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AUTISM: BIOMEDICAL PERSPECTIVES

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Autism is a syndrome characterized by social and communicative deficits of early onset accompanied by abnormal behaviors. The prevalence of autism is approximately 5 in 10,000. The diagnostic criteria include the following:

1. Early onset, before 36 months of age;
2. Severe disturbance of social relatedness;
3. Severe abnormalities of language development;
4. Elaborate repetitive routines;
5. Abnormal perceptual responses to sensory stimuli.

It is important to emphasize that autism is not a disease process but rather a syndrome. There is not one cause for autistic symptomatology, but rather many different biomedical causes can produce the same clinical and behavioral picture. It is very important to identify the various causes of autism because in some individuals pharmacologic or dietary interventions are possible, and in the others, due to genetic inheritance factors, family counselling is of benefit.

The onset of autistic symptomatology can be quite varied. In some individuals it is clear that abnormalities are present shortly after birth and that the disease process was one which took place in utero. In other cases, normal development up until the age of 18 or 24 months is followed by an abrupt regression with subsequent slowed recovery. This latter clinical course is suggestive of a monophasic disease process taking place at that time.

The purpose of this presentation is to discuss aspects of the various biomedical causes of autistic symptomatology so that potentially treatable conditions are not missed.

Genetic Causes of Autism

The fragile-X chromosome abnormality is felt to be the second most common cause of identified mental deficiency in the population. It is second only to Down's syndrome which is a triplication of the 21st chromosome. This fragile site on the long arm of the X chromosome can be revealed when fibroblasts or peripheral blood leukocytes are grown in folate-deficient media. More than half of the affected boys with this syndrome display autistic symptomatology. There are other clinical manifestations including enlarged ears, macro-orchidism and a slightly triangular facies. It is important to identify this diagnostic entity because of the maternal inheritance pattern and for the possibility of treatment with folic acid. The original reports concerning folic acid therapy in fragile X gave promising results. Subsequent larger population studies have revealed that some individuals may improve but not the majority. The exact role of folic acid therapy for autistic symptomatology in individuals with fragile-X chromosome abnormality is yet to be clearly delineated.

Tuberous sclerosis is an autosomal dominant disease whose hallmarks are mental retardation, epilepsy and skin lesions including adenoma sebaceum and the Sjogren's patch. Individuals with tuberous sclerosis can also be autistic. In fact, autism may be the presenting symptom. The clinical manifestations of tuberous sclerosis can be inconstant involving many organ systems to variable degrees. This may be an inherited disease in that approximately 60% of tuberous sclerosis cases are inherited ones, and only 40% are sporadic. Identification of tuberous sclerosis as a cause of autism is important for genetic counselling.

Another autosomal dominant disease which has been reported to be associated with autism

is neurofibromatosis. Here the peripheral manifestations include cafe-au-lait spots and neurofibromas. Since this is an autosomal dominant disease, identification is important for family counselling.

Metabolic Causes of Autism

One of the classic conditions associated with autistic symptomatology is phenylketonuria (PKU), a disorder of phenylalanine metabolism. Since newborn screening for this metabolic condition is prevalent throughout North America and Europe, and since it responds to dietary limits on phenylalanine intake, autistic symptomatology from phenylketonuria is by and large a preventable condition. Despite the mandated screening program cases are missed. All autistics should therefore be screened for an amino acid metabolic defect. It is important to realize that this severe disabling disease, PKU, may be completely prevented exclusively by an appropriate dietary approach.

Disorders in purine and pyrimidine metabolism have been recently described in a number of autistics. It is important to identify these individuals and also to identify their enzymatic pathway deficiencies, both because of genetic factors that may play a role in producing the enzymatic abnormalities, and also because dietary intervention may be of benefit.

There have been a number of individuals with autism described who have carbohydrate metabolism difficulties as manifest in lactic acidosis and pyruvic acidosis. Some of these individuals have been found to have pyruvate dehydrogenase deficiency or a mosaic form of this deficiency. These autistics may respond to dietary limitations on carbohydrate intake and to thiamine supplementation.

Calcium metabolism abnormalities in autism have also been identified. Usually this has been on the basis of hypocalcinuria with normal serum calcium levels. This finding seems to be more prevalent in those individuals who are self abusive, particulary of their eyes. Calcium supplementation can normalize the hypocalcinuria and can reduce the incidence of self-injurious behavior.

Congenital Infections As Causes of Autism

Congenital rubella infection has been associated with autistic symptomatology. Evidence has also suggested that congenital cytomegalovirus and neonatal herpes-simplex virus infections may play a similar role.

Toxic Exposures As Causes of Autism

There are a wide variety of neurotoxins which may affect the central nervous system, either transiently or permanently, to produce autistic symptomatology. This is particularly of concern with young children who may ingest toxic substances. In a recent case, a two and a half year old child acutely lost language skills and demonstrated behavioral abnormalities at times suggestive of psychosis. The pediatric and psychiatric hospital staff interpreted these findings to be compatible with the diagnosis of autism. On carefully reviewing the history, it became clear that both the child and the individual caring for the child, the grandfather, both had a very significant acute mental affliction. The child's symptoms were those of language regression and probable hallucinations, whereas in the grandfather the symptoms were those of severe depression. At the time of the neurologic deterioration, the grandfather and grandson were active gardeners and used a variety of herbicides and pesticides, some of which had accumulated over several decades. Since the symptoms in both the child and the grandfather remitted entirely over the next two months in a simultaneous fashion, the best explanation was an acute toxin exposure related to the use of old herbicides or pesticides. Another case was that of a child who had an entirely

normal development until 18 months of age when neurologic regression took place in an environment where there was extensive drug abuse. The details of what occurred over the two-month period while this child was cared for are not known, but it is reasonable to entertain the possibility of a drug ingestion which may have produced central nervous system damage.

Related to toxic exposures, one very important consideration is that of lead toxicity. Autistic children frequently engage in pica, that is, the eating of non-edible materials that they may find. In many older homes where paint and plaster may contain lead these children may become lead poisoned. When a history of pica is obtained, it is important to check and make sure that lead toxicity is not complicating the child's clinical course.

Endocrinologic Causes of Autism

In the published literature, endocrine dysfunction is not commonly associated with autism. However, it appears that there may be a fairly high incidence of maternal hypothyroidism associated with an autistic offspring. Most commonly it appears that the mothers had already been diagnosed and were on replacement thyroid medications throughout the pregnancy. How a chemically euthyroid female who has an appropriately treated underlying hypothyroid condition would have a higher chance of having autistic offspring is not clear.

There have been isolated cases of congenital hypothyroidism associated with the eventual development of autism. Also there is at least one case of congenital growth hormone deficiency associated with autism. In these cases, the diagnosis of the endocrine disturbance took place at approximately four or five months of age when children were having somatic growth failure. It is possible that endocrine disturbances at a critical neurodevelopmental time significantly contributed to the development of autistic symptomatology. If identification and treatment had taken place earlier, possibly autism could have been prevented in these cases.

Structural Causes of Autism

In the computerized tomographic brain scan literature concerning autism, a not uncommon finding is that of enlarged lateral ventricles. This is not a uniform finding, however. Enlarged lateral ventricles may simply be a non-specific sign of central nervous system maldevelopment or damage. Since autism may be produced by a wide variety of biologic causes of diverse nature, it is not surprising that diffuse structural maldevelopment or damage could be associated with autistic symptomatology. Also, there have been reports of arachnoid cysts in the temporal lobes associated with autistic symptomatology.

A recent study using magnetic resonance brain imaging techniques revealed cerebellar abnormalities in vermal lobules VI and VII. This finding was interpreted as revealing maldevelopment, not atrophy. It is possible that an intra-uterine insult took place at the time when these lobules were developing which resulted in their hypoplasia, and presumably in damage to other structures of the central nervous system which were developing at the same time. It should be noted that the results of this report have yet to be confirmed. There have been a number of studies indicating that this sort of abnormality can be detected in fragile-X individuals without autistic symptomatology, in mental retardation without autism, and even in normals.

In a clinical and in a pragmatic sense, it is difficult to justify routine magnetic resonance imaging of autistic individuals in a search for minor anatomic variations. It should be clearly borne in mind that for many autistics general anaesthesia is necessary to perform the imaging procedure. General anaesthesia does have a definite, although small, risk of morbidity and even of mortality. It is difficult to justify the costs and the potential risks of doing routine imaging studies in autistics, when potential findings are not treatable. Of course, should the differential diagnosis of a child being assessed for autism include

other conditions then brain imaging may be indicated.

Epilepsy Associated with Autism

Epilepsy is much more common in autistics than in the general population. Seizures may start early in life, as in the case of infantile spasms, or arise later, in adolescence. With age, between 20 to 40% of autistics will have recurrent seizures and will need to take anti-convulsants. The high incidence of epilepsy argues for the fact that there is a significant neuronal dysfunction in autism. However, earlier in life another phenomenon may take place which can mimic autistic and psychotic manifestations. This condition is epileptic aphasia. Epileptic discharges may be concentrated in the language processing centres of the central nervous system. This may be accompanied by both language regression and behavioral changes. In appropriate individuals, electroencephalograms should be performed since pharmacologic therapy for epileptic disturbances would be indicated.

Immunologic Abnormalities Associated with Autism

In the published literature, there have been reports of abnormal antibody responses in autistic individuals to rubella vaccine, to serotonin receptors and to neurofilament axonal proteins. Cell mediated immune abnormalities have also been reported concerning macrophage migration in response to myelin basic protein, mitogen-induced lymphocyte blastogenesis, and changes in the numbers of subtypes of circulating lymphocytes. In our laboratory, we have been investigating possible immune system dysfunction in autistics. In a recent study of 17 autistic individuals whose ages ranged from 8 to 23 years (16 males and 1 female), we found a number of significant abnormalities.

In studying the humoral immune system, we found normal quantitative IgG, IgA and IgM levels. Circulating B cell numbers were normal. IgG and IgM antibody production from B cells using pokeweed mitogen as a stimulus source gave normal results. We subsequently investigated the presence of circulating IgG and IgM anti-central nervous system antibody reactivity using Western blots prepared from normal human autopsy-derived central nervous system tissue. On these Western blots, we detected a very high incidence of anti-cerebellar immunoreactivity which was both IgG and IgM in nature. We did not detect any anti-frontal cortex immunoreactivity. With both IgG and IgM the majority of the reactivity was directed against a molecular weight epitope of 210 kilodaltons (K). The large subunit of neurofilaments migrates on Western blots at the molecular weight of 210 K. It is possible that this detected immunoreactivity is specific for the 210 K neurofilament subunit. However, we did not detect immunoreactivity against frontal cortex blots which are also rich in neurofilaments. It is possible that there may be another substance in cerebellar tissue co-migrating at that same molecular weight, or possibly antigenic epitopes are revealed in processing cerebellar tissue on the neurofilament subunit, an event which does not take place in frontal cortex immunoblots. Nevertheless, a consistent finding was the fact that there was a high incidence of anti-cerebellar immunoreactivity.

These findings may correlate with pathologic reports revealing microscopic abnormalities in the cerebellum of autistics and possibly even in the aforementioned magnetic resonance imaging changes noted in the cerebellar vermis.

Another area of immunologic investigation was that of lymphocyte function. Total numbers of CD4 ("helper") and CD8 ("suppressor") cells were normal in the autistic population. However, the ratio of CD4 to CD8 cells was abnormal. Here we found clusterings of approximately equal numbers of high and low CD4 to CD8 ratios. In and of themselves, these findings do not indicate an autoimmune disease process but do suggest that there is an abnormality in the circulating lymphocyte pool in these individuals.

Lymphocyte blastogenesis as studied with stimulation with concanavallin A and phytohemagglutinin revealed normal results. When we investigated DR expression in the

lymphocyte pool, we found a significant increase in DR percentage of T lymphocytes in 11 out of 17 studied autistics. Normally there should be no DR expression on T lymphocytes, and in our study we found numbers up to 20%. There were no individuals with interleukin-2 receptor positive T cells. This pattern of T cells expressing DR antigens and not interleukin-2 receptors is one that is observed in "late activation". This type of finding is seen in autoimmune diseases such as juvenile rheumatoid arthritis and systemic lupus erythematosus. Another significant finding concerning the percentage of DR activation was the fact that over the age range studied, namely from 8 to 23 years of age, there was a linear decrease in the percentage of this particular abnormality.

Our immune system investigations suggest that there may be circulating antibodies directed against neuronal antigens with a higher frequency in autism as compared to controls. Also, the pattern of reactivity in the lymphocyte pool suggests that in some autistics there may be an underlying or an associated autoimmune process. The pattern that we detected is one of late activation not of acute activation. It is possible that in this identified population, there may have been a much more active autoimmune disease process earlier in life. These immunologic findings have yet to be confirmed.

Other Conditions Associated with Autism

Not uncommonly, autistic children may be hyperactive and/or have significant attention deficit difficulties. These associated conditions may play a very significant role in their disability. Besides appropriate forms of educational intervention there may be a role for pharmacologic agents to treat the attention deficit.

There are autistics who have a strong family history of manic depressive illness and who have cyclic mood swings. If it is possible to identify periodicity in behavior in those autistics whose family history is positive for this mood disorder, then it may be reasonable to try pharmacologic treatment of disorder. In such cases it appears that autism is coincidental with manic depressive illness.

Misdiagnoses in Autism

Possibly one of the more important reasons for a thorough biomedical assessment of autistics is to make sure that other causes of neurologic impairment are excluded. In evaluating a child who has had difficulties with language development or who has had language regression, one of the most important questions to answer is whether there is a hearing loss. Also, children who have significant visual impairments may present with autistic features. On occasion deprivation can lead to severe social and linguistic maldevelopment.

There are many causes of mental retardation, some of which are potentially treatable and others have genetic implications. It is not uncommon to see a mentally retarded individual, with mild to severe mental impairment, who has minimal features of autism. For example, one recent case with a referral diagnosis of autism was in fact a mildly mentally retarded girl with the Beckwith-Widemann syndrome, a genetically inherited disease, which because of its oncogenic potential, is very important to identify in affected families.

Rett's syndrome is a disease process affecting girls associated with autistic features. It is important to distinguish this syndrome from autism since it most likely has a different pathogenesis and already has different pharmacologic treatment strategies associated with it.

Misdiagnosis may also take place in those children who may be psychotic and are afflicted with auditory or visual hallucinations. When young children become disturbed it is not surprising that they may also become mute. Strict criteria for the diagnosis of psychosis or of schizophrenia require the individual to communicate the presence of delusions or hallucinations. In fact it is only older children who already have well

developed language skills before the onset of their illness, who are able to verbalize their concerns. It is important to try and distinguish autism from childhood schizophrenia within the diagnostic grouping of "pervasive developmental disorders" in that the biomedical causation underlying these symptoms is probably different and the approaches and treatments would likewise be different.

With regards to assessment of hearing impairment in autistic individuals it is important to continue to monitor hearing functions because middle ear effusions may develop. It is not surprising that autistics who have impaired hearing perform less well than those with good middle ear function.

Conclusion

It is clear that there are many biomedical causes underlying and associated with autistic symptomatology. Regrettably, in the majority of cases definite explanations are not at hand. Nevertheless it is very important to thoroughly investigate all individuals with autism since in many cases treatments are available. Furthermore, in cases with an inherited disease genetic counselling may be of benefit for the affected families.

It should be noted that this review article was intended only to cover the highlights of the biomedical perspectives of autism. Discussion has been kept very brief and many important issues have not been raised.

For Further Reading

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