NEUROBIOLOGICAL ASPECTS OF AUTISM

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For a generation, countless parents of children with autism suffered from a prevailing opinion that autism was caused by poor parenting skills. Over the past 20 years, however, several lines of research have shown that autism is a disorder with a firm neurobiological basis and that it is associated with a number of known medical conditions. There is a wide range of biological differences in individuals who have autism and many pieces of the puzzle remain a mystery.

Autism and Known Medical Conditions

The majority of researchers have found that about 10% of persons who have autism also have an associated medical condition, more strongly seen in those with cognitive disabilities. Some of these conditions are outlined below.

Fragile X Syndrome — Initial research suggested a strong association (about 10%) between autism and fragile X syndrome (an inherited disorder characterized by cognitive impairments, a long, thin face, large ears and other physical abnormalities). With more careful clinical evaluations, it appears that there is a weaker association of about 2-3%. Confusion may relate to the fact that developmentally delayed children with fragile X syndrome often show social anxiety, gaze aversion, perseverative speech and hand flapping, but beyond this superficial similarity, they seldom share the profound social problems of children with autism.

Epilepsy — About 25% of children with autism develop a seizure disorder, most commonly in either the first year of life or in adolescence. Seizures are more frequently seen in autistic children who are also developmentally delayed. The majority will be easily managed with anti-epileptic medications. About 8% of children with autism will have any of a range of irregularities in the electrical activity of the brain as seen on the electro-encephalogram (EEG), although they do not have clinical seizures. Recently, it has been speculated that these irregularities may in part or in whole cause the autistic symptoms.

The Landau-Kleffner syndrome (LKS), known for over 40 years has recently received a great deal of attention. In this rare form of epilepsy, a child has normal development until about 2-8 years of age, followed by a profound difficulty with receptive language. Expressive language usually becomes impaired within a short period of time. In 80%, there are clinical seizures that may have begun before, after, or concurrent to the language problems. All children have epileptiform discharges on the EEG, especially during sleep. Not surprisingly, these children have similar behaviour problems to those seen in autism: social withdrawal, abnormal play, repetitive behaviours, overactivity or aggression. There has been an appreciation of the overlap between the two conditions — regression in language skills (present in about 30% of autistic children), diminished responses to verbal overtures, atypical social interactions and behaviour and EEG abnormalities. There is lively debate regarding the management of autistic children with epileptic EEGs during sleep but no clinical seizures, and how they theoretically relate to LKS.

Rett Syndrome — is a neurological disorder, affecting only girls. It begins with normal development in the first year of life, followed by an arrest in head size growth (microcephaly) and lack of developmental progress or regression. Prominent features include midline hand wringing, lack of purposeful hand movements, and intermittent hyperventilation. The disorder progresses through a series of stages eventually resulting in severe developmental delay, loss of ambulation and often seizures. In the initial preschool period, the girls tend to have social withdrawal and poor eye contact which makes them appear similar to children with autism. With time this improves and they become easily distinguished.

Tuberous Sclerosis — There is considerable support for an association between Tuberous Sclerosis (TS) and autism. TS is a genetic disorder which can cause skin and brain lesions, seizures, and cognitive impairments. As high as 30-40% meet diagnostic criteria for autism. This association appears to be restricted to TS accompanied by developmental delay and epilepsy. The proportion of children with autism who also have TS is very much lower with estimates ranging from 0.4 to 3.0%. Studies looking at other neurocutaneous syndromes (e.g. neurofibromatosis) do not show such a strong association.

Other Conditions — Early studies suggested a strong association between autism and both congenital rubella and phenylketonuria (PKU). Children with congenital rubella have developmentally delays, vision and hearing impairments. Those with PKU have severe developmental delays and seizures. These associations with autism have been challenged because of the difficulties diagnosing autism in very low functioning children and in children with hearing and vision impairments. Fortunately, these conditions are seldom seen in North America and there are few systematic studies.

There are numerous reports of various brain malformations being found in children with autism, including hydrocephalus and cystic brain lesions. Some children with chromosomal abnormalities have shown autistic features and a wide array of developmental syndromes have been associated with autism including William’s syndrome, Down syndrome, Moebius syndrome and numerous others. Finally, there are reports of prenatal insults being related to autism, including thalidomide, Fetal Alcohol Syndrome and both congenital herpes and cytomegalic virus disease (CMV).
Neurobiological Differences in Autism

Research is identifying numerous biological differences in autism, including neuroanatomical differences, genetic findings, and a host of other abnormalities.

**Neuroanatomical Findings** — Brain weight in children with autism has been found to be somewhat heavier than expected for age, corresponding to their slightly larger head sizes. Microscopic analyses of brains of children with autism have uniformly revealed abnormalities of major portions of the limbic system and cerebellum. Specifically, an increased number of small, densely packed neurons are found in the hippocampus, amygdala and other parts of the limbic system. Reduced numbers of Purkinje cells are seen in several areas of the cerebellum. These brain structures are believed to have functions that relate directly to the impairments seen in autism. Primates with surgical removal of these brain areas show autistic-like behaviours. The research suggests that autism can be thought of as a disorder of neuronal organization.

**Genetic Findings** — It is now 20 years since a study of twins with autism supported genetic underpinnings. Since then, numerous studies have provided further support, yet the gene or genes responsible remain elusive. What is known is that siblings have a 4-6% risk of having pervasive developmental disorder (PDD) (about 100 times higher than the risk of the general population). The increase in risk for full blown autism appears to be much more modest for second and third degree relatives, although mild variants of PDD may exist more frequently than by chance in these individuals. Yet, the concordance rate for autism is not 100% for monozygotic (identical) twins, suggesting that external factors must play a role. The search for autism susceptibility genes is currently in high gear, and it is realistic to expect a breakthrough soon.

**Other Findings** — While children with autism show a number of metabolic aberrations, the research has been far from consistent. Some have shown irregular immune responses, and there is speculation regarding reactions to immunizations. Again, this research is not yet clear, although this may be an important avenue to pursue. Finally, neurotransmitter levels have been studied and evidence of differences has been conflicting.

Medical Evaluation of Autism

Given the fact that 10% of autistic children will have an identifiable medical condition, a detailed medical history and thorough physical examination is necessary. As for any child with a developmental impairment, a careful evaluation of vision and hearing must be ensured. Conventional and play audiometry may not be adequate for this population, and threshold evoked potential audiometry is often necessary.

When no specific condition or pathology is suspected, it is complex deciding on which investigations to administer. The strength of associated disorders, the quality of the available tests (including sensitivity, specificity, patient acceptability, etc.) and costs to the system are some factors to consider. Experts have varied perspectives and there are currently no accepted clinical practice guidelines. Nonetheless, there is support for the routine testing of chromosomes. There is not support for routine metabolic studies or brain imaging such as computerized tomography (CT) and magnetic resonance imaging (MRI). The question of routine sleep EEGs and fragile X tests remains contentious and awaits further research. Searching for obscure immunologic, neurochemical or neurophysiologic pathology appears to be futile.

Conclusion

Autism is a neurobiological disorder of unknown cause in the majority of cases. For a small, but not negligible proportion of children with autism, a specific medical condition can be identified. Current theories suggest that there are susceptibility genes that lead to abnormal brain development. More research into the origins of autism is critically needed so that optimal care can be provided for children and their families.