

Environmental Health Factors for Motor Neuron Disease

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Abstract:

Motor Neurone Disease (MND) is a progressive disease and once the symptoms are jointly evident enough to allow diagnosis, MND is a rapidly terminal disease. A plausible mechanism is the enhanced Apoptosis of the Motor Neurones leading to the loss of skeletal muscular control and strength. This has led to the development of a hypothesis that attempts to explain the overall evidence pattern, including the seasonal MND related birth peak in Spring, the familial and occupational MND associations. The hypothesis proposes that the development of MND is based on a variable initial volume of Motor Neurons and the development of the disease through the enhanced cumulative Apoptosis rates over people's life-time, leading to premature loss of the Motor Neuron muscular control and premature death primarily through lung failure. The cumulative life-time damage from exposure to environmental neurotoxins, stressful activity that reduces sleep quality and melatonin, heavy work load periods, antioxidant levels in diets, are a complex set of factors that can enhance the Motor Neurone Apoptosis rate. This is connected to the lack of CNS neuron regeneration. The associated environmental neurotoxin effects include those from heavy metals, smoking, agricultural chemicals, water and air pollution toxic chemicals and genotoxic electromagnetic fields. The ubiquitous nature of any associated substance, especially dioxin and electromagnetic fields, suggests that they are the largest general population risk factor. Electromagnetic fields and some toxic chemicals have been found to pass cancer on to children from mother and/or father's exposures. This supports a genotoxic mechanism that is supported by many studies showing chromosome damage and DNA strand breakage. These disease agents are likely to reduce the initial Motor Neuron Volume and/or advance the rate of development of Motor Neuron Disease through enhanced Apoptosis rates. Reducing the general population's exposure to environmental and residential genotoxic and neurotoxic substances is likely to be associated with a significant reduction in the incidence of MND in future generations.

Introduction:

One of the first principles of Environmental Health is that we need to understand the natural system before we assess the human environmental impacts on people and the environment.

The Motor Neuron System, that controls our movement and skeletal muscular activity is not well understood by the general public and is usually taken for granted. Muscles are vital for life. Automatic and conscious control of muscles is basic. There is a Motor Neuron part of the brain, connections with all muscles through the Central Nervous System, the spine and to muscles where the peripheral Motor Neurons, that are dendritic (branched) cells, receive a signal to relax or contract the muscle. The muscular

cells are controlled by the Motor Neurons through regulation of an ion signal, usually sodium and calcium ions through voltage-gated ion channels, Alberts et al. (1994). In many circumstances groups of muscles are programmed to carry out particular movements. In sport this can be running, rowing, skiing, or throwing, catching or hitting a ball, for example. In normal life it includes coughing, sneezing, grasping, standing, sitting, talking, walking, running, etc.

The primary components of the Motor Neuron system are the Motor Neurons in the motor part of the Cerebral Cortex. This sends and receives electrical and biochemical signals that are transmitted between them through the Brain Stem and the Spinal Cord. The Brain Stem modulates the actions of spinal Motor Circuits. The Motor Neuron Nucleus along the Spinal Cord activates a cluster of Motor Neurons in the spine that send signals to the selected muscle. A typical muscle consists of many thousands of muscle fibres working in parallel and organised into a smaller number of motor units. The muscle is controlled by about a hundred motor neurons that lie in a distinct cluster, called the motor nucleus, in the Spinal Cord or Brain Stem. The axon of each motor neuron exits the spinal cord through a ventral root, or through a cranial nerve from the brain stem, and transverses progressively smaller branches of peripheral nerves until it enters the muscle it controls. There it branches widely to innervate anywhere from 100 to 1000 muscle fibers scattered over a substantial part of the muscle. Except during development, each muscle fiber is normally innervated by only one motor neuron in only one place near its midpoint. The ensemble of muscle fibers innervated by a single motor neuron is called a muscle unit. The number of muscle fibers constituting a single motor unit varies greatly in muscles in different parts of the body, Kandel, Schwartz and Jessell (2000).

While all cells have a membrane potential (voltage), only neurons (and muscle cells) generate electrical signals that can be conducted rapidly over long distances. Hence it is logical that neurotoxins and electromagnetic signals have been associated with enhanced incidence rates of MND in above average exposed workers. Hence both of these environmental factors are associated with enhanced MND rates in exposed groups and enhanced MND progression in the affected individuals.

As for other chronic neurological and carcinogenic diseases, part of the disease generation process is accelerated aging. Part of our daily life is cellular DNA damage and attempted DNA repair or damaged cell removal. One process of damaged cell removal is programmed cellular suicide, called Apoptosis. Another process involves the immune system identifying the "foreign" cells and the Natural Killer Cells killing them.

The processes that cause the advanced Motor Neuron cell death rate are under investigation. Free radical activity is a known cause of Apoptosis and oxidative and nitrogen free radical activity is associated with enhanced Neuron death. Exposure to Genotoxic and Neurotoxic substances directly enhances Apoptosis rates. Antioxidant activity of melatonin and some foods helps to reduce the oxidative damage through free radical scavenging.

Hypothesis:

A generally accepted concept is that the fetal development involves the development of the Central Nervous System (CNS), including the Motor Neurons, Interneurons and Sensory Neurons, all of which are generated synchronously, with the Motor Neurons

developed quite early. This produces a significant redundancy in the Motor Neuron system to cope with natural oxidative damage kills cells as part of the natural aging process. For most people this provides sufficient control of muscular activity for normal life spans, despite the progressive loss of some of their Motor Neurons over their life time.

The basic hypothesis is that we all develop a certain volume of Motor Neurons as infants. Natural oxidative processes, personal activity and environmental neurotoxins, enhance the Apoptosis rate of Motor Neurons in everyone. In some people this leads to premature loss of muscular control and strength, diagnosis with MND and earlier death. Therefore it is primarily the life-time cumulative neurological death rate that leads to MND, resulting in a mean diagnosis age in the range 55 to 65 years. Associated symptoms are highly likely to be present many years earlier as the Motor Neuron death rate progressive, with a higher rate in some particular organs.

Neurological degenerative diseases have a great deal of similarity to cancer with many common causes. The natural differences in all people make some more likely to develop cancer and others MND from similar circumstances and exposures.

The group of people who have enhanced Motor Neuron cellular death rates, who eventually show major symptoms and earlier death, have a probable combination of a wide range of factors that produce this situation. For some it could be neurotoxic damage of the foetus, or a genetic factor that leads to a reduction in the initial number of Motor Neurons. Some may have a genetic susceptibility that could be associated with a vulnerability to enhanced Apoptosis rates. Exposure to environmental toxins enhances the cell death rate, including the Apoptosis of Motor Neurons.

People with MND are often described as "high achievers". Heavy workloads with stress and reduced sleep (hence reduced melatonin) are logically associated with increased MND rates and high antioxidant levels in diets to reduced MND rates.

The Apoptosis Mechanism for MND:

A large body of research supports Apoptosis as the MND/ALS mechanism. "Programmed Cell Death", Apoptosis is a vital cell health protection mechanism, except in neurons. Neurodegenerative processes are generally characterized by the long-lasting course of neuronal death and the selectivity of the neuronal population or brain structure involved in the lesion. There is growing evidence supporting a role for apoptosis in some neurodegenerative diseases, Dragunow et al. (1997), Nieoullon (1998) and Offen, Elkon and Melamed (2000).

Familial Factors of MND:

Some people are more vulnerable to accelerated damage through their genetic differences. This makes them more susceptible to enhanced environmental toxic damage. It is generally accepted that the genetics doesn't cause the disease but increases the susceptibility. Hence there are strong reasons to clean up the environment to protect the susceptible people, which include the very young, very old and already sick people. Approximately 5-10% of MND cases have a family history of MND, Kamel et al. (2000). Family history of MND increases the incidence of MND in relatives, OR = 3.3, 95%CI: 1.1-9.9, Cruz et al. (1999). For a first-degree relative the

Odds Ratio is $OR = 3.1$, $95\%CI: 0.6-15.7$), while for a second-degree relative $OR = 4.0$, $95\%CI 1.0-6.6$. No significant associations were found for family history for Parkinson's Disease nor Alzheimer's Disease. About 20% of familial cases have mutations in a gene for Cu/Zn superoxide dismutase (SOD), a cytosolic enzyme involved in detoxification of reactive oxygen species.

Incidence, prevalence and mortality rates:

The annual mortality of MND/ALS is often cited as 1-2 per 100,000. This rate is higher in men than in women. Because there is no cure for MND and the diagnosis is relatively late and it is a terminal disease, the incidence and mortality rates are very close. The prevalence rate is typically 2 to 4 times the annual incidence rate because of the 2 to 4 year survival time. In New Zealand the MND prevalence rate is around 6 per 100,000 with a total number of cases between 200 and 250.

In Switzerland 1981-1990 the ALS incidence rate in the Zurich canton was 0.92, while the prevalence rate was 3.88 per 100,000, Huber and Henn (1995). In Japan the equivalent figures are 0.69 and 2.25, Okumura et al. (1992). In France the mortality rates averaged for men were 1.45 and women 0.9 in 1968-82, risen from 1.11 and 0.63 in 1968-71, to 1.95 and 1.12 by 1979-82. In Norway there is a significant, $p = 0.0001$, rising trend in ALS mortality from 1961 to 1994, from about 1.38 to 2.54 per 100,000 per year, Figure 1.

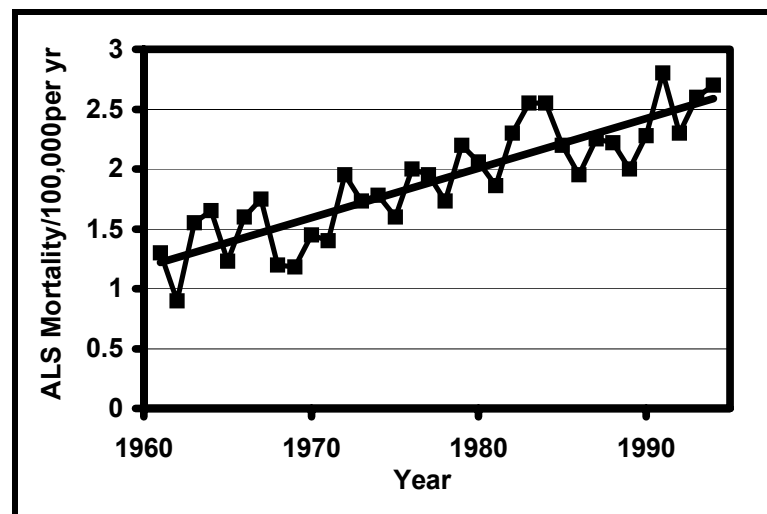


Figure 1: ALS mortality per 100,000 per year in Norway in the period 1961 to 1994, Trend $p = 0.0001$, Seljeseth, Vollset and Tysnes (2000).

The increase was larger in women than men. The trend was similar for Parkinson's Disease. Seljeseth et al. state that this increase agrees well with the data from Sweden, the United States, France, England and Wales. The increase is generally in women and in the elderly >65 years. The sex ratio change is significant. In the 1960's the ALS mortality rate for men was 1.61 and for women 1.17, Sex Ratio = 1.58. During the 1990-1994 period for men it was 2.58 and for women 2.50, Sex Ratio = 1.32. . The trend raises the question as to whether it is simply due to people getting older. Alternatively, are there any environmental factors that have contributed? Seljeseth et al. address these questions and found that the ALS rate rose in the 70+ age group by 275% whereas the general population in the age group rose by 69%. They concluded that this

showed that the increase in ALS mortality could not be solely explained by the increase in age of the general population.

Oxidative stress, reactive oxygen (ROS), and nitrogen (NRS) species have been known to be involved in a multitude of neurodegenerative disorders such as ALS and Parkinson's Disease (PD) and Alzheimer's Disease (AD), Iman et al. (2001). Therefore any factors that enhance the oxidative stress through their neurotoxic activity, or factors that reduce the scavenging of free radicals or reduce the repair mechanisms of damaged neurons, could be contributing to the rising trend of ALS/MND mortality.

Birth Month - Early Initiation ?:

One study has found a seasonal birth relationship to MND in Switzerland, Ajdacic-Gross, Wand and Gutzwiller (1998). The peak was associated with birth in Spring months. This raises the possibility of a winter cold but more likely the winter heating with higher electromagnetic fields and air pollution from solid fuel burning. This could have a relationship because the foetal develop is maximum during the winter season, in a similar fashion to Foetal Alcohol Syndrome. This would be plausible if it involves exposure to neurotoxins during the development of the Motor Neurone aspects of the Central Nervous System during foetal development. A hypothesis is proposed for early initiation of MND with a multiple decade latency period in parallel with genotoxins and cancer development and conditions. There is also scientific logic connecting genotoxins, that damage DNA and enhance Apoptosis (programmed cell death), with neurotoxicity that enhances the Apoptosis of Neurons.

Studies have been carried out to show what parental exposures are associated with childhood cancer. A MEDLINE search showed that no studies have been published showing any associations between parental occupational exposures and MND, PD, nor AZ, but many for increased rates of Childhood Cancer. This is logical because childhood cancer can develop quickly and the association is then sought and found. For degenerative neurological diseases that typically take 40 to 70 years to develop, the association with parental occupation is more difficult to identify because of the time delay and the general absence of knowledge of the possibility. Because of the joint mechanism, enhanced mutation and Apoptosis through DNA damage, it is likely that substances that cause childhood cancer from parental exposure, are likely to also enhance Motor Neuron cell death rates.

Occupations and substances that have been shown in multiple (3 or more) studies in a review of over 40 studies, Colt and Blair (1998), to enhance childhood cancer through parental exposures include: electromagnetic fields in electrical occupations and welding; lead in welding, solvents, paints and pigments in painting, printing and dry cleaners; employment in the motor vehicle related occupations; textile workers and metal industries. Specific chemicals involved include solvents, benzene, Xylene, Chlorinated solvents, Carbon Tetrachloride, TCE, spray paint, HCs, metal dust, vehicle exhaust gases, ionizing and electromagnetic radiation. There is evidence that all of these substances are genotoxic and hence they are also neurotoxic.

Genotoxic and neurotoxic substances are likely to be associated with enhanced development and mortality of Motor Neurone Disease with plausible development over a wide range of decades centred on the 55-65 period for diagnosis. However with the progressive accumulation of Motor Neuron enhanced cell death the onset of early

symptoms is likely to be much earlier. The diagnosis problem is having detectable and recognizable symptoms and the elimination of any other CNS diseases.

Environmental Factors of MND:

Neurotoxic chemicals and heavy metals:

Neurotoxic substances include methyl-mercury, lead, PCBs and organophosphorus compounds, Trask and Kosofsky (2000), and genotoxic chemicals including dioxin and benzene, agricultural chemicals and cigarette smoking. Occupational exposure to 2,4-D produces a significant increase of MND rates, RR = 3.45 (1.10-11.1), Burns, Beards and Cartmill (2001).

Lead has been associated with elevated rates of MND since 1850. In 1968 a letter to the British Medical Journal states that lead intoxication mimics Motor Neuron Disease, Livesley and Sissons (1968). Several occupational studies show lead exposures elevate MND. Kamel et al. (2002) studied MND and lead exposure in New England 1993-1996 with 109 cases. Overall the Odds Ratio was OR = 1.9, 95%CI: 1.1-3.3, with a non-linear dose-response relative to blood lead levels, Figure 2.

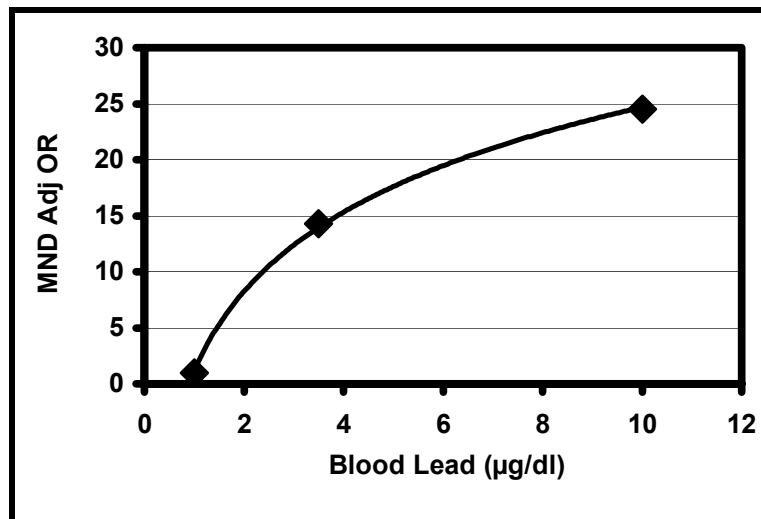


Figure 2: Enhanced MND (ALS) rates in workers exposed to lead, related to the measured blood lead levels, Kamel et al. (2002).

McGuire et al. (1997) found that farmers in western Washington State exposed to agricultural chemicals had elevated MND/ALS for men OR = 2.4, 95%CI: 1.2-4.8. They also found a significant dose-response, Figure 3. Classically a dose-response is supportive of a causal relationship, Hill (1965). Farmers chronically exposed to agricultural chemicals have a clear risk factor for increased MND.

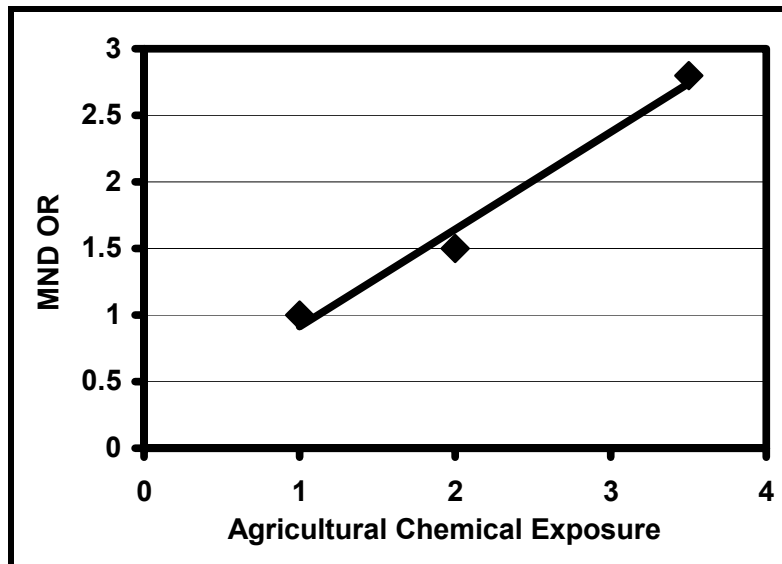


Figure 3: Dose response increase in MND with agricultural chemical level of exposure, no, median and high exposure levels, trend $p=0.03$, McGuire et al. (1997).

Cigarette smoking is associated with an increased incidence of MND/ALS, OR = 1.7, 95%CI: 1.0-2.8, Kamel et al. (1999). Nelson et al. (2000) found the association for MND/ALS in current smokers, OR = 3.5, 95%CI: 1.9-6.4), and for former smokers OR = 1.5, 95%CI: 0.9-2.4. Clearly smoking is a risk factor for MND.

Electromagnetic fields exposures:

Welders are occupationally exposed to a combination of lead and strong ELF/RF/MW fields. Welders have increased incidence of MND, OR = 5.3 and for electric plating OR = 8.0, 95%CI: 0.9-72, Strickland et al. (1996).

Electric utility workers are frequently exposed to elevated electric and magnetic fields and sometimes to electric shocks that send high currents through their bodies, including the Motor Neuron part of their central nervous system (CNS). Overall reported electromagnetic field exposures gave for MND/ALS, OR = 3.8, 95%CI: 1.4-13.0. For electric shocks producing unconsciousness, OR = 2.8, 95%CI: 1.2-9.9.

Parkinson's disease was also significantly elevated from ELF exposure, OR = 2.7, 95%CI: 1.1-7.6, Deapen and Henderson (1986). An independent study by Davanipour et al. (1997) compared MND/ALS rates between non-electrical and electrical occupations. They found that the higher the exposure the higher the rate of MND, Figure 4. Savitz, Loomis and Tse (1998) researched neurodegenerative disease and electrical occupations and found elevated Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS/MND). The highest rates were found in a very highly exposed group, the power plant operators:

For AD, Adj OR = 2.6, 95%CI: 1.3-5.1.

For PD Adj OR = 2.1, 95%CI: 0.9-4.7.

For MND Adj OR = 4.8, 95%CI: 1.9-12.4.

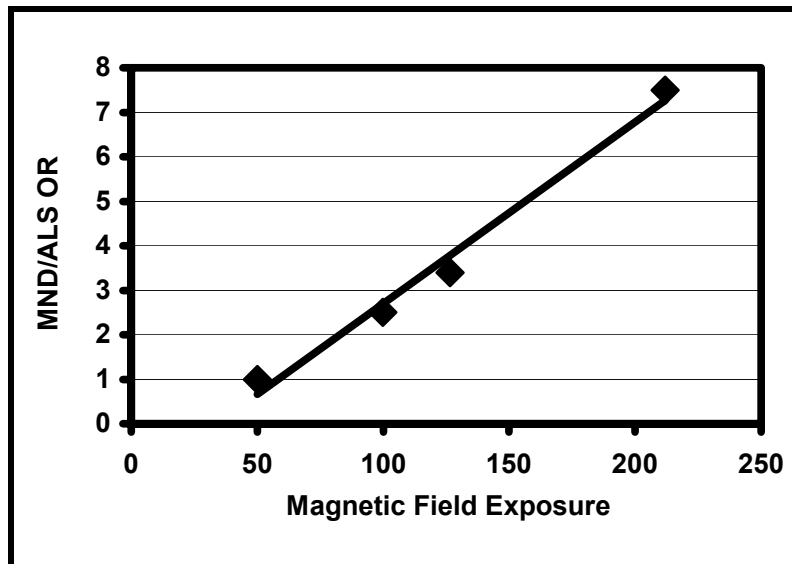


Figure 4: Dose-response increase in MND/ALS from chronic magnetic field exposures in electric utility workers, $p < 0.02$, Davanipour et al. (1997)

A follow-up study, Savitz, Checkoway and Loomis (1998) also found a positive association with duration of electric occupational work and MND (ALS), $RR = 2.0$, $95\%CI: 0.7-6.0$. They also found that the longer you worked in these electromagnetic fields the higher the MND rate rose, Figure 5.

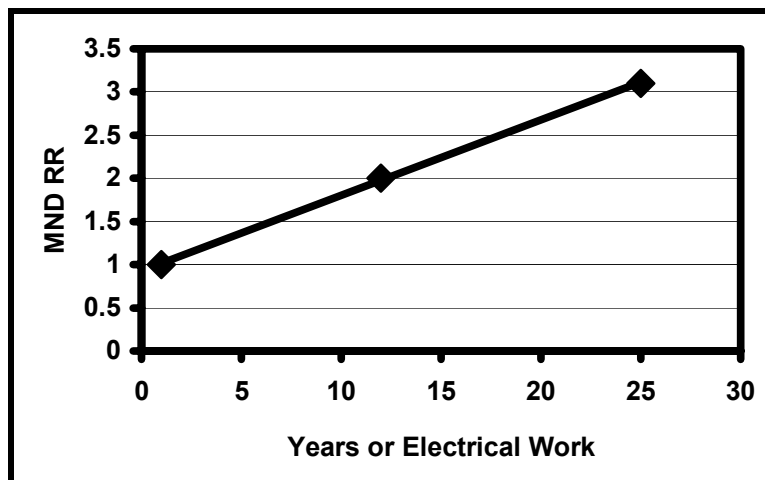


Figure 5: A significant dose-response relationship ($p < 0.001$) between years of electrical work and MND (ALS), Savitz, Checkoway and Loomis (1998).

Electric utility workers in Denmark have the same risk factor for MND as U.S. utility workers, Figure 6. These three dose-response studies of EMF exposure show a causal link between chronic exposure to EMF and Motor Neuron Disease.

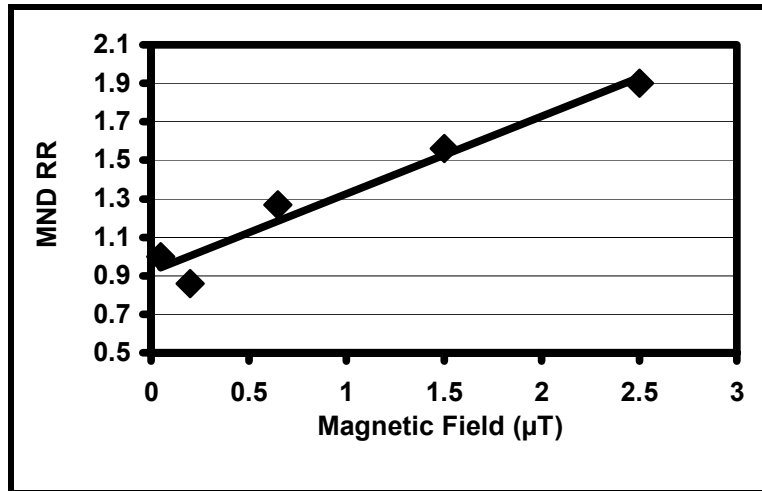


Figure 6: A significant dose-response ($p < 0.0001$) increase in MND correlated with long-term mean ELF magnetic field exposures in electric utility occupations, Johansen (2000).

A recent review of Neurodegenerate Diseases in relation to EMF, Ahlbom (2001), identified 7 studies involving ALS/MND and electrical workers. When they were appropriately grouped, each group shows a significantly elevated MND rate, Table 1.

Table 1: Pooling across groups of studies on EMF and ALS, Ahlbom (2001).

Pooled studies	Number of studies	RR	95% C.I.
All	7	1.5	1.2-1.7
Clinically and ALS society based studies	3	3.3	1.7-6.7
Mortality registry and census based studies	2	1.3	1.1-1.6
Utility cohorts studies	2	2.7	1.4-5.0

This review confirms that EMF exposure in various situations significantly increases the incidence and mortality of MND/ALS.

RF/MW Exposure MND association:

If ELF fields cause increased MND then RF/MW fields will have a far higher effect at even lower mean field levels because of the EMR Spectrum Principle.

Anne Silk, a public health researcher in the UK is investigating clusters of MND in English villages in order to determine probable environmental factors. So far every case, of over 5 villages, there is only one common factor, an RF/MW source such as a cell site, radio/TV mast or amateur radio operator neighbour.

There is a strong plausible mechanism to support the observations of clusters of MND around RF/MW radiation towers, including cell site base stations, through DNA damage advancing the rate of Motor Neurons cell death (Apoptosis). Many studies show that microwaves damage DNA through significant enhanced chromosome aberrations; micronuclei formation and DNA strand breakage, including several with dose-response relationships, Cherry (2002). This is specifically confirmed from cell phone radiation that

has been specifically shown to very significantly enhance DNA strand breakage, $p < 0.0001$, at very low exposure levels, around $1.2 \mu\text{W}/\text{cm}^2$, Phillips et al. (1998).

In addition to the genotoxic biological mechanism, the EMR Spectrum Principle also predicts that RF/MW radiation will have a stronger low-level exposure adverse health effect than ELF fields shown above to be causally associated with ELF chronic fields occupational exposures.

EMR Spectrum Principle:

It is observed that both biological effects and epidemiological effects appear to be the same or very similar from ELF exposure and from RF/MW exposures, including calcium ion efflux, melatonin reduction, DNA strand breakage, chromosome aberrations, leukaemia, brain cancer, breast cancer, cardiac malfunction, miscarriage and neurological effects.

The dielectric constant is approximately the AC equivalent of the DC Resistance. As the dielectric constant decrease the conductivity increases. The dielectric properties of biological tissue depend on the water content because the interaction of the RF/MW signal with the tissues. Two types of effects control the dielectric constant frequency dependence. One is the oscillation of the free charges or ions and the other the rotation of the molecules at the frequency of the applied electromagnetic signal, Johnson and Guy (1972).

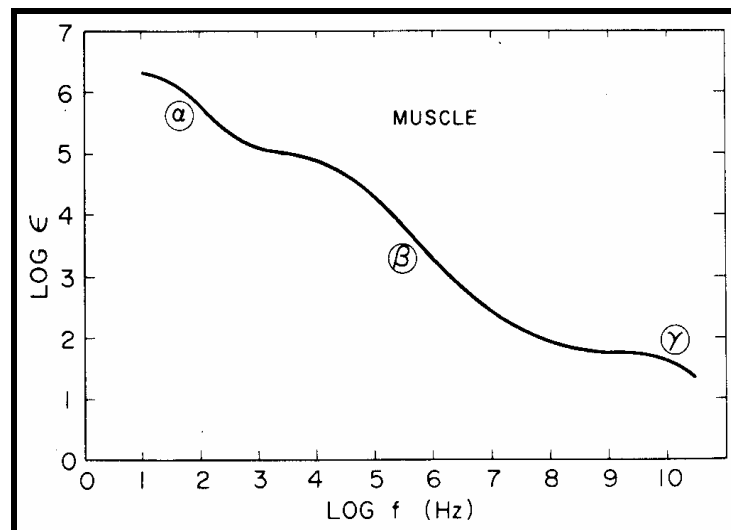


Figure 7: The dielectric constant of muscle as a function of frequency, Schwan and Foster (1980).

This results in a progressive reduction in the dielectric constant with rising frequency of the electromagnetic signal, Figure 7. The significant drop in dielectric constant with increasing frequency shows a linked process across the spectrum with increasing conductivity and higher induced currents as the frequency increases, Vignati and Giuliani (1997), Figure 8.

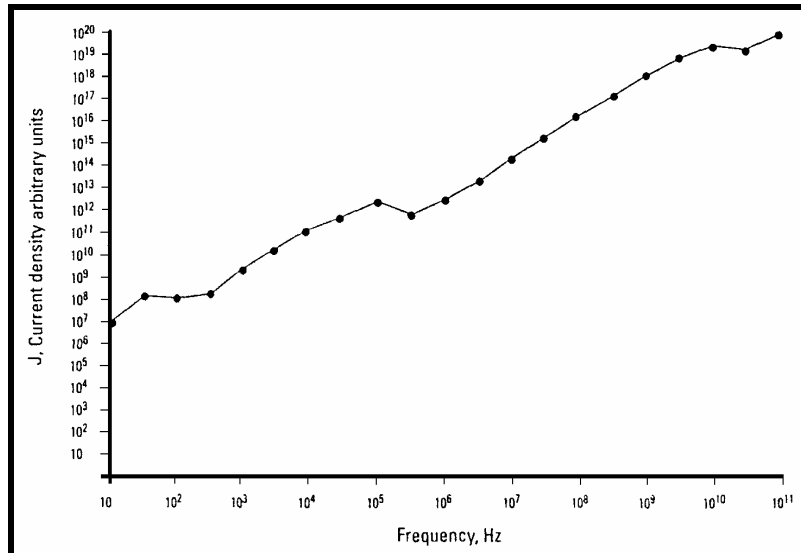


Figure 8: Capacitive induced current density in a toroid of human muscle tissue of unitary radius, exposed to a unitary magnetic field induction, Vignati and Giuliani (1997).

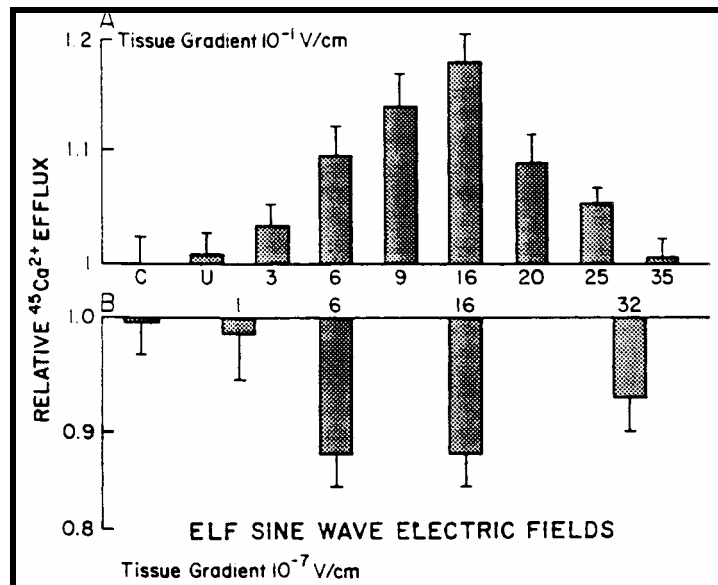


Figure 9: Relative Ca^{2+} efflux (positive and negative) from isolated chick cerebral hemisphere exposed to (A) weak RF field (147 MHz, 0.8 mW/cm^2 , 56 V/m in air), amplitude modulated at low frequencies (abscissa) and (B) ELF electric field (56 V/m in air) over the same ELF modulation frequencies, Adey (1988).

Figures 7 and 8 are consistent with data presented by Johnson and Guy (1972). Adey (1988) shows that a 56V/m ELF field induces a tissue gradient of 10^{-7}V/cm , whereas a 56V/m 147MHz signal, modulated by the same spectrum range of ELF fields, induces a tissue gradient of 10^{-1}V/cm , a million times higher, Figure 9. This is a close to the factor given by Figure 8 between 16Hz and 147MHz.

Figure 9 shows an electromagnetic field mechanism that involves Motor Neurons, the influx and efflux of calcium ions through the cell membrane, primarily through the voltage gated ion channels.

Conclusions and Recommendations:

Many environmental factors are associated with increased risks of Motor Neuron Disease. Strong attempts should be promoted to reduce all identified risk factors, including certain heavy metals, including lead from batteries and soldering, neurotoxic chemicals, including smoking and agricultural chemicals from dips and sprays, dioxin from log burners and open fires, benzene from petrol and all electromagnetic fields from power supply lines, appliances, computers, cordless and mobile phones, radars, radio and TV stations and more recently, cell sites. The most dangerous substances are those that chronically expose most people in their homes. Classically earlier this would have been smoking and fires. For over 50 years the EMF and EMR fields are exposing all of us to genotoxic signals that are associated with enhanced incidence of MND.

A widespread move to energy efficiency, passive solar heating, energy efficient urban form with public transport carrying most people, will drastically reduce toxins from burners, traffic and electromagnetic fields. This would not only significantly reduce the incidence of MND, but many other neurodegenerative diseases, cancer, cardiac and reproductive health effects that are all associated with genotoxic substances, including EMF and EMR in multiple, independent epidemiological studies.

We can use MND as our motivation to promote a much cleaner environment that will have a massive, widespread improvement of many health effects, personal and family wellbeing and major financial benefit through reduced health costs and new jobs, products and exports.

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