

The effect of Magnesium Deficiency on Brain Function: Autism Spectrum Disorder, Neurology, Genetics and Remedial Solutions

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Summary

Autism, a neurobiological condition, having its origin in the disturbance of the cellular structure of the brain during pregnancy, at birth, affects 1 child in 100 according to the latest worldwide statistics. The condition affects boys, in a ratio of 4:1 more than girls. Generally speaking there is no “cure” for children on the Autism Disorder Syndrome and the holy grail of finding a neuropharmacological reversal of symptoms is currently being researched worldwide. Research findings have shown conclusively that the disturbance of the cellular structure of the brain, leading to the manifestations of learning difficulty, behavioral, and mobility problems, a result of the mutation of specific genes, some mutations being passed from parents to children down the paternal or maternal line, others being created in utero as a result of exposure of the developing fetus to pathogenic exogenous agents, can be reversed by the use of neuropharmacology.

Published information suggests that a Magnesium deficiency in the electrolyte serum, resulting from a magnesium deficient diet, or a diet high in sugar, salt, and saturated fats, can have an effect on neural efficiency- neuronal homeostasis-, leading to conditions on the Autism Spectrum Disorder.

In view of this apparent relationship, is there justification to consider supplementing the diet of newly pregnant mothers and those contemplating pregnancy with easily digestible magnesium compounds, where deficient, in the same way that folic acid supplementation is proven to be efficient in reducing neural tube defects

Autism Spectrum Disorder and its Etiology

Preterm births are on the increase, this fact is as relevant in the UK as it is worldwide. Commentators agree that along with preterm birth, some form of learning disability, behavioural, and mobility problem may ensue. Many of these disabilities will not be instantly recognizable, many will go undetected and some will not manifest themselves until later in life. All these disabilities have their basis in mutated genetics, some mutations being passed from parents to children down the paternal or maternal line, others being created in utero as a result of exposure of the developing fetus to pathogenic exogenous agents.

Autistic Spectrum Disorder (ASD) is characterized by a systemic array of symptoms that has fascinated and frustrated researchers since its description over fifty years ago, the universally current view evolving the disorder from the psychological realm to the biochemical. Studies of neurochemical, neuroanatomical, immunological, genetic, neuropathological, metabolic, and pharmacological involvement have revealed the prevalence of over fifty biochemical, genetically or metabolically associated disorders with autism.

The autistic spectrum disorders are described in the DSM-IV (Diagnostic and Statistical Manual) under "Pervasive Developmental Disorders" (PDD): Autistic Disorder (AD), Rett's Disorder (RD), Childhood Disintegrative Disorder (CDD), Asperger's Disorder (AS) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

The diagnostic criteria for the autistic spectrum disorders are extensive. The autistic spectrum was originally incorrectly categorized as psychiatric and subsequently treated with therapies oriented to emotional disorder. Autism is not a constitutive disorder that is solely and statically genetic in nature, but rather may involve acquired deficits due to exposure in perinatal, prenatal or in the first few years of development to pathogens, toxins, creating systemic alterations on a cellular level mimicking a broad scope of disturbed metabolics with immune, central nervous system, gastrointestinal and endocrine involvement. Rather than the struggle of medical research focusing on the classification of a disorder when extensive overlapping of many disease states co-exist within autistic disorder, one is led towards the concept that expression of genetic disease states may be induced as is currently gaining ground in the literature. As judgment often exists that a genetic disorder is unapproachable, treatable only through gene therapy we must move beyond this limited concept. To approach the depth of complicated disorders the blending of the sciences such as psychoneuroimmunology, neuroendocrinology, and immunogenetics arose and therefore more individualized metabolic needs may be addressed. A merging of the sciences is paramount in grasping the complexity of autistic spectrum disorder, and should no longer be categorized or treated as a psychiatric condition.

In several previously published articles in www.theautismcentre.co.uk web site referring to the Etiology of the Autism Spectrum Disorder, reference has been made to the part played by various exogenous agents on the development of the fetus in utero. In addition, the replication of DNA, from both parents containing existing mutated genes, i.e. those genes with either deletion of proteins at specific sites or duplicated proteins, will ensure that the developing foetus will inherit and replicate the DNA with those defects.

The agents identified as playing a major role in events leading to early miscarriage, premature birth, and subsequent onset of conditions displaying mobility, behaviour, and learning difficulties are listed by various organisations as alcohol, nicotine, viral and bacterial infections e.g. rubella in the case of cerebral palsy. Viral infections affect cell permeability.

The organisation associated with Fetal Alcohol Syndrome has called for a notice to be added to the labeling of alcohol containing drinks warning of the consequences of alcohol intake during pregnancy. Smoking is universally accepted as cause of neurological dysfunction, resulting from central nervous system cell damage, and many articles have been published linking bacterial and viral infections to similar outcomes.

In case of infections during pregnancy, it appears that the ease at which pregnant mothers contract the illness, may be due to reduced immunity, as a result of increased age, or possibly, as some research shows, that, one of the outcomes of neurological dysfunction, is reduced immunity. Autistic children are subject in early life to regular bouts of middle ear and upper respiratory tract infections.

It is universally recognised, that, the ingestion of products produced by smoking will lead to the cancer of the respiratory system through cellular and genetic mutations, and, on the basis a link is formulated between Stop cassettes, and the ingestion of exogenous agents described above, then we have found the link to those products and cellular and genetic mutations, which may lead to the onset of Autism Spectrum Disorders.

The major feature of Autism spectrum Disorders is that they only manifest themselves after eighteen months and before the age of three and that some agreement exists to the opinion that ASD's are a disorder of brain function and not of brain structure, whereas structural anomalies have been identified using high definition scanners.

Magnesium deficiency and Neuronal homeostasis

In this respect consideration should be given to the effect of Magnesium deficiency on brain function. Magnesium deficiency is a common occurrence and whilst it is the least abundant serum electrolyte, it is important in terms of the neurobiology of the Central Nervous System,

metabolism of other electrolytes, acetylcholines, nitric oxide, and a large range of enzymes, intercellular homeostasis, and therefore a very wide range of crucial body functions. These observations have been commented on since the 1950's and referred to in Leaver et al (1987) All life is dependant on Magnesium, it is crucial to the function of Adenosine –triphosphate (ATP) the energy molecule of life, responsible for more than 300 crucial metabolic reactions , disease or ultimate pathology resulting from any deficiency or malfunction.

The range of pathologies associated with magnesium deficiencies as noted by Johnson (2001), is enormous and includes, recurrent bacterial infection due to low levels of nitric oxide in the sinuses, vagina, middle ear, and upper respiratory system, fungal infections due to depressed immune system, thiamine deactivation leading to behavioural disorders.

Magnesium levels are decreased by excess ethanol, cadmium from smoking tobacco products, salt, phosphoric acid, and caffeine, conversely are increased by high levels of magnesium in the diet and are hindered by excess fat.

Magnesium deficiency is associated with individuals on the autism spectrum disorder, in the case of Nitric Oxide (NO), is involved in synaptic plasticity, immunity, neurotransmission, electrolytic stability, neuromodulation, gastrointestinal and hepatic function.

According to Hartwig (2001), magnesium “ is required to maintain genomic stability, an essential cofactor in nearly all enzymatic systems involved in all DNA processing, nucleotide excision repair, is required for removal of DNA damage generated by environmental mutagens and DNA replication. Magnesium deficiency may be associated with decreased membrane integrity and function.

In their publication, echoing the implications of magnesium deficiency of Hartwig, adding that using positive emission topography as observed by Zilbovicius et al on primary autistic children, revealing a significant decrease in cerebral blood flow localised at the temporal lobes level, taken together the fact that Magnesium was shown to increase blood pressure, Mousain-Bosc et al (2006) hypothesized that intercellular magnesium depletion could be responsible for some central activity disorders observed in autistic children. On this basis, the authors Mousain-Bosc et al proposed two hypotheses:

- a metabolic inhibition of membrane Na/K ATPase with a resultant rise in intracellular Ca and decrease in intercellular Mg.

- a genetic defect in magnesium transport through the plasma membrane.(TRPM channels)

TRPM6 and TRPM7 are distinct from all other ion channels in that they are composed of linked channel and protein kinase domains. Recent studies demonstrate that the channels are essential for Magnesium homeostasis. This fact leads to the possibility that mutation of TRPM channels may cause disfunctions as a result of reduced intracellular magnesium levels. The genetic hypothesis is supported by a positive correlation between low intracellular Mg values in ASD spectrum children and their mothers, specifically those mothers having had pregnancy disturbances.

A study published in Annals of Neurology Nelson et Al (May 2001) showed that elevated concentrations of proteins present at birth in the blood may be associated with the development of Autism later in childhood. The investigators Nelson et Al measured concentrations of several neural growth factors and found these were significantly elevated in the neonatal blood of children who later developed autism, against blood from the normal controls.

Neural growth factors are important to the formation of the central nervous system during embryonic development, as well as playing a vital part in the production of new brain cells and the organization of those cells into distinct networks. The hypothesis is that an abnormal abundance of these proteins may disrupt the normal process of cell migration, differentiation and programmed death during early nervous system development.

Protein deficiency and duplication

Reinforcement of this point is made by Ramocki and Zoghbi (2008) “suggesting a model in which altered proteins that are themselves integral to neuronal homeostasis (for example, FMRP or MeCP2) or loss or gain of function of proteins that trigger homeostatic responses, lead to dysfunctional neuronal networks with weakened synaptic flexibility.”

Ramocki and Zoghbi go on to predict that “based on this theory of failed neuronal homeostasis in neuropsychiatric disease is that disorders such as schizophrenia, bipolar disorder, anxiety disorders and obsessive compulsive disorder will have two main etiologies. One will be genetic, with such disorders being caused by less severe alterations either in some of the genes or pathways that cause severe neurodevelopmental disorders such as autism (and whose effects often converge on the synapse) or in genes that have a crucial effect on modulating synaptic plasticity in adolescence and into adulthood”. “The second etiology is likely to involve acquired epigenetic changes that result in altered gene expression or RNA processing, often in the same pathways that cause autism or similar neuropsychiatric disease in children”.

Homeostasis is the ability of a system to return to a set point, Ramocki, Zoghbi (2008), following an irregularity or disturbance, and is characterized with healthy neurons with proteins in balance. Neuronal homeostasis can be affected by the loss or gain of protein or RNA function. The levels of RNA and protein are regulated by transcription and translation respectively and depending on the presence of RNA-binding proteins that regulate the translation of specific mRNA molecules whether a messenger RNA molecule will be translated into protein. Loss of protein or RNA function causes neurodevelopmental disorders with phenotypes overlapping those caused by gain of protein or RNA function.

Duplication, gain of protein, supports increased density of dendrites, resulting in increased number of synapses represented by dendritic spines, which in turn supports increased transmitted information, hyperactivity, deletion a loss of protein decreases the number of dendrites, or produces abnormal shaped dendrites, with reduced numbers of synapses.

A specific example of this loss or gain is characterized by Rett Syndrome where loss of function is symptomised by Regression, Microcephaly, Impaired autonomic control, and where gain of function, MECP2 duplication leads to Hypotonia, progressive spasticity, recurrent infections, and phenotypes common to both loss and gain of function are characterised by behaviour problems, autism, epilepsy, stereotypical behaviour and poor motor control. In discussing mutations in MECP2 gene causing Rett syndrome Ramocki, Zoghbi, conclude that as a result of investigations into deletions and duplications that these findings demonstrate that MeCP2 modulates gene expression in neurons, confirm its role in neuronal plasticity and conclude that disorders resulting from MeCP2 loss or gain of function are caused by failure of synaptic homeostasis.

In Journal of Clinical Investigation March 2007 investigators Furuichi et Al in mouse model research demonstrated that the mammals lacked a protein CADPS2 encoded by a gene in the autism susceptibility region of Human chromosome 7, exhibited autism like characteristics, impaired social interactions.

An abnormal mutated form of CADPS2 mRNA which is an intermediate in the conversion of the CADPS2 gene to CADPS2 protein was detected in individuals with autism and was never detected in their healthy immediate relatives. This suggests that defects in CADPS2 function may predispose individuals to develop autism.

Another piece in the jigsaw with reference to Autism Spectrum Disorder, (ASD) in terms of its understanding and potential long-term treatment, by the announcement from research workers at The University of Bristol.

The team led by Professor Jeremy Henley(2007) announced findings published in Nature of the role played by a small protein Small Ubiquitin-related Modifier SUMO 1 on its ability to attach itself

to and detach itself from other proteins in cells to modify their function.

The research team found that when one type of protein, receptors, the kainate receptor, present in synapses, the connections which chemically transmit information that control brain function between nerve cells in the brain, receive a chemical signal, the SUMO1 attaches itself to that kainate receptor. The SUMO 1 extracts the kainate receptor from the synapse stopping the flow of information from other cells reducing hyperactivity in that cell.

Kainate receptors are known to respond to the neurotransmitter glutamate, are involved in excitatory neurotransmission by activating postsynaptic receptors, and in inhibitory neurotransmission by modulating release of the inhibitory neurotransmitter GABA through a presynaptic mechanism. Kainate receptors play a role in both pre- and post synaptic neurons, have a more limited distribution in the brain compared to other receptors and have been implicated in causing epilepsy and sensory transduction.

In a healthy brain, synapses can modify how efficiently they work by increasing or decreasing the amount of information transmitted.

The children on the Autism Spectrum Disorder are known to be affected by sensory inputs via the visual, auditory, tactility, smell and taste sensory gathering systems, too much information transmitted to the Central Nervous System creates a hypersensitive condition, too little creates a hypo sensitive condition.

Sudfof (2008) discussing the role of neuroligins and neurexins in the way the synapses function suggests them for a role in cognitive neurodeficiencies such as autism, observation of epilepsy in ASD patients suggest that autism may be caused by imbalance of excitatory and inhibitory synaptic transmissions.

Recent studies have identified mutations in the genes encoding NRXN's and NLGN's as a cause of ASD. However these mutations may only increase the chance of autism rather than actually being the cause of autism, the relationship between NRXN-NLGN synaptic-cell-adhesion complex. It is postulated that NLGN's and NRXN's are activators of synaptic function and not components of synapses .

Remediation to Reverse Symptoms

A hyper visual and hyper auditory child in a noisy, busy environment shuts down the system to prevent disruption to the CNS already compromised by a mild diffuse brain injury, the same brain injury known to be affecting the efficient working of the brain. Hyperactivity is the behavioural condition affecting Attention Deficiency Hyperactive Disorder diagnosed children, the current treatment for which is administration of the drug Ritalin for which there a no recorded long term side effects. In Autism, hypersensitivity in the visual and auditory sensory gathering systems affects learning and in extreme situations affects speech.

Delacato in 1974 after many years of studying and working with autistic children worldwide published his book *The Ultimate Stranger The Autistic Child* in which he describes in great detail the types of "sensoryisms" affecting autistic children and how these affected senses, hyper sensory and hypo sensory affect the behaviour , learning ability and mobility problems autistic children are associated with. In his attempts to treat the causes of the disturbed senses he analysed the various methods available at that time, discussing amongst others behavioural modification, education, drugs and a dietary approach. On the use of drugs to facilitate the nervous system he notes that some drugs have an excitatory effect and others have a suppressive effect. However he noted that at that time, in spite of much research being carried out, the difficult area of research was not in the chemical analysis of the drugs but in the lack of knowledge of the function of the nervous system.

Delacato, on his approach to diet and nutritional supplements offers up the work of Linus Pauling (1968) and his ideas on orthomolecular therapy, which proposed that the creation of the optimum molecular composition of the brain is a way to treat behavioural disorders. Pauling goes on to speculate, that, our general diet did not provide the optimum concentrations of nutrients required by the brain. Additions of

Magnesium and folic acid were proposed, folic acid is accepted by the medical profession as a supplement during pregnancy to overcome neural tube defects.

Magnesium deficiency affects homeostasis, which in turn is loss or gain of protein or RNA function, loss of protein affects both the density of dendritic spines, dendrites and the number of synapses available as well as the numbers of abnormally shaped dendritic spines. In this case decreased synaptic activity slows down or inhibits information flow and creates a hypo sensory condition or, conversely, a duplication of protein increases synaptic activity by overabundance of dendritic spines, dendrites and synapses, increasing informational flow, therefore creating a hypersensitivity condition.

Recovery from which, using Sensory Modulating Therapy is a long term solution, thus in the future, boosting level of SUMO 1 in the brain could hold a beneficial solution without the side effects of currently used antipsychotic drugs.

The recent joint announcement by the Wellcome Trust and Rett Syndrome Research Foundation (2007) on the discovery of the remedial effect of Tamoxifen on the symptoms of Rett Syndrome in a genetic mouse model raises a number of interesting points.

The discovery that administering the drug Tamoxifen to mice, "switched on" the MECP2 mutated gene, and reverses the brain damage that gives rise to the symptoms of the condition known as Rett Syndrome.

Rett Syndrome is recognised as one condition of many associated with Autistic Spectrum Disorder, children on this spectrum suffer lack of speech have unusual movement e.g. tip toe walking and lack fine motor control as well as associated learning delay.

The reversal experiments were carried out, using technology known as Cre-lox recombination.

This recombination is a method to introduce transgenes into specific, single, defined sites within the mammalian genome to recreate a genetically reproducible environment for the study of expression of introduced transgenes.

In the virus bacteriophage ϕ 10, is an enzyme called Cre and particular DNA sequences called lox P sites.

The lox P sites work in pairs and flank a segment of DNA called a target. When the Cre enzyme binds to the lox P sites, it cuts the lox P sites in half and then splices together the two halves after the target DNA has been removed and degraded.

In this study mouse models were created, in which the gene MECP2 was silenced by inserting a Stop cassette into the gene, creating the neurological deficits exhibited by Rett Syndrome.

Removing the Stop cassette with the use of Tamoxifen could reverse the silencing, which stimulated the Cre enzyme to enter the cell nucleus where it could splice out the Stop cassette.

Another discovery in 2008 by researchers at UCLA discovered that an approved drug Rapamycin reverses the brain dysfunction tuberous sclerosis Complex (TSC). It is known that about half of TSC patients suffer autism. The team used mouse model technology to carry out their research.

In view of this apparent relationship between magnesium deficiency and neurological disfunction, is there justification to consider supplementing the diet of newly pregnant mothers and those contemplating pregnancy with easily digestible magnesium compounds, where deficient, in the same way that folic acid supplementation is proven to be efficient in reducing neural tube defects.

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