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The Iodine-Selenium Connection: Its Possible Roles in Intelligence, Cretinism, Sudden Infant Death Syndrome, Breast Cancer and Multiple Sclerosis

H. D. FOSTER

Department of Geography, University of Victoria, P O Box 3050, Victoria, British Columbia, V8W 3P5 Canada

Abstract—Several diseases and disorders display spatial patterns that suggest the involvement of both selenium and iodine deficiencies, or excesses, in their etiologies. It is suggested that many of these similarities in geographical distribution occur because both elements influence thyroid hormone metabolism.

Introduction

In an earlier issue of *Medical Hypotheses* (1), this author suggested that the incidence and mortality patterns of a wide variety of diseases showed strong positive and/or negative relationships. Such spatial correlations, it was argued, did not occur by chance, but often reflected the etiologic roles played by various bulk and trace elements, each of which was associated with its own 'disease family tree'. It was suggested further that horizontal links could be identified between such 'family trees', but only at the second order level or higher, in diseases or disorders involving at least two or more bulk or trace elements. This paper seeks to develop the concept further, by examining the spatial patterns of a group of such conditions, the etiologies of which appear to include deficiencies and/or excesses of both iodine and selenium.

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The iodine-selenium connection

Human Intellegence

(a) *Iodine*—There is an extensive literature establishing that iodine deficiency, during fetal development, is linked to reduced intelligence and, in some cases, with cretinism (2–6). In Baihuyaon, in north-central China, for example, 72% of those born during a period of severe iodine deficiency displayed depressed intelligence. Many of these individuals had nerve deafness and displayed a variety of other abnormal neurological signs (7). Similar regional depression of intelligence associated with iodine deficiency has been reported elsewhere in China (8, 9) and in South America (10). In highland Ecuador, for example, a region where goitre is endemic, Fierro-Benitez and co-workers (11) have been trying to raise childhood intelligence quotients through iodine ther-

apy. They point out that 'iodine correction early in the intrauterine life appears to be an important factor that contributes to improving the intellectual capacities of the child'. Providing additional iodine beyond the first month after birth seems to have little beneficial effect.

(b) *Selenium*—Kaschin-Beck disease, which is characterized by necrosis of cartilage and dystrophy of skeleton muscles, is widespread in parts of China. It is limited, however, to regions of severe selenium deficiency (12, 13). In the former USSR, Kaschin-Beck disease is known as Urov disease. Researchers there have been carrying out detailed psychological and neurological testing of children at all grade levels, in those areas where the disorder is endemic (14). These tests have been repeated using control groups from regions where Urov disease is rare. The results suggest that all children in the endemic provinces, that is those deficient in selenium, have retarded intellectual development, even if they show no signs of Urov disease. Impairment is greatest, however, in individuals who are suffering from it. Although these results do not prove that selenium deficiency causes retarded psychological development, since there may be some as yet unknown agent involved, they are highly suggestive of a link between intelligence and selenium. Interestingly, however, Marlow (15) and Ely (16) both reported elevated selenium in the hair of children with learning disabilities.

Cretinism

(a) *Iodine*—endemic cretinism occurs in areas that also suffer endemic goitre, which in turn is related to severe iodine deficiency. However, even within such regions, cretinism tends to be concentrated in certain locations, the remainder of the goitrous areas being free, or almost so, of the disorder. On Idjwi Island, in Kivu Lake in eastern Zaire, for example, iodine deficiency and endemic goitre are ubiquitous, but cretinism is found only in the north (17). Further proof that cretinism has an environmental etiology is provided by evidence from Mulia, New Guinea, where women, who have had normal children elsewhere, give birth to cretins after moving into this region (18). The clustering of cretins in pockets within goitrous areas has been known for centuries. Indeed, Napoleon ordered the abandonment of such locations in Europe to avoid the birth of any further cretins (19).

(b) *Selenium*—It has been suggested recently that the thyroid failure which typifies myxedematous cretins may occur because of a lack of selenium. This may cause an inadequacy of glutathione peroxidase, an enzyme which would normally protect the thyroid gland, already overstimulated by iodine deficiency, against peroxidative damage (20). Geographical evidence appears to support this hypothesis. Certainly, severe iodine and selenium deficiencies have been demonstrated in eastern Zaire on Idjwi Island and in the Ubangi in northern Zaire, both of which are African endemias of myxedematous cretinism (21). In addition, glutathione peroxidase activity in cretins appears to be only half that of normal subjects (22).

This is interesting since, in China, individuals suffering from more severe cases of the selenium-deficiency related Kaschin-Beck disease are intellectually retarded, dwarfed and quite similar in appearance to the myxedematous cretins, who are endemic to low iodine environments (23).

Sudden Infant Death Syndrome

(a) *Iodine*—The author correlated the US SIDS death rates for 1983 and 1984, at the state level, with 126 disease incidences or mortality rates and 219 environmental variables. The results are described in detail elsewhere (24, 25). It was found that for the year 1983, the strongest positive correlation was with goitre incidence in World War I troops ($r = 0.66745$, $p = 0.0001$). This was true also of SIDS mortality in 1984, when the correlation was even stronger ($r = 0.74416$, $p = 0.0001$). This association suggests that iodine deficiency may play a key role in crib death, a viewpoint which is supported by the elevated triiodothyronine levels found in many autopsied SIDS victims (26, 27).

(b) *Selenium*—Pearson correlations also indicated that, in 1983, at the state level, there appeared to be a strong environmental link between SIDS mortality and very selenium enriched soils ($r = 0.58794$, $p = 0.0001$). Another positive correlation of note was with soils having a very low content mercury, the selenium antagonist (28) ($r = 0.48459$, $p = 0.0005$). When this procedure was repeated using crib death data from 1984, the associations were $r = 0.54360$, $p = 0.0001$ and $r = 0.46494$, $p = 0.0009$ with elevated soil selenium and depressed soil mercury respectively.

These correlations tend to suggest that SIDS mortality, in the US, is highest where iodine is deficient or where goitrogens are common, and where selenium is easily bioavailable. Interestingly, however, the crib death mortality rate of 6.3 per 1000 live births in South New Zealand is one of the highest recorded (29), yet this region seems very deficient in both iodine and selenium (30).

Breast Cancer

(a) *Iodine*—It has been pointed out that elevated breast cancer in the US may tend to occur in the

goitre belt, that is in areas of iodine deficiency (31). Similarly, it has been reported that countries in which goitre is common also have elevated breast cancer incidence. The converse is also thought to be true: countries with high levels of iodine and little goitre also tend to have depressed breast cancer incidence rates (32, 33). This geographical relationship is particularly interesting, since fibrocystic breast disease, a known significant risk factor in breast cancer (34), can be largely prevented through the use of iodine (35).

(b) *Selenium*—Whether or not selenium deficiency is a major risk factor in breast cancer is the subject of considerable debate. Schrauzer, White and Schneider (36) for example, argued that in the 27 countries studied, breast cancer mortality was strongly inversely related to annual dietary selenium intake ($r = -0.80$, $p = 0.001$). However, Shamberger and co-workers (37) found no difference in blood selenium levels between breast cancer patients and controls. In contrast, McConnell and colleagues (38) reported depressed selenium status in such patients. Schrauzer and co-workers (39) also concluded that in both Japan and the US, selenium was depressed significantly in the blood serum of breast cancer patients. This relationship was contested by Meyer and Verreault (40). Various prospective studies also have linked selenium deficiency to cancer, but this association seems more pronounced for cancers of the digestive tract than those of the breast (41–43).

Multiple Sclerosis

(a) *Iodine*—This author has argued in detail elsewhere that multiple sclerosis appears to be an autoimmune disease, in which the immune system attacks the myelin sheath and probably certain endocrine glands, including the thyroid. Such malfunctions appear to occur most often in genetically susceptible individuals who, as infants and adolescents, drank milk from cows eating iodine deficient fodder (44). Such milk is deficient in both vitamin A and the essential fatty acids (45, 46).

Certainly, the disease seems most common in high latitudes, milk drinking societies (47, 48). The relatively low prevalence of multiple sclerosis in Japan, despite its temperate latitude, has puzzled many researchers. However, if the preceding hypothesis is correct, this absence of the disease is explicable since the Japanese drink little cow's milk and their soils have some of the world's highest known levels of iodine (49); probably caused by the use of seaweed as a fertilizer.

There is considerable experimental evidence to demonstrate a link between iodine deficiency and abnormal myelin development in animals. Dunn (50) states that 'myelin proteins are probably synthesized by mitochondria and are among the major proteins affected by thyroid hormones.' Similarly, Balazs (51) has demonstrated that, in rats, during the early postnatal period, thyroid deficiency results in a reduction of the myelin produced. It seems likely that this process will be exacerbated if the diet is deficient in essential fatty acids, as would be the case in infants weaned on cow's milk which was low in the antioxidant vitamin A (52).

(b) *Selenium*—While this author (53) did not find such an association in the US, Schalin (54) has argued that in Europe, multiple sclerosis is very common in regions where soils are selenium depleted. Such a relationship would be consistent with a link between the consumption of vitamin A deficient milk and multiple sclerosis. This is because selenium is an antioxidant, capable of protecting essential fatty acids from free radical damage, and hence increasing their availability for myelin formation (55).

Conclusions

There can be no doubt that both iodine and selenium are essential trace elements in humans (56, 57). However, similarities in their 'disease family trees' tend to suggest that some of their metabolic roles may be interrelated. A synergism between iodine and selenium has been suggested recently by Contempre and co-workers (58), who have shown that myxedematous cretins in northern Zaire are selenium and hence seleno-dependent glutathione peroxidase deficient. However, selenium supplementation, besides correcting this glutathione peroxidase deficiency problem, also induced a dramatic fall of the already impaired thyroid function in clinically hypothyroid subjects. These authors concluded that their results supported a role for selenium in thyroid hormone metabolism, arguing that in very iodine deficient regions, a lack of selenium may protect the general population and fetus against the full effects of iodine impairment, while simultaneously favouring the generative process of the thyroid gland that leads to myxedematous cretinism. If selenium is involved in thyroid hormone metabolism, this may help to account for depressed intelligence in both iodine and selenium deficient regions, since it is well established that thyroxine accelerates fetal brain development (59). A selenium-iodine link in thyroid hormone metabolism may also help to explain crib death, since many victims appear to suffer from subtle neurological abnormalities that might reflect thyroxine deficiencies during their fetal development (60). Clearly, it would also help to explain why myxedematous cretinism is endemic where environments are iodine and selenium

depleted, or where their antagonists are widespread or readily available. In addition, since thyroid hormones play a major role in the synthesis of myelin proteins, such an iodine-selenium association suggests a further potential role for both elements in the etiology of multiple sclerosis.

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