by genetic factors. Dependent on the definition used, 60–90% of monozygotic twins are concordant for autism spectrum disorder, compared with about 10% for dizygotic twins.⁷⁴

Autism spectrum disorder is multifactorial, with many risk factors acting together to produce the phenotype. The difference between monozygotic and dizygotic concordance rates suggests some risk factors interact (ie, gene–gene or gene–environmental interactions). These effects could be a result of toxic environmental factors or epigenetic factors that alter gene functions, in turn altering neural tissue. Epigenetic factors can be specific aspects of the physical environment (eg, biochemically active compounds) or specific types of psychological experiences (eg, stress) that alter brain chemistry, turn genes off or on at specific times during development, or regulate gene expression in other

ways. The possible role of environmental and epigenetic factors is an area being studied.

Autism spectrum disorder is associated with known genetic causes in 10–15% of cases. The most common causes include fragile X syndrome (about 3%), tuberous sclerosis (about 2%), and various cytogenetic abnormal findings such as maternal duplication of 15q1-q13 (roughly 2%), and deletions and duplications of 16p11 (about 1%).⁷⁵ None of these causes are specific to the disorder, but rather are specific to a range of phenotypes, including intellectual disability.

Genetics

Since 2003,¹² fundamental changes in our understanding of the genetics of autism have taken place. Previously, this specialty was guided almost exclusively by the common disorder–common gene model,⁷⁶ proposing that many genes frequently identified in the general population each confer small-to-moderate effects on the phenotype. Only a few common variants have been identified as possible candidate genes in linkage and association studies,⁷⁷ and many of these have not been verified in subsequent independent sample replication studies, pointing to the difficulty of finding common causes in a heterogeneous disorder. Difficulty in finding robust common variants is not unique to autism spectrum disorder. Encouragingly, the largest genome-wide association study⁷⁸ has identified a common variant of statistical significance—an intergenic region between cadherin 9 and 10. This finding is exciting because cadherins are important for neuronal connectivity, and thus represents a possible biological mechanism to explain under-connectivity.

Another promising development in understanding the genetics of autism spectrum disorder is the discovery of

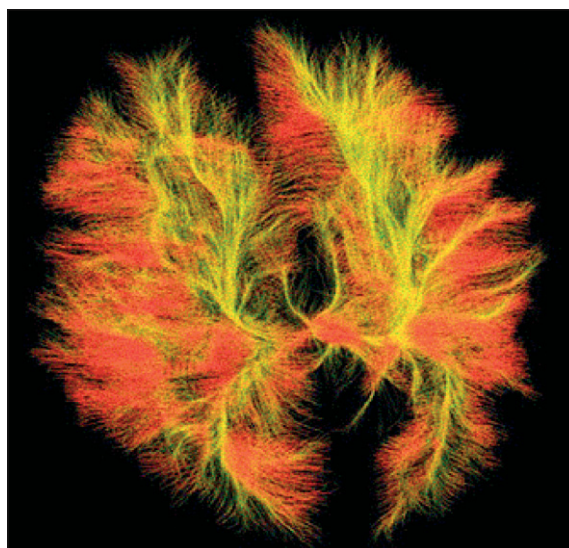


Figure 3: Diffusion tensor imaging
Used for measurement of axonal pathways, providing visualisation of connectivity of brain regions.

variations in the gene copy number as a risk factor.⁷⁹ Copy-number variation is a structural variation in the genome in which material is either duplicated or deleted. Copy-number variations can be de novo or inherited. Almost all these variations are deletions, with many fragments containing several genes.⁷⁶ De-novo copy-number variations seem to be strongly associated with intellectual impairment and dysmorphology.⁷⁹ Most seem to be individually unique, although we do not know the full implications of them because their relation to phenotype is not established,⁷⁶ and affected siblings do not always share specific variations.⁸⁰ Furthermore, to know whether a given de-novo variant is abnormal is difficult, because the population distribution of specific copy-number variations is unknown.

Insights into underlying biological mechanisms for autism spectrum disorder have been gained from study of syndromes with increased rates of this disorder. For example, functions of the genes underlying fragile X (*FMR1*) and Rett's syndrome (*MECP2*) implicate synaptic dysfunction in cause and pathogenesis.⁸¹ Further evidence⁸² for synaptic dysfunction as a unifying cause has come from findings of rare mutations in neural cell adhesion and synaptic molecules such as X-linked neuroligin 4 (*NLGN4X*) and neuroligin 3 (*NLGN3*). Convergence of genetic findings with implications for synaptic maturation is especially notable because findings from neuroimaging research also suggest that structural and functional brain connectivity is aberrant in autism spectrum disorders.⁶⁵ Thus, genetic and neurobiological evidence point to a good causal model of this disorder—namely, genetically mediated abnormalities of synaptic maturation and connectivity.

Researchers need to explain how genes that affect maturation of the synapse can account for specific behaviours and brain functions that are altered, while other processes are simultaneously spared. Possibly, problems of synaptic maturation are not ubiquitous in the brain and genes that affect brain function are regionally expressed, affecting only some systems. Alternatively, all circuits and synapses throughout the brain could be affected, but those mediating social and communicative skills and behavioural flexibility might be vulnerable to a common underlying synaptic defect. An important implication of this model is that an opportunity to intervene prophylactically during the first months of life might be available. With *Drosophila* models of fragile X syndrome and mouse models of Rett's syndrome, investigators have already shown that phenotype can be altered through administration of metabotropic glutamate antagonists (in the fragile X model),⁸³ or reinstatement of the *MeCP2* gene after birth (in Rett's syndrome).⁸⁴

Treatment

New developments

Advances in cognitive and affective developmental neuroscience, neurobiology, and the genetics of autism

Panel 2: Examples of treatments for core symptoms of autism spectrum disorder

Socialisation

Educational curricula⁸⁷

- Treatment and education of autistic and related communication handicapped children (TEACCH), strategies for teaching based on autism research (STAR), parent training, and inclusion with trained shadow

Communication and language⁸⁸

- Didactic and intensive training, and Milieu teaching

Social-skills training⁸⁹

- Social skills training and social stories

Behavioural treatment⁸⁶

- Discrete trial instruction, pivotal response training, and relationship development intervention

Communication

Communication intervention⁸⁸

- Within a comprehensive programme (eg, pivotal response training, or other centre), social pragmatics approach, and parent training

Augmentative and assistive communication⁹⁰

- Picture exchange communication system, sign language, and assistive technology (eg, vocal output devices)

Behavioural (eg, play, reciprocal communication)⁹¹

- Floor time/developmental, individual differences, relationship-based approach, applied verbal behaviour

Educational⁸⁷

- TEACCH, STAR

Behaviour

Behavioural intervention⁹¹

- Discrete trial instruction, and other comprehensive programmes using applied behaviour analysis

Psychopharmacology⁹²

- Selective serotonin reuptake inhibitors, anticonvulsants, atypical antipsychotics, α -2 agonists

spectrum disorder have resulted in potentially novel methods for early detection and improved targeting and effectiveness of treatments.⁸⁵ For example, neuroimaging strategies such as functional MRI and magnetoencephalography might provide biomarkers to monitor physiological changes before and after treatment. We still do not know which treatments or combinations of types of treatments will be most effective and for whom they will be effective.⁸⁶ Many interventions address core deficits (panel 2) and associated conditions (table 2). Core symptoms might be more malleable when treatment is initiated in early childhood, making early screening and diagnosis important.⁹³ Behavioural or developmental manifestations of core symptoms are most obvious, and thus are the main focus of treatment.

For most children, the main source of intervention is their family or educational system.⁷¹ Comprehensive treatment programmes include combinations of

specialised educational curricula, developmental therapies, behaviourally based treatments, and intensive parent training in the home, community, or school setting (panel 2).^{86,94,95} Parental stress might impede the effectiveness of early interventions;⁹⁶ hence, support for families must be integrated into treatment. Goals of treatment are to improve functional status of the individual through acquisition of skills in core deficit areas, and decrease effects of comorbid conditions. Medical treatments might be effective for addressing behavioural or medical comorbidities. No biological treatment to ameliorate all symptoms of autism spectrum disorder is presently available.

Psychosocial treatments

Increased numbers of children identified to have autism spectrum disorder and restricted availability of resources means that implementation of psychosocial interventions needs to include several approaches. Educational settings for interventions range from full time special education classes (in mainstream or special schools), part time or resource room special education support (eg, dual placement) in which the child is included in a typical education class, or typical class placement (mainstream) with supports provided to the child. In a US survey⁹⁷ of special education directors and autism consultants in Georgia, USA, researchers reported use of several strategies addressing socialisation or interpersonal relationships, acquisition of language, play, and other skills, and comorbid conditions such as cognitive deficits, physiological issues, and maladaptive behaviours.

Socialisation deficits can be addressed individually or in small group settings. Behavioural strategies and skills training can teach social skills, enhance peer interaction, and promote play skills. Because communication deficits are central to autism spectrum disorders, speech and language therapy is very important.⁸⁸ In young non-verbal children, strategies include use of principles of positive reinforcement to promote attention and imitation. For children with verbal apraxia, augmentative strategies such as the picture exchange communication system might improve communication and ameliorate behavioural difficulties. Assessment of the effectiveness of complex and technologically sophisticated augmentative systems is needed.⁸⁸

The most well researched treatment programmes are based on principles of applied behaviour analysis.⁷⁹ Treatments based on such principles represent a wide range of early intervention strategies for children with autism—from highly structured programmes run in one-on-one settings to behaviourally based inclusion programmes that include children with typical development. The first types of behavioural treatment programmes developed and examined were very structured, intensive, one-on-one programmes called discrete trial training, which were highly effective for up

to half of children enrolled in about ten randomised clinical trials⁹⁸ done in the past 20 years.

These intensive programmes are expensive, and children have difficulty generalising the information from a very structured session to group and community settings. Less structured, more naturalistic behavioural programmes have been developed, such as pivotal response training⁹⁹ and incidental teaching.¹⁰⁰ In individual and non-randomised group studies,¹⁰¹ researchers noted that about half of children have good outcomes in these types of programmes. Presently, even structured sessions typically include naturalistic methods for increasing generalisation and maintenance. A combination of these behavioural methods is more effective than is usual care for improvement of outcomes for children with autism.¹⁰²

Parent-mediated interventions have been shown in controlled studies to be an important aspect of intervention. Investigators identified that generalisation and maintenance of behaviour changes were improved when parents were trained in highly structured behavioural methods.¹⁰³ As behavioural programming for children with autism evolved from teaching one behaviour at a time to a broadened focus of increasing general motivation and responsiveness,¹⁰⁴ parent education also began to change. Parents were taught naturalistic strategies that were easier to use in the home, needed fewer hours of training, increased both leisure and teaching time, and improved parent satisfaction and enjoyment of the treatment. Parents are now thought to be important collaborators at all stages—from assessment through to goal development and treatment delivery.¹⁰⁵

Developmental models such as developmental individual-difference, relationship-based floortime model,¹⁰⁶ the social communication, emotional regulation and transactional support model,¹⁰⁷ and the Denver model¹⁰⁸ have shown some promising results. These models derive from research showing an association between social relationships and communicative development. Although the theory underlying these models differs from learning theory, many techniques used in naturalistic behavioural interventions are common to developmental approaches.¹⁰⁹

Pharmacological and medical approaches

Although existing pharmacotherapeutic agents are not effective for treatment of core symptoms of autism spectrum disorders, research has provided the impetus to study potential drug effects on core social and language impairment.¹¹⁰ In a double-blind, placebo-control cross-over study¹¹¹ of children with autistic spectrum disorders and comorbid attention-deficit-hyperactivity disorder, methylphenidate treatment was shown to have a positive effect on joint attention. Drugs might be helpful to address comorbid symptoms and as an adjunct to appropriate educational, behavioural, and developmental treatments (table 2).

The most common comorbid symptoms addressed by pharmacotherapy are attentional difficulties, hyperactivity,

affective difficulties (eg, anxiety and depression), interfering repetitive activity, irritability, aggression, self-injurious behaviour, and sleep disruption (table 2). Until recently, drugs were selected on the basis of extrapolation of their use in other disorders such as attention deficit-hyperactivity disorder and anxiety.⁹² Data from the Research Units on Pediatric Psychopharmacology¹¹² autism network provided support for use of atypical antipsychotics (such as risperidone) for treatment of irritability in children with autism spectrum disorders. Because evidence exists for abnormal serotonin function in individuals with this disorder, selective serotonin reuptake inhibitors have been used to treat anxiety, or rigid or repetitive behaviours. Results from clinical trials have been mixed. Unlike in adults, the side-effect profile (irritability and activation) might restrict use of these drugs in children with autism spectrum disorders.¹¹³ A multicentre trial¹¹⁴ of citalopram for repetitive behaviours showed that this drug did not improve these behaviours. Effectiveness of other widely used agents needs to be explored. King and Botsic⁹² reviewed pharmacological treatments for autism spectrum disorders.

Treatments should be prioritised by risks, dysfunction, and effect on the family of autism spectrum disorder.¹¹⁵ For example, a child with maladaptive behaviour in one situation might have an improved response to a behavioural plan after a functional behavioural analysis. Such an analysis would identify triggering events and consequences that might perpetuate undesired behaviour. Behaviours that are severe or arise in many settings, or both, and are not adequately treated with behavioural strategies alone might be helped by a combination of behavioural and drug treatment.¹¹⁵ Medical problems such as seizures and tics are more frequent in individuals with autism spectrum disorders than in those without the disorders, and should be treated appropriately.¹¹⁶

Complementary and alternative medical treatments are often used by families. Their popularity is in part attributable to the chronicity of symptoms of autism spectrum disorder and the absence of effective medical treatments. Popular biologically based treatments (panel 3) include supplements, specialised diets, immune therapies, gastrointestinal treatments, chelation, and withholding immunisations. Other non-biological treatments include manipulative and body-based treatments (eg, craniosacral manipulation, and auditory integration), mind-based and body-based therapies (eg, yoga), and energy medicine. Levy and Hyman¹¹⁷ reviewed studies of effectiveness of complementary and alternative medicine. So far, few studies have addressed safety and effectiveness of most of these treatments. Practitioners should support families as they assess the effectiveness, risks, and cost of treatments and assist in monitoring potential side-effects.

Although treatments might be effective for alleviation of symptoms, improvement of functional skills, and lessening of stress in families, no cure for autism

Panel 3: Examples of complementary and alternative medical treatments⁹⁷

Biological

- Supplements—eg, vitamin B6 or magnesium ion, dimethyl glycine, and cod-liver oil)
- Anti-infectives—eg, antibiotics, antifungals, and antivirals
- Immunoglobulins
- Off-label drugs—eg, secretin
- Chelation medications
- Gastrointestinal medications
- Elimination or special diets—eg, gluten free or casein free
- Hyperbaric oxygen administration

Non-biological

- Auditory integration training
- Chiropractic therapy
- Craniosacral manipulation
- Facilitated communication
- Massage and qigong
- Interactive metronome
- Reiki
- Transcranial stimulation
- Yoga

spectrum disorder is yet available. Outcomes are improved with early detection and intensive treatment.¹² Data for long-term prognosis are scarce. Factors associated with poor outcomes are intellectual function in childhood (intelligence quotient < 70), early communication deficits, and continued ritualistic and stereotyped behaviour.¹¹⁸ Some adults with autism gain employment, live independently, and establish relationships; however, most adults remain dependent on family or others for support.¹¹⁸

Future directions

In the past 10 years,¹¹⁹ much progress has been made with diagnosis and management of autism spectrum disorder. Hopefully, early detection and diagnosis of infants and children at risk will enable treatments to be designed and implemented to alter the course of early behaviour and brain development.⁸⁵ Amaral and colleagues¹²⁰ suggested that the heterogeneity of factors affecting brain development predicts a heterogeneous pattern of neuropathology. Through neuroimaging approaches such as diffusion tensor imaging, functional MRI, and magnetoencephalography, abnormal findings have been identified in neuronal patterning, cortical connectivity, synaptic organisation,⁶⁶ and electrophysiology. Improved early identification with phenotypic characteristics and possible biological markers should allow for increasingly individualised and effective treatment. Promotion of early identification, improved understanding of brain mechanisms, development of effective treatments, and strategies to moderate the effect of autism spectrum disorder on families is needed.

Contributors

All authors contributed to the design, search strategy, synthesis of information identified in the search, writing and editing, and integration of editing as suggested by co-authors. No medical writer was involved in creation of this Seminar.

Conflicts of interest

We declare that we have no conflicts of interest.

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