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Autism Spectrum Disorders: Clinical and Research Frontiers

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ABSTRACT

Autism spectrum disorders (ASD) are common neurodevelopmental disorders that occur along a broad continuum of severity with impairments in social interactions, communication, and behaviour. This review highlights recent advances in autism research that shed light on the causes of the disorder and that have implications for clinical practice. It focuses on 1) the rising prevalence of ASD with attention to recent epidemiological studies, 2) important genetic discoveries that may affect clinical evaluation of children with ASD, 3) active areas of research in cognitive neuroscience that seek to explain the underlying mechanisms of a complex disorder, and 4) important studies on clinical populations with implications for screening and early identification of infants and toddlers with ASD.

INTRODUCTION

Over the last decade, interest in autism spectrum disorders (ASD) has exploded in both research and public spheres. Prominent parent-led advocacy groups have successfully influenced public awareness of and interest in autism, at the same time that they have advanced public and private funding in autism research. What was once thought of as a rare, severe disorder caused by psychodynamic interactions is now recognised to be a common neurodevelopmental disorder, which occurs along a broad continuum of severity. Neuropathological abnormalities have been identified that can be traced back to events during foetal development, [1] and atypical behaviour and development are evident well before diagnosis during the toddler or early childhood years. [2] Autism is not thought to be a single disorder, but rather many different disorders described by a broad behavioural phenotype that is a final common pathway of atypical neurodevelopment. [3]

Despite the intense research focus on ASD in recent years, the underlying aetiologies remain obscure in most cases. The increasing prevalence of the disorders, in addition to the belief that early identification and treatment can improve outcomes for many affected children, impart a sense of urgency to the field, making it a fertile ground for research across many disciplines. This urgency also affects clinicians, who are asked to recognize the earliest signs of autism and to follow growing numbers of children with ASD in their practices. [4-6] With a rich and growing body of research in ASD, many of the basic science discoveries have shed light on the underlying neurobehavioral mechanisms (including neural circuitry and neurotransmitters that differ in individuals with ASD), linking them to genetic aetiologies and clinical presentation. Most research findings, however, are currently years away from having direct clinical applications. This review highlights some recent advances in autism research that are likely to influence clinical care, including diagnosis, evaluation, and treatment in the future.

CLINICAL CHARACTERISTICS

All individuals affected by ASD share a common triad of impairment in social interactions, impaired and atypical verbal and non-verbal communication, and repetitive and usual behaviour or play. [7, 8] Symptoms range from severe and unmistakable to subtle signs of social-communicative dysfunction. Significant impairments in the social aspects of communication and social reciprocity are what distinguish ASD from other developmental disorders. Autism in its most severe form was first described by Leo Kanner in 1943. His patients displayed severe language impairment, social isolation, insistence on sameness, and motor stereotypies. [9] Hans Asperger described what is now his eponymous disorder in 1944, but his publication was not translated and disseminated in the English language literature until the early 1990's.[10] Asperger's patients resembled Kanner's, though they had stronger cognitive and language abilities. DSM-IV TR uses the umbrella term of Pervasive Developmental Disorders (PDDs), encompassing five disorders: Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), Rett's Disorder, and Childhood Disintegrative Disorder. The term Autism Spectrum Disorders does not appear in DSM or ICD but is now widely accepted in both research and lay literature. Usually the term refers to the DSM diagnoses of Autistic Disorder, Asperger's Disorder,

and PDD-NOS. In clinical practice, however, the labels of ASD, autism and PDD are often used interchangeably. In this review we will follow the same convention.

The concept of the autism spectrum is useful clinically because of the dramatic variation in symptomology both within and between each diagnostic category, ranging from relatively mild to very severe symptoms in each of the three areas of impairment. Autistic Disorder is the most severe form of the disorder; many affected individuals are non-verbal or have significant cognitive impairment, and many have severe motor stereotypies and disruptive behaviours. Studies have shown wide variation in rates of mental retardation, with older studies, using earlier diagnostic criteria, showing most individuals with ASD having IQ's less than 70. Broader variation has been shown in more recent studies. Several have demonstrated that fewer than half of affected individuals had significant cognitive impairment when cases of PDD-NOS and Asperger's Disorder were included. [11-13**]** With the broadening of the concept of the autism spectrum and increasing prevalence of ASD, more individuals with milder symptoms of autism and less cognitive impairment have been identified. Population-based studies using current diagnostic criteria will be necessary to resolve this question. "High functioning" individuals meet DSM criteria for Autistic Disorder; however, they do not have significant cognitive impairment, at least when assessed on measures that do not have significant language demands, and they may function with minimal supports or show giftedness in one or more areas.[14] Asperger's Disorder is often referred to as "a mild form of autism," which underestimates the negative impact of the disorder on many affected individuals. Those with Asperger's Disorder have, by definition, average or above average cognitive abilities and acquire language by the preschool years; they may have advanced language and interests that are atypical in subject and/or intensity of focus. PDD-NOS is a diagnosis of exclusion, referring to a significant level of impairment on functioning with sub-threshold symptomology or atypical presentation.

EPIDEMIOLOGY

Recent epidemiological studies from the United States and Great Britain point to dramatically increased rates of ASD. In the 1970's and 1980's, reported prevalence was around 5/10,000.[15, 16] Since the mid-1990's, rates of ASD have risen steadily. Large epidemiological studies in 2003 demonstrated a prevalence of 1/166-1/250 in a large US metropolitan area.[17] A more recent study from 14 different US states showed variability based on geography, race, and source of diagnostic information, with an overall prevalence of 1/152.[11] Another recent study from the UK, which included direct assessment of many of the individuals in the sample, reported a higher rate of about 1 in 100.[18] In these studies, the more extensive the clinical information available (for example, direct assessment of subjects as opposed to educational and/or medical record abstraction), the higher the prevalence of autism identified.

Thus, even these high rates may be underestimates of the true prevalence of ASD in the 21st century. It is clear that much of the dramatic increase in prevalence is due to broadening of diagnostic criteria over time with the adoption of the concept of the autism "spectrum" and the new category of Asperger's Disorder in the early 1990's, which includes individuals with relatively subtle symptoms who would have been given

different developmental or psychiatric diagnoses in the past.[19] In addition, some studies suggest that diagnostic substitution from mental retardation or learning disabilities to autism in educational administrative data sets contribute to the increase.[20] It is possible increasing prevalence reflects, in part, a true increase in the incidence of autism. Such an increase could not be easily explained by genetic causes alone, which should not change over such a short timeframe. To explain this rapid increase, Baron-Cohen has theorized that individuals with high functioning autism and Asperger's Disorder may demonstrate characteristics of an "extreme male brain," with an over-developed systemising approach to the world. According to Baron-Cohen, these individuals (like many typical men) tend to gravitate towards rules-based vocations and avocations. He proposes that this leads to assortative mating of similarly inclined systemisers, which could explain high rates of autistic traits and ASD among individuals in highly technical and systemized field, such as computers or engineering, and their children.[21]

Many hypotheses of environmental aetiologies of autism are fuelled by the increasing prevalence and awareness of ASD. To date, large epidemiological studies have not supported a causal link between autism and some of the most well publicized controversies about aetiologies of ASD, such as the MMR vaccine or thimerosal. [22-24] Debates in this area of study continue to rage and are a source of much distrust between the lay and research communities. Recent studies focusing on different types of environmental factors (for example, paternal age) expand our conception beyond traditional toxins to broader elements of the prenatal environment that may influence expression of susceptibility genes.[25] The technical challenges of performing epidemiological studies on environmental influences of neurodevelopment are legion, but large scale studies investigating the role of the environment in the aetiology of ASD are in development in the US, through the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health and in Denmark, through a collaborative program with the CDC. Because of tremendous heterogeneity of the disorders included in the autism spectrum, it is likely that research will ultimately uncover a variety of environmental factors interacting with a number of genes in different ways that contribute in part to the increase in prevalence, rather than a single environmental culprit.

While epidemiologic studies content with a vast number of potential environmental influences that may be causal in ASD, laboratory researchers attempt to identify the basis of ASD in controlled settings. In recent years there has been a surge in research in the areas of genetics and cognitive neuroscience. Investigators search for causal links between genes, their molecular functions, and the neural pathways that appear to be disrupted in ASD, manifesting as its distinctive behavioural phenotype.

GENETICS

Despite uncertainty regarding specific aetiology in most affected individuals, the genetic underpinnings of autism are indisputable. Studies of monozygotic and dizygotic twins show that autism is highly heritable.[26] Family studies demonstrate that elements of a broader autism phenotype are common, so that first and second degree relatives of affected individuals may display elements of the required triad of symptoms (such as language delay or social phobia) without meeting full criteria for one of the ASD.[27-29]

Conversely, many cases are sporadic. There are thought to be many genes associated with autism, and it is likely that most affected individuals carry several genes that predispose them to the disorder. What gene-gene, gene-environment, or epigenetic interactions cause one child to develop the disorder and another to be spared is not well understood. Published studies regarding routine clinical genetic testing recommended for individuals with ASD that reflect recent advances in the field are now emerging in the United States, [30,31] although consensus guidelines in the US and UK have been limited to endorsements of high resolution chromosomes and Fragile X testing.[32-34] Currently, clinical practice of genetic testing for ASD beyond karyotype and Fragile X in both the US and the UK is not consistent and is influenced by available resources and cost. Some authors have advocated a tiered approach to genetics evaluation for idiopathic ASD, with high resolution chromosomes and Fragile X in all cases; if results are unrevealing, further evaluation is recommended.[35] It is important for physicians who send genetic testing to have familiarity with the interpretation of results, or to have access to clinical geneticists who can aid in interpretation.

The diagnosis of ASD is an increasingly common indication for a clinical genetics evaluation, depending on clinical setting and resources. Genetic evaluations can be especially useful in cases of "syndromic" ASD; that is, cases in which there are dysmorphisms, neurocutaneous findings, significant cognitive impairment, abnormal neurologic examination or seizures. In clinical practice, many individuals with "idiopathic" autism, who lack the comorbidities listed above, are less likely to be referred for more complete genetic evaluation. Newer, longitudinal studies of infant siblings of children with ASD indicate that recurrence risks in families (at least in this specific sub-population) may be even higher than reported in older twin studies, with up to 20% of baby siblings meeting criteria for ASD at age two or three in one published study.[36] If these higher rates are replicated, having more than one affected family member, even in "idiopathic" autism, may also be a strong indication for clinical genetic evaluation.

Though currently ASD is diagnosed on the basis of behavioural phenotype, the importance of a genetic evaluation may be realized with the diagnosis of a specific chromosomal disorder, single gene disorder, or genetic syndrome associated with ASD. A genetic diagnosis may result in better anticipatory guidance, more precise genetic counselling with more accurate recurrence risks, and the possibility of future prenatal diagnosis, if desired. A recent study in a knockout mouse model of Fragile X showing improvement in clinical symptoms with reduction of a glutamate receptor expression (mGluR5) points to a future in which pharmacological treatment may target products of gene expression in neurodevelopmental disorders, including ASD.[37] As more informative genetic testing becomes widely available, more extensive testing will likely become the standard of care at the time of an ASD diagnosis and will take on a larger role in evaluation. Indeed, failure to diagnosis Fragile X in a timely manner, for example before the birth of a second affected child, may be considered negligence (“loss of chance doctrine”) with associated liability.

A clinical genetics evaluation attempts to identify a known disorder by a complete dysmorphology assessment and Wood’s lamp exam. Metabolic testing may be

appropriate if symptoms associated with an inborn error of metabolism are present (for example, clinical decompensation with illness or regression of motor or cognitive skills), but such testing is not routinely recommended. Neuroimaging may also be helpful when there are abnormal findings on neurologic exam or a history suspicious for seizures. Targeted genetic testing may be available if a specific diagnosis is suspected because of physical or behavioural characteristics (for example, Angelman syndrome, Neurofibromatosis type 1, Smith-Lemli-Opitz syndrome, Smith-Magenis syndrome, Sotos syndrome, Tuberous Sclerosis). Even in children without obvious dysmorphisms, visible cytogenetic abnormalities may be present in up to 5% of individuals with ASD, so high resolution chromosome analysis is now a standard recommendation.[38] Fragile X DNA analysis should be part of the evaluation of all individuals with ASD, whether or not they have cognitive impairment and/or physical stigmata of Fragile X, as reported rates approximate 3%.[39]

Recent publications have established the utility of identifying cryptic chromosomal deletions/duplications by whole genome microarray analysis in both clinical and research ASD populations. [40-43] Single nucleotide polymorphism (SNP) microarray analysis is a whole genome approach to identifying cryptic chromosomal copy number changes (deletions or duplications at the level of a single nucleotide). Increased sensitivity in detection of these copy number changes is demonstrated using these techniques in comparison to the earlier targeted arrays. Whole genome microarray analysis not only identifies microdeletions/microduplications and subtelomeric deletions/duplications known to be associated with ASD, but also identifies such alterations in genomic areas containing genes not previously implicated in the aetiology of ASD. This new, powerful approach can be clinically useful for genetic counselling, especially in evaluation of "syndromic" autism, and it may uncover additional genes responsible for the ASD phenotype.

Specific focus on the chromosome 15q11-q13 region is warranted as the maternally inherited duplication has been described in approximately 1% of individuals with ASD.[44] Individuals with this duplication have the behavioural phenotype of ASD in addition to increased incidence of seizure disorder, hypotonia, and moderate to severe mental retardation with associated absent or delayed speech. The *MECP2* gene, which causes most cases of Rett syndrome, is likely the etiologic factor in a small number of cases of ASD. Sequencing and deletion/duplication analysis of the *MECP2* gene is often requested in those females with atypical Rett phenotype. Several additional X-linked genes (i.e., *ARX, STK9, Neuroligin-3* and *4*) as well as autosomal genes (for example, *PTEN* for those with pronounced macrocephaly) are also clinically available and may be indicated in those ASD patients with a previous unrevealing evaluation.

In addition to the specific genes noted above, genome wide linkage and association studies have implicated multiple loci associated with an ASD phenotype.[45] Whole genome microarrays and candidate gene testing will likely identify a host of new genes associated with the ASD phenotype. Clinical testing for these genes is anticipated in the future, adding to the ever-expanding list of specific genetic testing for ASD. It is hoped that as genetic understanding of ASD continues to advance, the underlying mechanisms

of the disorder will be uncovered, leading to earlier diagnosis and more effective treatments.

COGNITIVE NEUROSCIENCE

In the same way that numerous genes and areas of the genome have been implicated in autism, differences in diverse areas of the brain have been found to be associated with autism. Neuroanatomical studies have demonstrated differences in volumes of different regions, including cortical lobes.[46,47] white matter,[48,49] corpus callosum,[50] and amygdala[51] and variations in neurotransmitters, including serotonin[52] and GABA.[53] Recent studies suggest that these neurobiological differences need to be considered within a developmental perspective.[54-56] Research using functional brain imaging methods is of particular interest currently, because of its ability to elucidate underlying mechanisms of impairments in social communication and cognition that are characteristic of ASD. Despite wide variation in ASD phenotypes, specific brain regions and neural circuits have been repeatedly implicated in functional imaging studies.

Atypical eye gaze has long been recognised as a clinical hallmark of ASD. It is unclear, however, whether it is a primary cause or a result of the social impairments or anxiety in autism.[57-58] Sophisticated eye tracking technology has been utilised alone and in conjunction with functional imaging techniques to investigate what brain areas are activated in individuals with autism, their siblings, and other unaffected individuals when different social stimuli are presented.[59-60] Most subjects in these studies are high functioning because of the need to have subjects cooperate with lying still in an enclosed MRI machine. The generalisability of the results of the studies to more cognitively impaired individuals is not clear. Different investigators have used a variety of paradigms involving presentation of photos of faces with different emotions and with a variety of physical distortions. Several investigators have shown that individuals with autism spend less time looking at eyes, and more time looking at mouths or other objects that are presented.[61,62] Other studies have demonstrated hypoactivation of the fusiform gyrus and superior temporal sulcus, brain regions implicated in face and gaze processing in unaffected individuals; however, the degree of activation is directly related to the time spent looking at the eyes.[59] Interestingly, unaffected siblings of individuals with ASD may show an intermediate level of activation of these circuits, between those with autism and unaffected individuals.[60] This may have implications for the clinical evaluations of unaffected siblings, who can show subtle atypical behaviours without achieving the threshold for diagnosis of ASD. Differences in emotional processing have also been suggested, with variation in size and activation of the amygdala when affected individuals are presented with pictures of faces demonstrating different types and degrees of emotion.[59,60,63]

A characteristic of the social cognition of people with autism is impairment in Theory of Mind (ToM), or the ability to understand others' intentions or mental states.[64] Differences in processing of faces or eye gaze are likely associated with difficulties in social perception or the ability to "read" others' emotions by looking at their faces. Recent studies in the neural circuitry of what is called the Mirror Neuron System (MNS), has implications for the development of ToM in autism, and presents an intriguing

hypothesis for a neuronal basis of the core deficits of ASD.[65,66] Mirror neurons were first described in 1996[67] when primate researchers noted that the same motor neurons fired in macaque monkeys whether they carried out a specific action or observed another monkey or human do the same action. During imitative learning, the same neurons were activated. Even more remarkable, the same neurons activated when the monkey saw another start to do the action, though the action itself was shielded. This implies that the neurons fired based on the monkey's understanding of the goal of an action or of the intention to do an action. This has been hypothesised to be the neural basis for understanding more complex intentions, or mental states, of others.[68] Functional imaging studies have shown analogous results in humans,[69] and differences have been shown in activation of the human MNS in autistic and unaffected individuals.[65] Whether differences in facial and gaze processing, in conjunction with differences in mirror neurons, can explain core deficits in social mirroring, social learning, and difficulties in understanding others' mental states or intentions has not yet been clearly demonstrated; however, this is an area of active study.

CLINICAL STUDIES: INFANT SIBLINGS AND HEAD CIRCUMFERENCE

A new and exciting area of study in recent years involves prospective, longitudinal studies of infant siblings of children with ASD, which are currently in process in several centres around the world.[2] Other studies investigating early indicators of ASD have relied on retrospective parental report or home videotapes in the first year of life, presenting methodological limitations.[70] Because of the increased risk of having another child diagnosed with autism in families with one affected child, cohorts of infant siblings offer the potential for in-depth, prospective study of affected children very early in development that is not feasible in studies of the general population. Most of these studies compare groups of siblings of children with autism to groups of siblings of typically developing children. Assessments focus on development and behavioural markers from the age of six months to at least 36 months, when the diagnosis of an ASD is stable. This research promises to uncover the earliest signs and symptoms of autism, with important implications for the development of screening tools, diagnosis, and treatment.

In these studies, a number of developmental and behavioural markers have been found to be associated with later diagnosis of autism. These findings expand upon those of earlier retrospective studies. In general, most infant sibling studies find few significant differences before the age of 12 months in language or cognition, though several identify subtle differences in social engagement.[71,72] Consistent findings in a variety of studies include the core deficits of ASD, with some intriguing behavioural differences between siblings later diagnosed with autism and those who do not meet criteria for diagnosis. In general, siblings at 12 months who are later diagnosed with ASD show delays in receptive and expressive language (including babbling), gestures, initiation of and response to joint attention, pointing, showing, imitation, response to name, visual attention to objects, social responsiveness, and temperamental characteristics. [2]

Results from these studies push the lower age limits of diagnosis, presenting new challenges for clinical diagnosis in very young children for whom the nature of

appropriate and effective treatment is not clear. Once thought to be difficult to diagnose before the age of four or five years, the diagnosis of autism at age two has been shown to be stable over time and is a goal for age of diagnosis in order to maximise potential for early treatment. Unfortunately, there continues to be significant lag between the time that parents report concern about their child's development and when the child is actually diagnosed with an ASD. A recent epidemiological report from the United States showed the mean age of diagnosis to be between the age of four and five years. [11] This may be due, in part, to inclusion of children with milder symptoms of ASD and Asperger's Disorder who are more difficult to diagnose before school age because of relatively subtle symptoms. Because of the efficacy of early intensive treatment for many children and continued late identification of ASD overall, the development of sensitive and specific screening tools in the first years of life is critical. Tools under development target children as young as 12 months. [73] Results from studies of infant siblings should shape the development of screeners and inform the diagnosis of autism in the youngest children. For example, in one recent study, three-fourths of 12-month olds who failed to respond to their names had developmental delays at 24 months, many of whom met criteria for ASD.[74] In the absence of genetic or other bio-markers of autism, diagnosis will continue to rely on behavioural observations and clinical judgment including research findings such as this which can be easily translated to the clinical setting to inform clinical assessment.

One potential low-tech and accessible biological marker for autism is head circumference or trajectories in head growth the first two years of life. Numerous studies have shown differences in head circumference in children with ASD compared to unaffected individuals.[75] Initial studies focused on macrocephaly in a subset of young children with ASD between the ages of two to five years, followed by return to average head circumference by adolescent or adult years. [76] These children had normal or small head size at birth. No one region of the brain is implicated in this enlargement, though it has been hypothesised that synaptic proliferation which characterises early neurodevelopment may not be balanced by the normal check of synaptic pruning. Others have suggested that variation in myelination may be involved.[77] More recent studies have shifted focus from brain size to rate of brain growth. In a large study, a rapid and unexplained acceleration of brain growth has been demonstrated during the first year of life that is followed by a relative deceleration after the first year of life.[78] There have been conflicting results about the level of functioning of children who showed this brain growth pattern. The fact that the acceleration occurred before clinical symptoms were noted has clinical relevance, as monitoring of rate of head growth may serve to identify children at higher risk of developing ASD before clinical presentation. At this time, accelerated head growth or macrocephaly alone cannot be used to identify toddlers at risk for autism. It may be one of several risk factors that, in combination with other concerns such as family history or lack of response to name at 12 months of life, should signal increased vulnerability ASD, prompting closer developmental monitoring in the clinic setting or earlier referral for specialist evaluation.[77]

CONCLUDING REMARKS

With growing interest in ASD by researchers and clinicians over the last decade, there is optimism that the field is on the cusp of making great advances. The broad phenotypic variation in the disorder complicates research design, clinical diagnosis, and treatment. The answer to the fundamental question of what causes autism remains shrouded in mystery in most cases, much to the dismay of many families affected by the disorder. Solutions to this complex problem and clear biomarkers of the disorder are unlikely to be revealed quickly or easily. Epidemiological studies describe alarming increases in prevalence without clear precipitants. Dramatic advances in molecular genetics and genomics uncover candidate regions that may elucidate fundamental mechanisms to be explored by cognitive neuroscientists. Far from bench research, meticulous studies of infant siblings of children with ASD reveal the earliest, subtlest signs that development has gone awry and will result in autism. Despite their limitations, research advances promise to inform clinical care, optimizing our ability to diagnosis and treat ASD appropriately, thus enabling all individuals with ASD to realise their full potential.

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