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AUTISM SPECTRUM DISORDERS: POTENTIAL CAUSES

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INTRODUCTION

Autistic disorder, more commonly called autism, is a condition in which the individual exhibits communication difficulties, impaired sociability, inappropriate behaviour and language problems. It may or may not be accompanied by mental retardation. There are multiple other "autistic-like" conditions that, together with autism, are referred to as Autism Spectrum Disorders (ASD). Other conditions include Asperger's Syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

The severity of symptoms can range from almost imperceptible to profoundly disabling. ASD comprises the third most common developmental disability, nearing the prevalence rate of Down's Syndrome. Males are three to four times more likely to be affected than females. Despite considerable research, the cause (or causes) of ASD remains elusive. This paper considers the potential factors that have been proposed.

BACKGROUND ON ASD

Efficient diagnosis of autism, or other ASD, is difficult due to the spectrum of symptom severity and because the cause, or causes, have not yet been identified. Although young infants may in some cases exhibit subtle indications of the disorder, autism is generally not diagnosed before the child has reached 18 months of age. At this age, delays in communication skills and emotional attachments can become apparent. However, because some individuals might show only slight disturbances in behaviour or mild developmental delays, diagnosis is difficult.

Some recent reports have suggested that autism and ASD prevalence rates are on the rise.(1) Although the evidence for this claim is not conclusive, the number of children receiving these diagnoses is increasing, leading to a greater demand for services.(2) It is possible that the increased number of diagnoses may reflect enhanced awareness of ASD and changing diagnostic criteria, rather than a change in the actual prevalence of the disease. However, research continues worldwide into the possible causes of ASD, focusing notably on genetic and environmental factors.

POSSIBLE CAUSES OF ASD

Autism was first described in the early 1940s by Dr. Leo Kanner. Until the 1960s, it was thought to be caused by poor parenting that might have included neglect and withdrawal of affection. Since the 1970s, it has been clear to researchers and clinicians that autism is not caused by such emotional abuse. Children who are subject to such neglect or abuse might exhibit similar behavioural disturbances, but these are distinct from ASD.

Individuals with ASD have been shown to have structural and chemical differences in their brains compared to normally developing peers. However, the manner by which these differences come about is the subject of considerable research. Autism and ASD are believed now to be multifactorial disorders; that is, many factors come into play when determining the cause. These factors include complex genetic interactions, nutritional deficiencies or overloads, pre- and post-natal exposure to chemicals or viruses, errors during the embryonic neural tube closure process, dysfunctional immune systems, and even allergies. The issue of vaccines as a possible cause of ASD will also be discussed here, although there is now sufficient scientific evidence for most researchers to dismiss the argument.

A. Genetics

There is considerable evidence that ASD is determined largely by genetics, but the issue is very complex. Numerous studies involving families in which more than one member is affected with ASD have provided enough information for researchers to conclude that: the

(1) Statistics Canada, *Canadian Community Health Survey 2003*; numbers compiled for the Library of Parliament.

(2) Health Canada, *Healthy Development of Children and Youth: The Role of the Determinants of Health*, December 1999, p. 146.

identical twin of an individual with ASD has a better than 90% chance of also being affected; a fraternal twin or sibling of an affected individual has a 15% chance of having ASD; and an ASD parent has a 10% chance that his or her offspring will also have ASD.

The difference between the probabilities that identical versus fraternal twins will be affected by ASD indicates that genetics is a strong determinant, since both identical and fraternal twins experience the same *in utero* environment while only the identical twins share the same genetics. The observation that the identical twin of an individual with ASD is not at a 100% risk of also having ASD indicates, however, that there is more at play than simply genetics. Finally, the broad range of symptoms, even within a family, has led researchers to conclude that multiple genes, possibly even an unfortunate combination of normal ones, are involved in causing ASD. Many of the physiological observations reported by researchers, such as faulty neural tube closure at the embryonic stage and abnormal brain physiology, may in fact be the result of the ASD genes involved. Research into the genetics of ASD will be discussed in more detail later.

B. Environmental Pollutants and Toxins

Another factor that may be a potential cause of ASD is exposure to pollutants and toxins during foetal development. This possibility has been put forward due to the perceived increase in the prevalence of ASD over recent years, the belief that it has appeared as a disorder only recently, and the detection of geographic areas with slightly higher rates of ASD. Although no conclusive evidence has been found to date, this has become an active area of research; see the section below entitled “Current Research Projects.”

C. Vaccines, Viruses and Impaired Immune Systems

In recent years, considerable public attention was given to the theory that the measles-mumps-rubella (MMR) vaccine, or other combination of vaccines, potentially contributed to the development of autism due to the mercury-containing thimerosal used as a preservative. This theory came about during research into whether this vaccine could be linked to the intestinal disorder Crohn’s disease, and involved a very small number of children. Since that time, no scientific evidence has emerged to substantiate the theory. On the contrary, the observation that the introduction of the MMR vaccine was not followed by a surge in ASD

diagnoses is just one of the epidemiological findings that have essentially disproved the vaccine theory. Canada's National Advisory Committee on Immunization issued updated recommendations for thimerosal-containing vaccines in December 2005. The updated recommendations, based on the best available scientific evidence, reaffirm the Committee's earlier position that "there is no legitimate safety reason to avoid the use of thimerosal-containing products." Nevertheless, due to the speculation and public criticism, thimerosal has been phased out in most vaccines and very few available in Canada still contain the preservative.

Exposure to cytomegalovirus and rubella during early pregnancy is thought by some researchers to increase the risk of having an autistic child. Possibly related to viral exposure is the observation that many autistic individuals have impaired immune systems. Some researchers believe that viral infections may be responsible for the fact that many ASD individuals have a decreased number of helper T-cells, which assist the immune system in fighting infections. Other findings indicate that early immune response to viral infection, either *in utero* or during infancy, may somehow cause the immune system to malfunction, resulting in the production of antibodies against the foetus' or child's own brain tissue and hence in the brain damage seen in ASD.

D. Nutrition, Food Sensitivities and Digestive Disorders

Some attention has recently focused on digestive problems and sensitivities to certain foods, not so much as potential causes of ASD but as possibly contributing to autistic behaviour. Researchers have found that autistic individuals are unable to break down, or digest properly, two kinds of protein: gluten, found in grains like wheat, barley and oats; and casein, found in dairy products. Further aggravating the problem is the fact that these same foods tend to be craved by ASD individuals. Eliminating or restricting the presence of these proteins in the diet of ASD people has been found to improve their health and behaviour in many cases.

Further, scientists have noted that some ASD people have excessive amounts of the yeast *Candida albicans* in their intestinal tract. As yeast grows, it releases toxins into the bloodstream, and high levels of the yeast in turn mean higher toxin levels. These toxins are thought to contribute to autistic behaviours. However, the reason for elevated *C. albicans* levels in the intestines has not been identified.

Finally, some improvements in communication skills, awareness and attention have been noted as a result of supplementing the diet of ASD individuals with magnesium, vitamin B6 and dimethylglycine. These observations are consistent with the other digestive abnormalities seen in autistic people and may be related to poor intestinal absorption of some nutrients. Other nutritional factors that may be involved include a lack of essential minerals such as calcium, zinc, iodine, lithium and potassium.

E. Additional *in utero* Factors

Although not currently a primary focus of major research, several factors experienced by the embryo or foetus have been identified as potential causes of autism. Studies have suggested that major psychological stress, such as death of a loved one, during the 24th to 28th week of pregnancy increases a woman's chance of having an autistic child. This timing agrees with the development of the foetal cerebellum, that portion of the brain that is structurally different in autistic children. It is possible that expression of some of the "autistic genes" is induced, or activated, by stress. Several genes have been identified that are induced following different types of stressors.

Other research has explored the role of substances intentionally consumed by expectant women that may have a toxic effect. Retinoids have been studied in this respect. Thousands of retinoids have been either isolated or synthesized for potential pharmaceutical applications, mostly for treatment of skin diseases and cancer. Other retinoids may be environmental pollutants. Some researchers believe that these substances could cause brain abnormalities that resemble those seen in autism. Retinoids may also be taken as nutritional supplements, such as retinoic acid and vitamin A. While a deficiency of vitamin A could lead to abnormal neural tube closure in the embryo – thus providing a possible link to autism – studies have suggested that excesses of these compounds may also produce birth defects. That is, animal model studies have suggested that brain damage similar to that seen in ASD may be caused by overexposure to retinoids. The genetics of autism and the role of retinoids in ASD have recently overlapped with the discovery that retinoids are known modifiers of the proposed autism genes that are members of a family of genes known as the Hox genes. This suggests that an individual's predisposition to autism by virtue of carrying an "autism gene" may be further endangered by exposure to retinoids that modify the gene, producing an autistic behaviour or physiological marker.

CURRENT RESEARCH PROJECTS

Numerous researchers worldwide are attempting to find solutions in the field of ASD. Their research focuses not only on finding the causes of these disorders, but also on defining the spectrum of disorders more efficiently in order to improve diagnosis as well as to study treatments and therapies. There are currently two main areas for research in Canada and the United States into the causes of ASD, although several other potential causes are still being pursued. These are the identification of genes involved in ASD, and the identification of environmental forces that provide the additional push to cause these disorders.

The United States, through the National Institutes of Health and the Environmental Protection Agency, announced in October 2001 the creation of four new Children's Environmental Health Research Centers (bringing the total to twelve). Two of these – located at the University of California at Davis, and the University of Medicine and Dentistry of New Jersey's Robert Wood Johnson Medical School – will focus their attention on environmental factors that may be related to autism. Another important organization is the National Alliance for Autism Research (NAAR), which promotes and funds biomedical research into autism.

In 2003, NAAR and the Canadian Institutes of Health Research (CIHR) formed a partnership to co-fund a pair of interdisciplinary programs, also supported by the Fonds de recherche en santé du Québec, that include investigations focusing on both the genetics and the epidemiology of autism. The programs are based at McGill University and Queen's University in Kingston. One of the interdisciplinary teams that will study the genes involved in autism is led by Dr. Jeannette Holden of Queen's University; it is called the Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) and includes researchers from across Canada and the United States. In total about 50 groups are involved, accounting for essentially all of the major autism researchers.

The National Epidemiologic Database for the Study of Autism in Canada (NEDSAC), a recent initiative of ASD-CARC, is a database of Canadian children up to and including 14 years of age who have been diagnosed with, or who are suspected of having, an ASD. NEDSAC should prove to be a helpful tool for identifying how many children who live in Canada have been diagnosed with an ASD (the prevalence), how many children are diagnosed each year with an ASD in Canada (the incidence), whether there are variations in prevalence and/or incidence of ASD among regions or across age groups, and how the prevalence and incidence vary over time. NEDSAC is unique in that it will provide reliable and regularly updated estimates of ASD rates for many parts of Canada.

THE DIRECTION OF GENETICS RESEARCH

Currently, research has shown that a gene on chromosome 7 is almost certainly involved in autism, but it is evident that there are multiple genes involved in these disorders. Genes on chromosomes 13, 15, 16 and 17 have also been implicated, but their involvement is not clearly established. The sheer variability with which the disorders manifest themselves leads researchers to conclude that the genetics of autism is very complex, involving multiple genes, possibly normal "susceptibility genes" that are triggered by specific environmental factors, and perhaps even the unfortunate combination of normal genes. An example of a susceptibility gene is the HoxA1, a normal gene that was identified after the observation that about 25% of the children born to women who had taken thalidomide between days 20 and 24 of their pregnancy were autistic. The HoxA1 gene is involved in early brain development and is expressed only during the very early stages of pregnancy. Thalidomide is believed to modify the gene by a single base substitution, rendering the gene product faulty, if not useless.

The Manitoba Autism Research Team began a program in 2002 entitled Genetics and Dysmorphology of Autism Spectrum Disorders to identify the unique genetic and physical features of individuals affected by ASD. The goal is to match up these physical features with genetic markers. Recruitment for this study is ongoing and involves the participation of families in both Canada and the United States with more than one ASD-affected member. Another aim of ASD-CARC's research is to develop reliable genetic testing in order to provide early diagnosis for those at risk of developing ASD so that early therapy intervention may be started to minimize the symptoms.

CONCLUSION

Autism and autistic spectrum disorders are difficult to diagnose due to the variability with which the disorders manifest themselves and because no causes have yet been definitely identified. Considerable research is under way worldwide to improve diagnoses and treatment as well as to identify the multiple contributing factors linked to ASD. Many researchers are optimistic that ASD will ultimately be preventable in many cases and that more effective treatments will be developed.

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