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Autism: An epigenomic side-effect of excessive exposure to electromagnetic fields

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Autism is a disorder which mainly involves the nervous system. It is characterized by lack of communication, incoherent language and meaningless repetitive movements. Its onset is in early childhood and its incidence has been reported to be increasing. Several genes and environmental factors have been implicated in the causation of autism, and electromagnetic fields may be one of those environmental factors. Industrialization has added a large number of electronic gadgets around us. Indiscriminate use of these gadgets, particularly mobile phones, has raised the question of electropollution and health hazard caused by their usage. Electromagnetic fields emitted during their operation do not have enough energy to cause DNA alterations directly; however, ample evidence is available from *in vitro* and *in vivo* studies to demonstrate their ability to cause DNA alterations indirectly as well as epigenetic modifications. In addition to genetic alterations, the epigenetic modifications may have an important role in causing disruption of the nervous system leading to neurodegenerative disorders, including autism.

Key words: Autism, neurodegenerative disorders, epigenome, electromagnetic fields, electronic gadgets, mobile phones.

INTRODUCTION

Autism is an example of a disorder caused by disruption of the nervous system. It is a severe neurodevelopmental disorder with an onset in infancy (Ploeger et al., 2010), and occurs more often in males than in females with a ratio of 4:1. It is characterized by social and communicative impairment accompanied by hyperactivity, repetitive and stereotype behavior (Fatima et al., 2006). IQ varies from normal (or even above normal) in more than 50% of the cases and mental retardation occurring in 30 to 50% of them. Various parts of the brain have been identified to be involved leading to neuronal disconnection or circuit disruption. Using diffusion tensor imaging, Weinstein et al. (2011) observed differences in white matter of the brain between autistic children and controls. They suggested that abnormal white matter integrity in young children with autism may adversely affect connectivity between different brain regions. Voineagu et al. (2011) carried out microarray analysis on RNA of more than 30,000 genes in three regions of post-mortem brains among 19 autistic individuals and 17 controls. They identified 444 genes in cerebral cortices of the autistic patients that showed significant expression changes as compared to the controls. Of these 444 genes, downregulation was seen in 209 genes which were related to synaptic and neuronal signaling functions, and upregulation was observed in

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235 genes which were connected with immune and inflammatory response. The authors strongly suggested convergent molecular abnormalities involving transcriptional and splicing disregulation in the temporal and the frontal cortical regions in autism. This study was supported by an earlier study by Zikopoulos and Barbas (2010), who carried out anatomical studies on 5 cases with adult autism, and observed typical ultrastructure abnormalities in their frontal regions of the cortex.

RELATIVE ROLE OF GENETIC AND ENVIRONMENTAL FACTORS IN AUTISM

Autism is a familial disorder with high heritability. Genome-wide association studies as well as studies on submicroscopic and chromosomal structural variations (polymorphisms and copy number variants) suggest the involvement of a large number of genes in the causation of autism (Veenstra-Vanderweele et al., 2004). Being a polygenic disorder, autism is attributable to the effect of an unknown number of mutations and their possible interactions. These mutations and their interactions, *inter se,* as well as with the environmental factors, display a wide phenotypic spectrum, known as the autism spectrum disorder (ASD) (Currenti, 2010). The recurrence rate of an autistic child in a family is about 5% if one child is already affected with autism. The concordance rate of autism in monozygotic twins has been reported to range between 50 and 90% (Abrahams and Geschwind, 2008). The very fact that the concordance in monozygotic twins is short of 100% and autism has a wide phenotypic spectrum, it is reasonable to assume that environmental factors have a significant role to play in the causation of this disorder. Interestingly, according to Hallmayer et al. (2011) environmental factors play a larger role than genetic factors in the pathogenesis of autism. Various environmental factors like copper, lead, mercury, arsenic, fertilizers and pesticides, at toxic exposure levels have been implicated in autism. Not only are the higher levels implicated, but even the lower levels of some of the essential elements may also be involved in autism. For example, lower concentrations of magnesium, selenium, iodine and lithium have been observed in autistic individuals (Herbert et al., 2006; Adams et al., 2006, 2007; Lakshmi Priya and Geetha, 2011).

ELECTROMAGNETIC FIELDS AND THEIR BIOLOGICAL EFFECTS

We are surrounded by electrical/electronic gadgets at home as well as in the work place. These gadgets operate at a broad-range of electromagnetic frequencies, e.g., extremely low frequencies (AC:10 to 60 Hz) for domestic and power lines; medium-range radio-frequencies and microwave radiations (AC:1 to 900 MHz) for FM radio, television and mobile communication; and very high frequencies (AC:2 to 10 GHz) for microwave ovens and satellite communications. Biological systems have been shown to be sensitive to external magnetic fields in several investigations. Magnetic fields affect the basic life processes, like growth and development, orientation, structure and function of proteins, lipids, metabolic pathways, membranes, antioxidant defense and genetic material (Todorovic et al., 2012). Experimental studies on invertebrates and vertebrates alike confirm a higher sensitivity to low frequency magnetic fields (LF-MFs) during embryonic stages and development (Graham et al., 2000; Saunders et al., 2005). For an adult stable nervous system, such a response may amount to little more than transitory and barely detectable perturbation. On the other hand, for a developing fetus or an infant in which the nervous system is still in their formative stages, these very same mild perturbations could be catastrophic. For example, Ravera et al. (2006) exposed fertilized eggs of the sea urchin (*Paracentrotus lividus*) to extremely low frequency electromagnetic fields (ELF-EMFs) and observed a dramatic loss of synchronization of the first cell cycle accompanied by irregular separation of chromatids, resulting in the formation of anomalous embryos.

Endogenous direct current (DC) electric fields play an important role in embryonic development, particularly in the development of the nervous system. Precise interconnections need to be made between neurons migrating to the proper place at a particular time. Any exogenous electric fields that have a tendency to modulate the endogenous fields could conceivably modify the synaptogenesis (Saunders and McCaig, 2005). Disruption of endogenous electric fields in amphibians has been seen to result in aberrant development of the nervous system. Electromagnetic radiations emitted by electronic gadgets in the environment during their operation are not strong enough to cause DNA alterations directly, though indirect DNA alterations have been shown through the production of reactive oxygen species (Lai and Singh, 1997). Moreover, *in vitro* and *in vivo* studies have demonstrated the ability of electromagnetic fields (EMFs) to cause epigenetic modifications (Ahuja et al., 2005). Recently, Sarimov et al. (2011) have demonstrated the mechanism of transcriptional activation/silencing at the chromatin level during exposure to EMFs. They exposed lymphocytes from two healthy men to extremely low frequency EMFs, and observed significant differences in chromatin conformation in them depending on the initial state of chromatin and temperature during exposure. In general, the magnetic field of 50 Hz at peak amplitude within the range of 5 to 20 μT condensed the relaxed chromatin and relaxed the condensed chromatin. In this report, focus has been laid on the epigenomic disturbances induced by the excessive exposure to EMFs leading to neurodegenerative disorders, including autism.

ELECTROMAGNETIC FIELDS AND THEIR EFFECTS ON HEALTH

The health effects of modulated EMFs have been a subject of debate. There are reports showing beneficial as well as deleterious effects. For example, magnetic fields (MFs) are used in medicine for diagnostic and therapeutic purposes. MFs have shown promise in improving the management of osteoarthritis as well as the pain associated with it (Vavken et al., 2009) and they have also been used in enhancing the rate of healing of fractured long bones (Strauch et al., 2006; Gao et al., 2004), nerve regeneration (Walker et al., 2007) and spinal fusion (Gan and Glazer, 2006). Recently, Costa et al. (2011) and Zimmerman et al. (2012) have reported anticancer properties of EMFs. Magnetic fields used in magnetotherapy are effective at specific frequencies as well as densities at regulated durations of exposure. On the other hand, variable and chronic exposure to magnetic fields has been implicated in the induction of cancer and neurodegenerative disorders. Ever since the report made by Wertheimer and Leeper (1979) on increased cancer mortality among children living in homes located near power lines, there have been a large number of studies on the health effects of elevated exposure to magnetic fields. Although, the results of these studies are controversial, the International Association on Research (IARC) in Cancer Working Group classified ELF-MFs in category 2B (that is, possible human carcinogen) (IARC, 2002). A comprehensive document of the World Health Organization confirmed the IARC evaluation (WHO, 2007). Several studies have also reported an association between exposure to ELF-EMFs and neurodegenerative disorders. Recently, in a comprehensive review, Maes and Verschaeve (2012) highlighted that *in vivo* as well as *in vitro* exposure to ELF-EMFs is associated with cytogenetic aberrations, some of which in turn may be related to genetic abnormalities seen in Alzheimer's disease.

ELECTROMAGNETIC FIELDS AND AUTISM

Among the natural sources, sun is a major source of radiofrequency radiations (RFRs). Lately, telecommunication systems and gadgets using microwaves, like microwave ovens, have added RFRs into the environment, thousands of times higher than those received from the sun alone. While operating an RFR gadget, not only will the user, but also those in the surrounding vicinity will be exposed to similar biologically interactive levels of EMF intensity. Some of the RFR-producing gadgets are routinely utilized in monitoring embryonic, fetal and neonatal wellbeing. Ultrasonography is commonly used in pelvic examination at regular intervals during pregnancy, and this radiation is used to observe the developing embryo or fetus during pregnancy.

Modulation is used in all wireless communication systems to enable the signal to carry information. Some studies have shown that there may be specific effects from amplitude modulated radiofrequency fields on the human central nervous system (Juutilainen et al., 2011). The range of RFR exposure from mobile phones is 0.1 to 10 mW/cm^2. Philips et al. (1998) have reported that RFRs as low as 0.1 $\mu W/cm^2$ (< 1000 times the RFR of cell-phone range) can induce significant changes in the biological processes or molecular repair mechanisms. Some of the observed effects of exposure to RFRs include cognitive impairment (Chiang et al., 1989) and memory deficit (Lai et al., 1994), both of which are seen in autism.

The incidence of autism before 1980 was reported to be 1/2000, while the present incidence has increased to about 1/100 (Toro et al., 2010). Although, the question of actual increase in incidence is debatable (Newschaffer et al., 2007) a review of epidemiological surveys by Fambonne (2003) support the proposition that the increased incidence of autism has an origin around the 1980s, the very same time that telecommunication devices, particularly mobile phones that emit RFRs came into popular use. On the basis of these observations, Kane (2004) suggested that fetal or neonatal exposure to RFRs associated with the use of these devices may be associated with autism.

In the grey matter of brain of humans, there is a subset of neurons called the mirror neurons which respond when an individual performs certain actions and also when one observes others performing the same movements. Mirror neurons may also underlie the ability to imitate and learn the action of others making the mirror mechanism a bridge for communication and connection on multiple levels. As mirror neurons appear to be involved in social interaction, dysfunctions of this neural system could explain some of the primary symptoms of autism, including isolation and absence of empathy. Studies of people with autism show a lack of mirror neuron activity in several regions of the brain (Ramachandran and Oberman, 2006). Decrease of gray matter in the area belonging to the mirror neuron system has also been observed in autism. Developing nervous system network of an infant may be particularly prone to environmental factors like temporal noise. According to Thornton (2006), the most likely source of temporal noise in the environment is due to artificially generated electromagnetic radiations, which may be involved in disturbing the development/function of mirror neurons. This disturbance in mirror neurons, due to temporal noise from EMFs may be involved in the causation of autism.

ENVIRONMENTAL VERSUS EPIGENOME FACTORS

Prenatal and postnatal environmental factors have the potential to modify epigenetic programming and bring about subsequent changes which may have relevance in

health and disease. In complex diseases like cancer, diabetes and neurodegenerative disorders environmental factors, in addition to genetic factors, have an important role to play, and the contribution made by environmental factors may be mediated through epigenetics (Herceg, 2007).

Epigenetics may be defined as the heritable/transient changes in phenotypes that cannot be explained by changes in DNA sequence. Epigenetic mechanisms provide an extra layer of transcriptional/translational/post-translational controls that regulate how genes are expressed. The epigenetic changes are mostly the result of altered DNA methylation, histone modifications, non-coding RNAs and protein interactions (Richards, 2006; Ahuja et al., 2009).

ELECTROMAGNETIC FIELDS, EPIGENOMIC DISTURBANCES AND AUTISM

With the increasing number of electronic gadgets being used worldwide today, EMFs have become an important environmental source of electropollution. The central nervous system is sensitive to the action of EMFs, which can alter the bioelectric activity of the brain (Tattersal et al., 2001; Sidorenko and Tasaryuk, 2002). At non-thermal levels (with no increase in temperature), EMFs have been seen to bring about changes in biogenic amines involved in neurotransmission, like acetylcholine in the hypothalamus (Inaba et al., 1992; Lai et al., 1998). JorgeMora et al. (2011) exposed the paraventricular nucleus (PVN) of rat hypothalamus to 2.45 GHz microwave radiation at non-thermal specific absorbance rate (SAR) levels and observed its reactivity through c-Fos expression. PVN is a regulatory center for homeostasis (Sawchenko and Swanson, 1981) and the most important nucleus in relation to neurocircuitry stress (Herman and Cullinan, 1997).

EMFs of mobile phones (890 to 915 MHz) with (SAR 0.95 W/kg) were seen to be associated with increased free radical production and lipid peroxidation levels in both brain tissue and blood of guinea pigs (Meral et al., 2007). The brain seems to be especially sensitive to the influence of high frequency EMFs (Sidorenko 1999) causing oxidative stress in brain cells, which may lead to neurodegenerative diseases (Polydoro et al., 2004; Lima et al., 2005). Zhao et al. (2007) studied gene expression profile of rat neurons exposed to mobile phone radiofrequency (1800 MHz) electromagnetic fields with cDNA microassay. Among 1200 candidate genes, 24 up-regulated genes and 10 down-regulated genes were identified. From these studies, they concluded that RF exposure might alter the cytoskeleton and central nervous system functions by activating signal transduction pathways, thus leading to the abnormal neural growth and metabolism. Some effects of radiofrequency and power fields that have been observed affecting the brain functions by other investigators, include increased blood brain barrier permeability and neuronal damage in cortex, hippocampus, and basal ganglia (Salford et al., 2003), memory impairment (Krylov et al., 1993; Lai et al., 1994, 1998) and changes in choline uptake (Lai et al., 1989, 1990). Excessive exposure to EMFs has also been implicated in disturbing the epigenetic patterns as well as the rise of neurodegenerative disorders (Levin, 2003; Ahuja et al., 2005).

During early growth and development, epigenetic mechanisms like DNA methylation, histone modifications, non-coding RNAs and regulatory proteins are involved. During further growth and differentiation of the embryo and fetus, switching on and switching off of specific genes at specific times, is also governed by epigenetic mechanisms. Disturbance of epigenetic imprints due to endogenous or exogenous factors may lead to death or a diseased condition. There is ample evidence to support the contention that EMFs affect the gene expression and differentiation process through epigenetic mechanisms (Ahuja et al., 2005; Akan et al., 2010; Munshi et al., 2011). This contention is further supported by the following studies. Chung et al. (2010) compared the gene expression pattern in the thymus taken from 3 mice exposed to 83.3 μT polarized magnetic field and controls; the expression change was over 1.5 times in 100 preselected genes in the thymus of exposed mice as compared to the controls. Frahm et al. (2010) exposed mouse macrophages to ELF-MFs (50 Hz, 0.1 mT) and observed immune cell activation, in response to an increased production of reactive oxygen species, which in turn was due to modulation of the expression level of important proteins acting in redox regulatory processes. Collard et al. (2011) applied extremely low frequency electrical fields to human epidermal cells and carried out microarray analysis of 38500 human gene expression. Among the deviant genes identified by the authors were 4 up-regulated genes (DKK1, TXNRD1, ATF3 and MME) and one down-regulated gene (MACF1), all the 5 genes being involved in the regulation of cell proliferation and differentiation. Bisceglia et al. (2011) exposed human bone cell line (SaOS-2) to a low frequency electric field from apparatuses used in clinical therapies, and observed a significantly increased alkaline phosphatase enzymatic activity in the exposed cells as compared to the controls. Enhanced bone repair has been seen after exposure to low frequency electromagnetic fields, and the authors have demonstrated the molecular mechanism for this enhancement, that is, through an elevated level of alkaline phosphatase, which was previously demonstrated to be involved in bone mineralization (Anderson, 1989). Aydin and Akar (2011) exposed immature and mature rats to 900 MHz for 2 h/day for 45 days and observed oxidative stress metabolism in all the three lymphoid tissues studied (spleen, thymus and bone marrow). As compared to the mature rats, damage found in the immature animals was greater and there was less

recovery from oxidative stress injury after the specified recovery period study. Exposure to EMFs conspires to threaten epigenomic stability in the nervous system, because neurons are particularly susceptible to oxidative stress,

Evidence is accumulating that, in addition to deleterious mutations in genes of pivotal importance, epigenetic dis-regulation of DNA methylation and histone modification, which are important for regulation of chromatin structure and function, could play a prominent role in the patholo-physiology of autism and related neurodegenerative disorders (Thatcher and LaSalle, 2006; Schanen, 2006; Petronis, 2010). Using deep sequencing of DNA, Shulha et al. (2012) observed that there was loss or excess of a histone mark, trimethylated H3K4 (H3K4me3), at hun-dreds of loci in prefrontal cortex but not in other parts of the brain, in a subset of autistic individuals. The affected loci were associated with disregulated expression of transcripts implicated in neuronal communication and other higher order communication. Since, it has been suggested by various investigators that epigenetic distur-bances appear to play an important role in the causation of autism (Migliore and Coppede, 2009; Dufour-Rainfray et al., 2011), role of excessive exposure to EMFs emitted by electronic gadgets in causing these disturbances seems likely.

CONCLUSION

Different approaches have been considered to identify susceptible loci or genes (having mutations) for the causation of autism. Using various models, researchers have now begun to link novel molecular mechanisms of transcriptional regulation to intellectual and cognitive dys-functions in autism. Such studies highlight an increasing recognition of the key role epigenetic regulation plays in silencing and induction of the genes linked with distinct genotypes and phenotypes contributing to autism. Besides other environmental factors, electrical and mag-netic fields also have the ability to modify the epigenome. Epigenetic aberrations of certain loci, which are possibly triggered by undesirable doses of electromagnetic radiations from electronic gadgets during early develop-ment (particularly first trimester), may lead to autism in a certain set of infants carrying abnormal genetic and epigenetic modifications.

In future, it would be interesting to evaluate *in vivo* and *in vitro* epigenetic modifications in some of the major genes associated with autism, e.g. gaba-amino-butyric acid (GABA) receptor, serotonin transporter (SLC6A4) and neuroligin (NLGN), in normal cells after exposure to EMFs at different doses and durations.

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Abbreviations: AC, Alternate current, **DC,** direct current; **cDNA,** complementary DNA; **DNA,** deoxyribonucleic acid; **ELF,** extremely low frequency; **EMF,** electromagnetic field; **FM,** frequency mode; **GHz,** Gega Hertz; **Genotype,** genetic composition; **Hz,** Hertz (cycles/second; named after German scientist Henrik Hertz); **LMF,** low magnetic field; **MF,** magnetic field; **MHz,** Mega Hertz; **µW,** Micro Watt; **mW,** Milli Watt; **Phenotype,** result of interaction between genotype and environment (end product due to epigenetic modifications of gene expression); **RFR,** radiofrequency rays; **RNA,** ribonucleic acid; **SAR,** specific absorption rate; **T,** Tesla (unit of magnetic field; named after an Italian scientist); **W,** Watt (unit of power; named after a British scientist); **W/Kg,** Watts/kilogram.

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