

What's New In Autism: Etiologies and Treatment

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Autism is a neurodevelopmental disorder characterized by abnormalities in the development of reciprocal social interaction and communication and by repetitive and/or ritualistic behaviors (American Psychiatric Association, 1994). It differs from mental retardation in that the problems with socialization and communication in autism are qualitatively, as opposed to quantitatively, different from typical development. That is, children with mental retardation are simply delayed in the development of social-communication skills but children with autism display behaviors not usually seen in children with mental retardation or in young, typically developing children. For example, affected individuals often do not appropriately establish eye contact when others talk to them or show interest in sharing attention with others. As young children, they usually do not use gestures to communicate but, instead, guide others to want they want. Vocally, they may meaninglessly echo what others say to them; insist on talking to others about topics of conversation that are of little interest to their partners; communicate with an unusual vocal intonation style, etc. Repetitive or ritualistic behaviors often displayed include hand flapping or bizarre finger movements, unusual gait patterns, meaningless spinning of self or objects, excessive fascination with parts of objects, severe self-injury, etc.

Autism is a member of a class of conditions that fall under the general rubric of Pervasive Developmental Disorder. These other similar autistic-like conditions include Asperger's, Rett's, and Childhood Disintegrative Disorders. People with social interaction abnormalities that do not meet full criteria for autism or these other conditions are diagnosed with Pervasive Developmental Disorder - Not Otherwise Specified.

Autism occurs more frequently in males than in females with a ratio of about three or 4 to 1. About 80% of affected individuals have intelligence levels in the mentally retarded range and females tend to be more impaired, intellectually, than males. Most of these children appear physically normal, if not attractive, at first glance. A significant percentage, however, display minor physical anomalies (typically of the hands and ears) suggestive of first trimester disturbances in development (Rodier, Bryson, & Welch, 1997).

Autism presents a serious challenge to caregivers as well as to those involved with the affected person's education, treatment, and employment. Issues of diagnosis, etiology, treatment, prognosis, and family planning are matters of major concern to parents, clinicians, and researchers. Unfortunately, there usually exists no rational biomedical intervention for this disorder because, in most instances, the biological mechanisms responsible for this condition have not been clearly elucidated although progress is being made. In this paper, I will briefly cover what we know or think we know about the causes of autism, as well as which interventions are helpful.

Etiology. Despite early claims by persons such as Bruno Bettelheim, autism is not caused by psychological mistreatment of children by mothers (or fathers). Unfortunately, this belief still persists in certain countries of the world. Instead, research indicates that, in most cases, autism results from an aberration in genetic functioning (see below). That is, this

aberration, either directly or indirectly (e.g., by making the individual more susceptible to exogenous infectious or teratogenic agents), disturbs the normal course of central nervous system (CNS) development. These disturbances in CNS structure and/or function are then responsible for the phenotype that we call autism. However, controversy exists as to whether autism is the only phenotypic expression of this altered CNS development.

When the genetic mechanisms responsible for behavioral disorders are studied, crucial questions are, "What is inherited?" and "How should it be measured?" Fortunately, techniques have been devised that allow for the reliable diagnosis of autism, when assessment is carried out by highly trained personnel and for quantitative assessment of the severity of various aspects of the disorder (Cohen, Schmidt-Lackner, Romanczyk, & Sudhalter, 2003). However, autism may only be one segment of a "broader phenotype" of behavioral dysfunction that is inherited in families. This "broader phenotype" is characterized by oddities in language and/or social skills, with or without the presence of repetitive or ritualistic behaviors and there is evidence that such a broader phenotype is present in some first degree and extended relatives of affected children. Whether to focus on well-defined cases or to include this broader phenotype in studies of genes that may cause autism is unclear.

Known Genetic Syndromes and Autism. Non-genetic causes of autism exist. For example, insults to the CNS caused by viruses such as maternal rubella or teratogens such as thalidomide can produce autism. In most instances, however, autism (as well as its associated, co-morbid deficits such as mental retardation) is likely to be the end product of an abnormal genotype.

An increasing number of disorders with a known genetic etiology have been reported to be associated with autism and many have been documented extensively (Gillberg & Coleman,

2000). These disorders include untreated phenylketonuria, tuberous sclerosis, fragile X syndrome, Hurler's syndrome, Down syndrome, and Williams syndrome, amongst others.

Deletions at the long arm of chromosome 15 (in the q11-q13 region) have been reported in association with Prader-Willi and Angelman syndromes. In these syndromes, the expression of the genotype is determined by which parent contributes the mutation to the child. In Angelman syndrome (also known as “Happy Puppet Syndrome”, characterized by severe retardation, frequent smiling and awkward gait), the child inherits the mutation from the father whereas in Prader-Willi syndrome (associated with extreme obesity, and mild retardation), the mutation is inherited from the mother. Interestingly, several studies have reported chromosome 15 duplications (including the Angelman/Prader-Willi regions) in people with autism with all cases being maternal in origin.

Of all the chromosomal disorders associated with autism, the fragile X syndrome is the one most commonly reported (Cohen et al., 1991). Fragile X syndrome is due to a malfunction at the base of the long arm of the X chromosome (at region q27.3) and is a member of a new class of disorders with expanded trinucleotide repeats. Regional expansion of a (CGG)_n repeat sequence, in the 5' untranslated region of a gene designated as *FMRI*, across successive generations, results in cessation of functioning of the gene (this is due to methylation of the promoter region. This is the region of the gene where transcription starts). It is the lack of expression of the *FMRI* gene that appears to be responsible for the physical and behavioral manifestations of the disorder.

It is therefore evident that autism is etiologically heterogeneous. It is important to recognize, however, that the genetic disorders described above do not uniformly cause autism. Rather, they produce a variety of disturbances in development. It is unclear what other genetic

or endogenous environmental factors may be necessary to cause autism in such conditions. It is likely, however, that different genotypes (or teratogenic effects) result in similar effects on the developing CNS and that this similarity, at a "neuro-computational" level (Cohen, 1998), is responsible for the similarity in behavior pattern that we see across different etiologies.

Genetic Factors in Etiologically Unknown Cases. In most cases, the etiology of autism cannot be easily identified. However, sibling recurrence risk and twin studies have indicated that genetic factors play a very strong role with broad heritability estimates exceeding 0.9 (Bailey et al., 1995). This means that genetic, and not environmental, effects explain most cases.

The risk of a sibling of an autistic child having autism had been assumed to be about three percent. However, in families with a handicapped child, so-called stoppage rules apply. That is, parents are less likely to have an additional child given that they already have one with a handicap. More recent studies that have taken stoppage rules into effect suggest that the risk to siblings is about nine percent. This results in risk ratios (ratio of risk to siblings relative to the population prevalence) ranging from 43 to 450, depending upon the actual prevalence of autism.

Twin studies further support a genetic basis for autism. In a comparison of monozygotic (MZ) and dizygotic (DZ) twins, concordance rates for the former have ranged from 36 to 96%. Concordance rates for dizygotic twins have been considerably smaller, ranging from zero to 24%, suggesting that the base rate for this group is not significantly different from the overall sibling risk.

Complicating this analysis is the definition of the phenotype, as discussed above. It has been found that in families with a child having autism, siblings, parents, and extended family members often have milder social, language, and/or cognitive problems. Thus, what is inherited may not be autism, per se, but a social-language-cognitive disorder that, when severe enough,

manifests itself as autism. When this broader phenotype was considered, then 92% of MZ twins and 10% of DZ twins were considered to be "affected" (Bailey et al., 1995).

The marked difference in MZ-DZ concordance rates for autism suggests that autism is, most likely, a polygenetic disorder in which multiple genes interact to produce the phenotype. That is, mutations in certain genes might affect the development of social and language skills only when these mutations interact with certain mutations in other genes.

There has been a strong effort by many different centers throughout the world to identify the genes involved with autism. Most of these studies have focused their efforts on families with more than one individual affected with autism. In these “multiplex” families (e.g., with two or more brothers or sisters with autism), genetic factors are probably quite strong and it is therefore hoped that gene finding will be made quite a bit easier as a result. A number of these centers have continued to report significant association of autism with the chromosome 15 region cited above. Other centers have found associations with other chromosomal regions including regions on chromosomes 5, 8, 19, and X.

Recently, in collaboration with a group in Canada, we have found that severity of autism and level of cognitive functioning are associated with a variant in the gene that codes for an enzyme important in brain development and functioning – monoamine oxidase-A (Cohen et al., 2003). This finding has implications for prediction of outcome and for treatment. More information about our genetic research can be found at the following website: <http://www.autismresearch.ca>.

The Prevalence of Autism. It should be noted, at this point, that there is no evidence that autism is caused by childhood exposure to vaccines and recent studies indicate that the incidence of autism may actually be higher in infants who have not received such vaccinations. The belief

that vaccines may play a role stems, in part, from a post-hoc study of the prevalence of autism carried out in California. These researchers retrospectively examined all cases diagnosed with autism in the California state system that tracks individuals with developmental disabilities. When they plotted the number of such cases relative to the birth year of those individuals, there was a rather dramatic increase in the numbers of affected persons born since 1978. One researcher noted that the use of the measles, mumps, and rubella vaccine began in the USA in 1976 and speculated that this was the cause of the rapid rise in autism cases.

However, something more obvious may explain this change in numbers of diagnosed cases. Autism was first defined as its own entity in the DSM-III in 1980 and it was at this time that the term Pervasive Developmental Disorder (PDD) was introduced. Prior to this publication, autism was considered to be a form of childhood schizophrenia and was poorly defined. The DSM-III had three types of PDD: Infantile autism; Childhood-Onset PDD and Atypical PDD. In 1987, the DSM-III-R revised this to two types: Autistic Disorder and PDD-Not Otherwise Specified, with autism more broadly defined. Finally, the DSM-IV lists five types of PDD: Autistic Disorder; Childhood Disintegrative Disorder; Asperger's Disorder; Rett's Disorder; and PDD-Not Otherwise Specified. Now, a child born in 1978 would be 2 years of age by the time the DSM-III came out. Children are often first diagnosed somewhere between 2 and 5 years of age and children born after 1977 would be more and more likely to have been diagnosed by professionals using the DSM-III. Children born several years later would be diagnosed by professionals using even broader DSM criteria. Thus, changes in diagnostic criteria could readily explain the "rapid" increase in autism cases. This was also evident in data supplied to this author by the New York State Department of Education. While the percentage of young children diagnosed with autism registered in this system has increased linearly over the

years from 1994 to 1998, the percentage of children diagnosed with mental retardation has linearly decreased by the same amount. Clearly, if something in the environment is causing the increase in autism cases, it must be curing mental retardation. This seems unlikely.

Of course the implications of the change in diagnostic criteria implies a major problem. The “epidemic” of autism cases is not to be found in young children. Rather, there should be a large number of undiagnosed teenagers and adults in the community. This prediction has not been tested.

Intervention

The types of intervention used in cases of autism and related disorders depend on the age of the individual, severity of the disorder, and presenting “co-morbid” diagnoses. Unfortunately, the research support for many therapies (such as sensory integration, speech and language therapy, play therapy, etc.) is extremely limited.

There exists a substantial body of research (using both single-case and group designs) supporting the use of applied behavioral analysis (ABA) procedures for the purpose of teaching new skills and reducing the severity of “challenging” behaviors at all age levels (see the following websites for more information: <http://www.health.state.ny.us/nysdoh/eip/menu.htm> and <http://www.asatonline.org>). Ivar Lovaas has popularized this intervention strategy through several important research studies, along with many others in the field.

In very young children, there is always the possibility of altering the developmental path of the affected child towards “normality” given sufficiently intense and relevant intervention using ABA (Perry, Cohen, & DeCarlo, 1995). This was implied in two studies carried out by Lovaas (see above website). Similar changes have been noted in at least one other study besides our own. In this author’s clinical observations, such dramatic improvements have been in noted

in a small percentage of cases when intervention started at a very young age – about 2 years. Some have argued that this is because autism was not the “correct” diagnosis in such cases. But autism is not defined on the basis of prognosis. Rather, it is a behaviorally defined disorder based on history and current status. Early intervention is effective in many disorders of development, perhaps because it alters the structure and function of the brain. It is therefore extremely important to effectively diagnose children at very young ages so that intervention can be initiated as soon as possible.

Toward this end, developing reliable procedures to detect autism as early as possible is extremely important. Progress is being made at both the physiological and behavioral levels. At the physiological level, one laboratory has identified, from neonatal blood spots, a group of neuropeptides that, taken together, strongly predict (>90%) which children will develop either autism or mental retardation, relative to typically developing children or those with cerebral palsy (Nelson et al., 2001). This important study needs to be replicated. Psychologists are working on developing rating scales for the purpose of early detection of autism in infancy with promising results (Robins, Fein, Barton, & Green, 2001).

Co-morbid diagnoses often complicate interventions for such individuals. A variety of such diagnoses occur frequently in persons with autism including seizures, tic disorders, panic attacks and other anxiety disorders, depression, and mania. Seizures require assessment by a neurologist. While it can be difficult to diagnosis DSM disorders in those with developmental disabilities who have limited verbal abilities, it is not impossible. Clinical studies suggest that recognizing such diagnoses can lead to relevant and effective use of psychotropics (Tsiouris, Cohen, Patti, & Korosh, 2003). At the same time, it should be noted that certain DSM disorders are more common in families of people with autism (siblings, parents, aunts and uncles, cousins)

than in comparison samples, perhaps providing clues as to the likelihood of the person with autism having such disorders. These over-represented disorders in extended family members include major depressive disorder (pre-existing), obsessive compulsive disorder, and social phobia (Piven & Palmer, 1999), indicating the need for examining autism treatment within a broader picture that includes the family.

Summary. Autism is part of a broader spectrum of conditions that include other pervasive developmental disorders, mood and/or anxiety disorders, and more subtle problems in communication and socialization. It may best be seen as one possible outcome of a disturbance in CNS development that, in turn, results from anomalies in interactions among genes. Existing research suggests that multiple, interacting genes are involved in the causation of autism. The developing child's social environment has not been found to cause autism. However, a proper behavioral-educational environment can significantly improve outcome. As research in mapping the genome continues, we can look forward to more exciting discoveries regarding the genetic bases of this complex set of disorders and their implications for prevention and treatment.

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