Cretinism: The Iodine-Selenium Connection

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Summary

The major clinical and geographical differences, characteristic of the three distinct forms of endemic cretinism, are thought to be due to unique thyroid hormone imbalances. Neurological cretinism appears to reflect the negative impacts of severe foetal T_4 deficiency, particularly during the second trimester. The dwarfism and mental retardation seen in Kaschin-Beck disease (grade III) may be caused by foetal and postnatal T_3 inadequacy; whilst myxoedematous cretinism seems due to concurrent T_4 and T_3 deficiencies, especially during late foetal development and infancy.

Such thyroid hormone inadequacies can occur in a variety of ways, most commonly reflecting maternal diets deficient in iodine and/or selenium, which also may contain goitrogens and heavy metals. Excesses of iodine and possibly of selenium also appear capable of depressing both maternal and foetal thyroid hormone production.

This hypothesis, if correct, requires a reevaluation of both iodine deficiency disorder control programmes in areas of myxoedematous cretinism and of the treatment of congenital hypothyroidism. In both cases, iodine prophylaxis alone, whether as salt, oil or as L-thyroxine, will not prevent subsequent developmental deficits if T_3 deficiency is due to either selenium shortage or excess, or to a biochemical abnormality preventing the conversions of T_4 to T_3.

Introduction

Worldwide, 800 million individuals are at risk in iodine deficient environments and some 190 million of these are goitrous.[1] Demand for iodine peaks during pregnancy and lactation when severe inadequacy affects thyroid hormone homeostasis in the developing foetus and neonate.[2] In extreme cases, cretinism occurs.[1-3] This is not a single disease but rather a syndrome of great diversity which ranges from severe hypothyroidism to major neurological disorder, with many intermediate gradations. Currently an estimated 3.15 million individuals suffer from some type of cretinism.[1]

In the most common form, neurological cretinism, those affected are normally goitrous but biochemically euthyroid. Such cretins are typically of normal stature and show no obvious signs of hypothyroidism. They are characterized, however, by specific neurological deficit, including severe mental retardation, squint, deaf mutism, spastic diplegia, and spastic rigidity, resulting in a disturbance of gait.[1,4]

In contrast, the less common myxoedematous cretin is dwarfed, and displays all the classical features of hypothyroidism, including mental retardation, apathy, coarse skin and husky voice. Whilst electrocardiograms are normal for neurological cretins, those of myxoedematous cretins show small voltage QRS complexes and other abnormalities indicative of heart disorders.[1,4] There has been disagreement over the severity of mental deficiency in myxoedematous cretinism. Some observers claim that retardation is less than that found in neurological cretins,[1,4] whilst others argue that there is little, if any, difference.[3] It is possible, therefore, that the degree of mental retardation in myxoedematous cretinism varies from place to place.

Beyond such distinctive clinical presentations, neurological and myxoedematous cretins have fundamentally different geographical distributions.[1,3] Whilst neurological cretinism is found in all iodine deficiency endemias, the myxoedematous form is relatively rare and is restricted to parts of central Africa, Nepal and western China, where it may predominate. In some areas, such as the Qinghai endemia in western China, however, both forms of cretinism occur in close proximity.[3]

It is contended here that there is a third type of endemic cretinism that occurs in endemias of extreme selenium deficiency, even when no dietary iodine inadequacy is present.[5] Known as Kaschin-Beck disease

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(grade III), severely affected individuals are dwarfed, mentally retarded and suffer from necrosis of cartilage and dystrophy of skeletal muscles.[5] Such "selenium cretins" typically occur in regions where Keshan disease, a cardiomyopathy related to selenium inadequacy,[6] also is found. Clinically, myxoedematous cretins appear to have more in common with individuals affected by Kaschin-Beck disease (grade III) than they do with neurological cretins.

Earlier Causal Hypotheses

Since field trials with iodized oil have been able to greatly reduce the incidence of both neurological and myxoedematous cretinism, iodine deficiency clearly plays a major etiologic role in both.[1,7,8] There is still no consensus, however, over the causes of the major clinical differences betwen the two forms, nor can their distinct spatial distributions yet be adequately accounted for. Several causal hypotheses have, however, been presented.[3,9-13] Costa[9] suggested that cretinism was essentially a neurological disorder, a conclusion that was based on findings of normal thyroid function, radiological abnormalities of the skull and disturbed electroencephalograms. In contrast, Stanbury and coworkers[10] proposed that endemic cretinism was caused by a functional thyroid hormone deficiency, occurring during embryogenesis, or early postnatal development. More recently, Boyages and Halpern[3] have suggested that differences between the two forms of endemic iodine-related cretinism reflect the length and severity of postnatal thyroid hormone deficiency. Endemic neurological cretins were thought to have experienced only transient hypothyroidism in the postnatal period, evidenced by their near normal thyroid function; whilst myxoedematous cretins were considered characterized by permanent and severe postnatal thyroid hormone deficiency.

Such hypotheses, however, fail to satisfactorily explain why temporal variations in thyroid hormone availability would result in such different spatial distributions for the two forms of iodine deficiency related endemic cretinism. For this reason, other researchers have argued that myxoedematous cretinism must involve a second risk factor, in addition to extreme iodine inadequacy. Contempré and colleagues,[12] for example, have suggested that the myxoedematous cretinism of North Zaire occurs in regions of both extreme iodine and selenium deficiency. They further argue that thyroid dysgenesis in myxoedematous cretinism is due to damage caused by hydrogen peroxide excess. This in turn is thought to reflect inadequate maternal dietary selenium intake, resulting in limited foetal availability of the protective selenoenzyme, glutathione peroxidase. The strongest argument against this hypothesis is the high prevalence of myxoedematous cretinism in the Tarim basin, where the Chinese population's selenium status is normal.[14]

Thyroid Hormone Deficiency

Thyroxine (T_4) deficiency can occur in several ways. Most commonly, it is associated with environmental and hence dietary iodine deficiency, often exacerbated by goitrogens in food or water supplies.[15] T_4 deficiency, however, may also occur in individuals consuming excessive iodine, such as those drinking water containing >300 μg/l, or eating large quantities of iodine enriched seaweed.[5] Depressed serum T_4 levels, however, do not necessarily imply low serum triiodothyronine (T_3). When severe iodine deficiency is present, serum T_3 usually remains at normal levels, or may even rise as T_4 levels fall.[16] This is because T_3 contains less iodine, weight for weight, than T_4, yet it is metabolically more active. It is, therefore, produced by the thyroid when iodine is at a premium.[1,16] Only when iodine deficiency is extreme and there is insufficient iodine to produce even T_3 does its level fall. The T_4 to T_3 conversion process requires the catalytic selenoenzyme iodothyronine deiodinase.[17-18] For this reason, combined T_4 and T_3 deficiency is most common in environments which are depleted in both iodine and selenium, whilst depressed serum T_3, without abnormally low serum T_4, characterizes regions where diets are lacking selenium but not iodine. Heavy metals, such as mercury, are selenium antagonists and their presence in soils and food supplies can greatly reduce this trace element's bioavailability.[19] There is evidence also from animal studies that just as excess iodine consumption results in low serum T_4, very

high selenium intake may depress serum T_3.[20] Elevated selenium is associated also with serious birth defects in animals.[21,22] That is, both thyroid hormones appear to display bimodal relationships, T_4 to iodine and T_3 to selenium.

Cretinism: An Alternative Hypothesis

Neurological Cretinism

It is postulated that each of the three distinct forms of endemic cretinism, neurological, Kaschin-Beck disease (grade III), and myxoedematous, reflects unique foetal and postnatal thyroid hormone imbalances. Foetal thyroid function is established in the second trimester, which also is a time of maximal brain growth.[3,23] Thus the ontogeny of both the brain and thyroid appear to be crucially associated during the second trimester. Furthermore, animal studies have shown clearly that low levels of foetal T_4, but normal or elevated levels of circulating T_3, result in severe central nervous system damage.[1] For these reasons it is suggested that severe foetal T_4 deficiency, especially during the second trimester, results in neurological cretinism, with its complex of central nervous system deficits. Further support for this suggestion comes from Pharoah and coworkers[7] who have shown that such neurological foetal damage can be prevented in areas of iodine deficiency if pregnant women are given iodized oil prior to the second trimester. Since there is some maternal transfer of thyroid hormones to the developing foetus, the T_4 status of both is probably very significant.[13]

Kaschin-Beck Disease (Grade III)

Since T_4 can only be converted to T_3 in the presence of the selenoenzyme iodothyronine deiodinase,[17,18] the clinical effects of T_3 deficiency are likely to be most obvious in populations living in extremely selenium deficient environments. By far the largest of these is the disease belt which crosses China from northeast to southwest.[5,6]

Within this region, 1.76 million individuals, living in 303 counties, suffer from the osteoarthropathy, Kaschin-Beck disease.[5,6] In its most extreme form, grade III, this disorder is associated with both dwarfism and mental retardation. Whilst some of the affected counties are also iodine deficient, others are not, indicating that a severe inadaquacy of selenium, not of iodine, is necessary for the development of Kaschin-Beck disease.[5,6] Within this disease belt, daily dietary selenium intake is frequently <10 μg, some 5-6% of the typical North American intake.[24] Kaschin-Beck disease clearly is associated with selenium deficiency since field trials using selenium enriched fertilizers and table salt have significantly reduced the incidence of the disorder.[5,6] Selenium supplements also have been successfully used to treat milder cases of Kaschin-Beck disease.[6] Whilst published research has focused on extreme deficiency of selenium-dependent glutathione peroxidase in the aetiology of the disorder, it seems likely that T_3 deficiency, brought about by decreased availability of iodothyronine deiodinase, also plays a key role. Evidence for this comes from the observation that total thyroidectomy in infancy, obviously accompanied by extreme T_3 deficiency, but not necessarily a lack of glutathione peroxidase, used to result in two of the major clinical features of Kaschin-Beck disease (grade III), namely dwarfism and mental retardation.[1]

Myxoedematous Cretinism

Congenital hypothyroidism, formerly called sporadic cretinism,[1] is a disorder characterized by very inadequate thyroid hormone production in neonates. It can be caused by the absence of the thyroid, abnormal foetal position (ectopia) or biochemical defects preventing the production of T_4 and/or T_3.[1] If untreated, severe congenital hypothyroidism, like total thyroidectomy in infancy, sometimes results in cretinism that appears virtually identical to the endemic myxoedematous form.[1] Although the screening of neonates in western countries has established that this abnormality generally occurs in approximately 1 per 3500 live births, in iodine deficient endemias in which myxoedematous cretinism is common, so too is congenital hypothyroidism.[1] In parts of Zaire, for example, the incidence of congenital hypothyroidism reaches 10%, whilst in Nepal and adjacent Northern India its incidence varies between 5 and 10%. Further evidence of the impact of selenium deficiency in myxoedematous cretinism may

come from the ECG abnormalities found in the disorder, since a deficiency of this trace element is known also to be a significant causal variable in Keshan disease, a cardiomyopathy.[6] All of these observations seem consistent with the hypothesis that myxoedematous cretinism, with its associated severe hypothyroidism, occurs as a result of concurrent severe deficiencies of both T_4 and T_3, especially during late foetal and postnatal development.

The manner in which such T_3 deficiency occurs may cause differences in the level of mental retardation associated with myxoedematous cretinism. When T_3 deficiency is the direct consequence of extreme maternal dietary iodine inadequacy, perhaps exacerbated by goitrogens, it must occur concurrently with very low foetal T_4. However, when T_3 deficiency occurs because of a shortage of dietary selenium, it will, to some degree, protect against extremely low foetal T_4, since none of the latter hormone can be converted to T_3.[25] It might be expected, therefore, that in the former case, the degree of mental retardation in myxoedematous cretinism would be similar to that in neurological cretinism. In the latter case, where T_3 deficiency is associated with selenium inadequacy, mental retardation might be expected to be less severe. This may account for the current disagreement over the severity of mental deficiency in myxoedematous cretinism.[1,3]

Implications of Hypothesis

This hypothesis has significant implications for both national and international IDD (Iodine Deficiency Disorders) Control Programmes[1] and for the treatment of congenital hypothyroidism. To illustrate, Kaschin-Beck disease (grade III) is characterized by marked mental retardation.[6] In selenium deficient endemias where this disease is prevalent, even children without any clinical symptoms display impaired mental function.[26] This demonstrates that severe foetal and postnatal T_3 deficiency alone (possibly associated with depressed glutathione peroxidase) can lower human intelligence. It follows, therefore, that where myxoedematous cretinism is prevalent because depressed dietary selenium intake has led to subnormal T_3 during early development, iodine prophylaxis alone will not prevent future widespread depressed intelligence. In such endemias, this trace element must be provided in conjunction with selenium. Care is required, however, since in areas of endemic goitre, selenium supplementation by itself has been shown to induce a dramatic fall of the already impaired thyroid function in clinically hypothyroid subjects.[25] This is probably because such supplementation accelerates the conversion of T_4 to T_3, which, in the presence of iodine deficiency, rapidly lowers T_4 reserves.

Turkey does not have a neonatal thyroid screening programme for congenital hypothyroidism.[27] As a consequence, sufferers are first diagnosed at a mean age of about 4 years. Of these, 26.7% demonstrate growth failure. Similarly, in Taiwan,[28] experience before mass screening began showed that the most common symptoms of untreated congenital hypothyroidism, when first diagneosed at age 3, were short stature, constipation, dry skin and periorbital oedema. This evidence suggests that many cases of severe untreated congential hypothyroidism show clinical symptoms that are virtually identical to those of myxoedematous cretinism.[1] Certainly, many infants identified with congenital hypothyroidism have abnormally depressed serum T_3 levels which seem later to be associated with retarded bone and intellectual development.[29,30] Nevertheless, except in China where thyroid gland desiccant is used,[31] the conventional treatment for congenital hypothyroidism is generally L-thyroxine replacement therapy.[29,30] If the preceding hypothesis is correct, there will be a subgroup of congenitally hypothyroid infants suffering from depressed serum T_3 that will not respond adequately to this treatment. They should also receive L-triiodothyronine, since L-thyroxine replacement alone will not necessarily raise their serum T_3 levels. This may explain why, in England, children whose neonatal T_4 and/or T_3 values had been very low recorded significantly lower IQ scores at age 3 than both other hypothyroid children and matched controls.[32]

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