Parkinson's Disease, Multiple Sclerosis and Amyotrophic Lateral Sclerosis: The Iodine-Dopachrome-Glutamate Hypothesis

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Abstract

Background. Globally, Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis mortalities tends to increase with latitude. These disorders also display a north-south gradient in the coterminous United States. This spatial distribution suggests their etiologies are significantly influenced by one or more geographical variables.

Methods. Pearson's correlation was used to compare mortalities, at the state scale, in the United States, from these three neurologic disorders and the spatial patterns of 81 other diseases and 219 environmental variables.

Results. The resulting correlations suggest that mortality from Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis occurs most often in recently glaciated, iodine deficient regions, that were formerly marked by elevated goiter prevalence.

Conclusions. Long-term iodine deficiency appears linked to abnormalities in the dopaminergic system that include an increased number of dopamine receptors. It is argued that this raises susceptibility to dopamine oxidation which, in turn, causes deficiencies of the antioxidant enzymes Cu/Zn superoxide dismutase, glutathione peroxidase and catalase. Dopamine deficiency also leads to elevated cytotoxic glutamate levels. Implications of the iodine-dopachrome-glutamate hypothesis, for treatment of these three neurologic disorders, are then discussed. Possible interventions include the use of levodopa, vitamin B_3, Coenzyme Q_{10}, various antioxidants, amino acids, iodine and glutamate antagonists.

Key words: Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, glaciation, iodine, goiter, dopamine, dopachrome, glutamate, oxidative stress.

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Latitude

Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis are all more common at higher latitudes. Incidence and prevalence rates for Parkinson's disease in United States' whites, for example, display a "gradient" with a latitudinal component, with mortality being some 20 percent lower in the southeast than elsewhere in the United States.[1] Comparable north to south gradients in the prescription of levodopa, used predominantly to treat Parkinsonism, have been reported from both Spain[2] and Sweden.[3] This relationship between Parkinson's disease and latitude was confirmed on a global scale by de Pedro.[4]

Latitude and the prevalence of multiple sclerosis also are linked.[5] This is highest in a zone that includes northern and central Europe into the former USSR, southern Canada and the northern United States, New Zealand and southeastern Australia, where prevalence rates reach 30 or more per 100,000. This high risk zone is bounded by regions displaying prevalence rates of between 5 to 29 per 100,000, including most of Australia, the southern United States, south-western Norway and northern Scandinavia, the Mediterranean basin from Spain to Israel and that portion of the former USSR that stretches from the Urals into Siberia and the Ukraine. Whites in South Africa and probably central South America also are included in this medium risk zone. Elsewhere, the prevalence of multiple sclerosis is lower than 5 per 100,000, as for example in Japan, Korea, Africa, Mexico and the Caribbean.

A similar relationship has been established between latitude and amyotrophic lateral sclerosis mortality. Goldberg and

Kurland,[6] for example, published annual age-adjusted death rates for a number of neurologic diseases, for 33 countries, at five year intervals, during the 1950s. With the exception of Czechoslovakia, the lowest annual age-adjusted death rates for motor neuron disease were associated with lower latitudes, occurring in Israel, South Africa, Chile and Mexico, which had average annual age-adjusted rates of 0.4 per 100,000 or less. In contrast, rates of 1.0 or more per 100,000 were reported for the Netherlands, New Zealand, Norway, Switzerland and Scotland. These spatial differences were confirmed by a global review of amyotrophic lateral sclerosis mortality, conducted by Olivares and colleagues[7] in 1972. Kondo and Tsubaki[8] also published worldwide data on motor neuron disease, comparable to that of Goldberg and Kurland,[6] but for the period 1966 to 1971. They again established that the highest mortalities from motor neuron disease had occurred in temperate countries, such as New Zealand, Sweden, Norway, Finland, Denmark and Switzerland. Furthermore, Snow[9] subsequently demonstrated that 79 percent of the U.S. states with above average mortality from amyotrophic lateral sclerosis, during the period 1959 to 1961, were located at or above 40 degrees latitude (p=0.001, rr=12.188).

Regional Spatial Variations

Not only are Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis generally more common at higher latitudes, but their prevalence and mortality rates show spatial similarities even at the regional scale. To illustrate, Lux and Kurtzke[10] have established that, in the United States, there are statistically significant correlations between multiple sclerosis mortality and prevalence and death rates from Parkinson's disease. Similarly, Schwartz[11] argued that in the United States and elsewhere, the geographic distributions of multiple sclerosis and Parkinson's disease were significantly related. To examine this relationship further, the current author correlated death in the United States from multiple sclerosis, by place of birth, with both mortality from Parkinson's disease in individuals of all ages (r=0.77555, p=0.0001) and in those aged 65 and over (r=0.71663, p=0.0001). Multiple sclerosis mortality also displayed a significant positive correlation with death from amyotrophic lateral sclerosis (r=0.43952, p = 0.0019). The analysed data had been abstracted from the Epidemiology of Neurologic and Sense Organ Disorders[12] and was limited to whites, for the period 1959 to 1961.

Identifying Possible Causal Variables

A database, described elsewhere,[13] has been developed, at the state scale, for the United States that contains incidence, prevalence and mortality data for 84 diseases or disease groups, for 128 time periods. Correlations between the three neurologic disorders and other diseases in the database established that white mortality, from Parkinsonism (r = 0.50875, p = 0.0002) and multiple sclerosis, (r=0.53513, p=0.0001), during the period 1959 to 1961, displayed statistically significant relationships with the prevalence rate of goiter, experienced by World War I troops.

A second previously described database,[14] containing information on the spatial patterns of 219 environmental variables, was then used to identify possible links between mortalities from these three neurologic disorders and aspects of the geography of the United States. Of particular interest were the strong positive correlations identified between white mortality from Parkinsonism (r=0.50564, p=0.0003), multiple sclerosis (r=0.47944, p=0.0006) and amyotrophic lateral sclerosis (r=0.38225, p=0.0091) and iodine deficient soils.

Iodine Deficiency

These analyses suggest that all three neurological disorders are commonest in the iodine deficient temperate regions. As

pointed out by Goldschmidt,[15] soils in areas covered by Pleistocene ice sheets or glaciers, especially during the most recent Wisconsin glaciation, are typically very iodine deficient. This is because old soils, which had been enriched by iodine from precipitation, were removed during glaciation. As a result, soils in the north of the United States, where mortalities from Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis are elevated, tend to contain much less iodine than those in the south, the latter being unaffected by the major ice sheets, or by deposition of wind blown loess. Interestingly, the "dividing line" in the United States between high and medium - prevalence multiple sclerosis zones is at about 37 - 38 degrees north latitude,[16] very close to the southern limit of such Wisconsin glacial deposits.[17]

The hypothesis that Parkinson's disease may be linked to soil and hence dietary iodine deficiency, associated with glaciation, is not new. In 1987, de Pedro[4] concluded that Parkinsonism had the strongest links with "Early life exposure to a geochemical imbalance, related to the last glaciation, associated to iodine washing out, present in soil, water and diet." He reached this conclusion based on Parkinson's disease prevalence and mortality in selected age groups and similarities between current levodopa use and goiter distribution, during the period 1920 to 1935. As early as 1959, Warren[18] also argued that multiple sclerosis was more common in regions that had suffered recent continental glaciations, where it tends to develop most frequently in individuals who, as newborns, were fed milk from iodine deficient cows.[19] It has been hypothesized that a lack of iodine in fodder deprives cattle of thyroxine, a deficiency which in turn prevents the conversion of carotene to vitamin A. Milk short of this vitamin also lacks the essential fatty acids because the latter, which form the main constituents of the myelin sheath, are oxidized rapidly in the absence of vitamin A. Certainly, a thyroid deficiency in rats has been liked to reduced myelin formation.[20]

The current author was not the first to recognize a spatial association between amyotrophic lateral sclerosis and goiter. Gajdusek and Salazar[21] noted that in south west New Guinea, amyotrophic lateral sclerosis, endemic goiter and cretinism all had analogous spatial distributions. To test the possibility of a relationship between amyotrophic lateral sclerosis and iodine deficiency further, Snow[9] collected questionnaire data from 50 British Columbian amyotrophic lateral sclerosis patients and a similar number of gender and age matched controls. He concluded that the risk of developing amyotrophic lateral sclerosis was significantly increased ($p=0.001$, $rr=3.807$) when blood relatives of patients had been afflicted by those diseases that Foster[22] had claimed were linked to iodine deficiency, namely multiple sclerosis, goiter, Alzheimer's disease, Parkinson's disease and cancers of the central nervous system and thyroid.

The Iodine-Dopamine Connection

Overstreet and colleagues[23] demonstrated that male rats, raised on iodine-deficient diets, developed an abnormally high (28% increase) number of dopamine receptors in the striatum. Gilbert[24] has argued also that long exposure to a lack of iodine, seen for example in many Africans and Chinese, results in a crucial dopamine-thyroid action that slows cell timing mechanisms. Certainly, dopamine D1 and D2 receptors are consistently elevated in Parkinson's diseased striata from patients who have not been medicated pre-mortem with levodopa.[25] Interestingly, in women suffering from multiple sclerosis, the rate of relapse declines during pregnancy as dopamine levels increase.[26] In contrast, pregnancy often is associated with a depressed thyroid function, which in some cases culminates in goiter.[27, 28]

While, as yet, the evidence is not conclusive, it suggests that early iodine deficiency may cause abnormalities in the dopaminergic system[24] and so increase susceptibility to some dopamine-related diseases, such as Parkinsonism, later in life. Certainly there is a link between dopamine and the thyroid since Kaptein and colleagues[29] have shown that dopamine reduces serum TSH and aggravates low thyroxine levels in patients for whom it is prescribed.

Dopamine Abnormalities

If this iodine-dopamine hypothesis is correct, there should be evidence of dopamine deficiency in Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis. This is obviously the case in Parkinsonism[30] where levodopa and its agonists play a key role in therapy. Dopamine inadequacy also has been shown to occur in multiple sclerosis. Berne-Fromell and coworkers,[31] for example, have described a clinical study conducted in Linköping, Sweden. Here 300 multiple sclerosis patients were treated with levodopa and tri- and tetracyclic antidepressants. After one to two months, 75% had substantial sensory, motor and autonomic symptom improvements. Many also experienced the return of functions previously lost for several years. There is also considerable evidence of a dopamine deficiency in amyotrophic lateral sclerosis.[32] Cerebrospinal fluid levels of homovanillic acid, a major catabolize of dopamine, appear to be substantially lower in amyotrophic lateral sclerosis patients than in controls.[33] Mendell and colleagues[34] suggested that this anomaly was indicative of diminished central dopamine synthesis. Nevertheless, in a levodopa trial involving 21 amyotrophic lateral sclerosis patients, they were unable to show any beneficial clinical effects at doses and treatment durations adequate to produce improvements in Parkinson's disease. Despite this, researchers continue to identify dopamine anomalies in amyotrophic lateral sclerosis patients. Sofic and coworkers[33] discovered significantly lower concentrations of dopamine in the thoracic and lumber segments of postmortem spinal cord in amyotrophic lateral sclerosis patients in comparison with controls. Similarly, Borasio and colleagues[32] used [I-123] IPT single photon emission computed tomography to show a moderate, but significant reduction in striatal IPT binding, and therefore a dopaminergic deficit in amyotrophic lateral sclerosis, compared with controls. Antibodies, found in the serum of amyotrophic lateral sclerosis patients, also inhibit dopamine release mediated by L-type calcium channels.[35] These observations appear to support the involvement of a dopamine deficiency in amyotrophic lateral sclerosis.

The Dopamine-Dopachrome Link

Hoffer[36] has suggested that in Parkinson's disease, dopamine deficiency is due to the excessive oxidation of dopamine to dopachrome. This oxidative process may also occur in multiple sclerosis and amyotrophic lateral sclerosis. Cu/Zn superoxide dismutase, glutathione peroxidase and catalase are the three main enzymes involved in cellular protection against damage caused by oxygen-derived free radicals.[37] If these three neurologic disorders involve the excessive oxidation of dopamine, they should each be accompanied by abnormal stores of these three enzymes.

There is an extensive literature suggesting that oxidation stress is indeed involved in the three neurologic diseases under discussion. To illustrate, Damier and coworkers[38] investigated the distribution of glutathione peroxidase - containing cells in the midbrain of four control subjects and four Parkinson's disease patients. In the latter, there appeared to be an increased density of glutathione peroxidase-immunostained cells surrounding the surviving dopaminergic neurons. Furthermore, Johannsen and colleagues[39] have estab-

lished that erythrocyte glutathione peroxidase levels are significantly lower in advanced cases of Parkinson's disease than they are in recently diagnosed patients. In addition, using PC12 cells over-expressing glutathine peroxidase, Kim-Han and Sun[40] were able to demonstrate that, in Parkinson's disease, levodopa appears to cause neuronal cell death by an oxidative pathway and that glutathione peroxidase may play an important role in cellular defence against such stress.

Shukla and coworkers[41] also have shown a significant decrease in glutathione peroxidase activity in the erythrocytes of 24 multiple sclerosis patients, compared to that in normal controls. This relationship was confirmed subsequently by Szeinberg and coworkers.[42]

Evidence of oxidative stress in amyotrophic lateral sclerosis has been found in plasma, red blood cells and brain tissue of patients. Moumen and associated research workers[43] have shown, for example, that plasma glutathione peroxidase activity is significantly reduced in amyotrophic lateral sclerosis patients. In contrast, malone dialdehyde and superoxide dismutase activity is significantly higher than in controls, providing indirect confirmation of excess liperoxydation in the disease. In confirmation, Apostolski and colleagues[44] have shown that a disturbed oxidative/antioxidative balance exists in both the motor neurons and the blood of amyotrophic lateral sclerosis patients. Their results indicated significantly decreased glutathione peroxidase and Cu/Zn superoxide dismutase activity in 35 patients compared to controls. Abnormal superoxide dismutase activity has been recorded also in Parkinson's disease[45-47] and in multiple sclerosis.[48] Interestingly, the pathology of familial amyotrophic lateral sclerosis has been attributed to oxidative damage caused by a mutant Cu/Zn superoxide dismutase enzyme.[49]

Furthermore, Ambani and coworkers[50] have demonstrated that catalase activity is reduced in the substantia nigra and putamen of the Parkinsonian brain. Abnormal catalase activity has been reported also in the granulocytes and erythrocytes of multiple sclerosis patients,[51] being decreased in the former and increased in the later, compared to normal controls. Taken as a whole, the available literature, therefore, appears to confirm that, in all three neurologic disorders abnormalities are present in the major enzymes involved in cellular protection against damage caused by excess oxidation and free radical production.

Dopamine-Glutamate Relationships

Glutamate is an excitatory amino acid neurotransmitter that is cytotoxic when over-expressed at synaptic terminals. As a result, elevated glutamate appears to play a role in several diseases, including ischemia and methamphetamine-induced toxicity. Berman and Hastings[52] have shown the reactive oxygen species and dopamine oxidation products can modify glutamate transport function, resulting in the elevated levels implicated in such neuro-degeneration. It follows, therefore, that if the three neurologic diseases under discussion involve the excessive oxidation of dopamine, abnormally high levels of cytotoxic glutamate will also be present in patients suffering from them.

Interestingly, while Iwasaki and coworkers[53] have identified elevated plasma glutamate in Parkinson's patients, Mally and coworkers[54] have demonstrated that this amino acid is depressed in the cerebrospinal fluid, results consistent with an alteration of glutamate neurotransmission in Parkinsonism.

Glutamate abnormalities have been found also in multiple sclerosis where elevated levels are related to relapses. Increases in serum glutamate do not occur sharply during relapses, rather they rise gradually for a month or two prior to the onset of a clinical relapse, peak during it

and then slowly decline.[55] Barkhatova and coworkers also have established elevated glutamate levels in the cerebral fluid of patients with multiple sclerosis.[56]

A large number of studies have documented that glutamate abnormalities occur in amyotrophic lateral sclerosis patients,[59] or in their postmortem tissue. These abnormalities have been found related to altered synthetic enzymes, tissue glutamate levels, transporter proteins and postsynoptic receptors. To illustrate, Rothstein and coworkers[58] measured high-affinity, sodium-dependent glutamate transport in synaptosomes from neural tissue, taken from 13 amyotrophic lateral sclerosis patients, 17 patients with no neurologic disease and 27 patients with either Alzheimer's or Huntington's diseases. They concluded that "Amyotrophic lateral sclerosis is associated with a defect in high-affinity glutamate transport that has disease, region and chemical specificity. Defects in the clearance of extracellular glutamate because of a faulty transporter could lead to neurotoxic levels of extracellular glutamate and thus be pathogenic in amyotrophic lateral sclerosis."

Implications for Treatment

Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis each appear to involve an iodine deficiency before and immediately after birth, which affects the dopaminergic system. In adulthood, this abnormality seems to increase susceptibility to the oxidation of dopamine and to an associated glut of cytotoxic glutamate. If this hypothesis is correct, it implies treatment avenues that should be further explored. Firstly, levodopa seems likely to be beneficial in all three disorders, but should probably be accompanied by vitamin B_3 and coenzyme Q_{10}. Shulz and coworkers,[59] for example, have found that, in animals given Parkinsonism by the administration of MPTP, vitamin B_3 and coenzyme Q_{10} provide protection against dopamine depletion and, therefore, help prevent the psychotic effects of its associated oxidative by-product, dopachrome. This may explain Hoffer's success in adding high doses of vitamin B_3 and coenzyme Q_{10} to the normal treatments for Parkinsonism.[36]

Secondly, all three disorders appear to involve the depletion of the enzymes which protect against oxidative stress, Cu/Zn superoxide dismutase, glutathione peroxidase and catalase. This may be why antioxidant supplementation, especially selenium, vitamin E and vitamin C, is now recommended for multiple sclerosis patients.[60] It also may account for some of the success of the Swank diet[61] in the treatment of this disorder, since this diet is very high in the antioxidant vitamin A and in the essential fatty acids, which are easily oxidized and create prostaglandin deficiencies. Beyond this, Apostolski and coworkers[44] have shown, in clinical trials, that the course of amyotrophic lateral sclerosis can be slowed by the administration of selenium, other antioxidants, amino acids, and a Ca2+ channel blocker such as nimodipine. Only the use of all of these components together enhanced glutathione peroxidase activity, increased plasma vitamin E levels and appeared to slow disease progression. Hoffer and Walker [62] also have discussed the long-term survival (22 years) of an amyotrophic lateral sclerosis patient receiving coenzyme Q_{10}, selenium, zinc, dolomite, niacinamide, thiamine, folic acid and vitamin E. Thirdly there would also seem to be a role for glutamate antagonists in all three disorders. Finally, given the apparent relationship between iodine and dopamine, it seems logical to further explore the value of this mineral in the treatment of these neurologic diseases.

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