NEUROLOGICAL DAMAGE TO THE FETUS RESULTING FROM SEVERE IODINE DEFICIENCY DURING PREGNANCY

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Summary Endemic cretinism is characterised by multiple neurological defects including deaf-mutism, diplegia, squint, and mental deficiency. The condition is widely prevalent in the Highlands of New Guinea in association with severe iodine deficiency. Previous studies have shown that iodised oil provides a very satisfactory correction of severe iodine deficiency in New Guinea. A controlled trial on the use of intramuscular iodised oil in the prevention of endemic cretinism was carried out in the Western Highlands of New Guinea and involved a population of approximately 8000. Subsequent follow-up over four years revealed 26 endemic cretins out of a total of 534 children born to mothers who had not received iodised oil; the mothers of 5 of these cretins were pregnant at the start of the trial. In comparison, 7 cases of endemic cretinism occurred among 498 children born to mothers who had been treated with iodised oil; in 6 of these 7 cases, the mother was pregnant when the trial commenced. It is concluded that intramuscular iodised oil is effective in the prevention of endemic cretinism and that, for it to be effective, it should be given prior to conception. This suggests that severe iodine deficiency in the mother produces neurological damage during fetal development.

Introduction

THE known causes of fetal damage during pregnancy include rubella and thalidomide, which produce widespread effects. Endemic cretinism has long been known to occur in areas of severe iodine deficiency in association with endemic goitre.[1] Evidence to be presented in this report suggests that it results from fetal damage early in pregnancy.

The syndrome of endemic cretinism seen in New Guinea is one of retardation of motor milestones due to an upper-motor-neurone type of lesion, deaf-mutism, squint, and mental deficiency. The earliest descriptions are of the condition in the Alpine regions.[2] It has also been described in South America,[3,4] the Himalayas,[5,6] Eastern New Guinea,[7,8] Western New Guinea,[9] and Africa.[10]

Recently iodised oil has been shown to correct severe iodine deficiency in New Guinea people living in mountainous areas.[11,12] An attempt was made to determine whether endemic cretinism was the result of severe iodine deficiency by setting up a controlled trial with iodised oil in the Jimi river valley of East New Guinea, where the incidence of endemic cretinism is known to be high. Alternate family units have been treated with either iodised oil or saline solution in a single intramuscular injection given to each person in the unit. Subsequently all children born to the two groups have been examined for evidence of endemic cretinism.

Patients and Methods

The Jimi river is in an isolated valley in the highlands of East New Guinea to which the only access is by light aircraft. Within the valley, the majority of villages can only be reached on foot and are found at altitudes varying from 1000 to 1800 metres above mean sea-level. The people have a subsistence economy, though recently coffee has been introduced as a cash crop. Their diet consists mainly of sweet potatoes and taro and is low in protein.

The controlled trial was started in August to September, 1966, in collaboration with the local administration, who were due to conduct a census. Twenty-seven villages with a population of 16,500 were seen during a walking patrol lasting six weeks. At each village all the people were gathered in order to have a census taken, and the name of every man, woman, and child together with an estimate of their age was noted. Each woman of child-bearing age was asked if she was pregnant; if she answered affirmatively, this was recorded. However, no formal examination to confirm or deny this was carried out.

Alternate families were injected with either iodised oil or saline solution, each member receiving 4 ml. if aged 12 years or over and 2 ml. if under 12 years of age. The nature of the injection given was recorded on the census sheet.

Subsequent follow-up patrols were carried out in July, 1967, November, 1969, and January, March, and November, 1970. Sixteen of the original twenty-seven villages were visited, all mothers and children in each village were assembled and checked against the census sheets. All infants born since 1966 were identified, their names recorded, and their birth-dates obtained from mission and administration records. Every child was then examined for evidence of motor retardation; this was accepted to be present if the milestones of sitting unsupported, standing unsupported, and walking had not been reached by the ages of 12, 18, and 24 months respectively.

The parents of any child who showed motor retardation were questioned as to whether they thought the child was deaf or mentally normal. Deafness was formally assessed by noting any response of the child to a tuning-fork, or, if this was negative, the response to a handclap. Formal assessment of mental development was not attempted. A squint, if present, was also noted.

The clinical diagnosis of endemic cretinism was accepted if motor retardation was present together with deafness and/or a squint. The diagnosis was made without knowledge of whether a mother had received iodised oil or saline.

In March, 1970, blood-samples were taken from 22 of the 33 mothers of endemic cretins for serum-protein-bound-iodine (P.B.I.) estimations.

Results

In the four years since the start of the trial 1047 births have been recorded; 164 of these children have

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TABLE I—CHILDREN BORN IN JIMI RIVER SUBDISTRICT CLASSIFIED ACCORDING TO TREATMENT RECEIVED BY MOTHER

Treatment received by mother	Total no. of new births	No. of children examined	No. of deaths recorded	No. of endemic cretins
Iodised oil	498	412	66	7*
Untreated	534	406	97	26†

*6 already pregnant when injected with oil.
†5 already pregnant when injected with saline solution.

TABLE II—SERUM-P.B.I. VALUES OF MOTHERS WITH CRETINOUS CHILDREN

Group of mothers	Values (μg./100 ml.)	
	Range	Mean
Untreated (values obtained for 17 out of 26 cases)	1·4–6·6	3·7
Treated (values obtained for 5 out of 7 cases)	4·7–8·2	6·4

died. 832 of the 883 children still alive have been examined; 33 of those examined were classified as endemic cretins. Table I divides all children born since August to October, 1966, into two groups according to whether the mother was treated with iodised oil or was untreated. 7 endemic cretins have been born in the oil-injected group. In 6 of these 7, the mother was pregnant at the time of injection; in the 7th instance the precise date of birth is not certain, but it is possible that this mother was pregnant when the trial began.

These results are illustrated in fig. 1. The horizontal line separates cretins whose conception occurred before from those whose conception occurred after the trial commenced, assuming a normal gestatory period of 40 weeks.

Serum-P.B.I. values are shown in fig. 2. All 5 values in the treated group were over the normally accepted lower limit of 4 μg. per 100 ml., whereas in the untreated group the mean serum-P.B.I. was below the lower limit of normal and in only 5 instances were values within the normal range obtained.

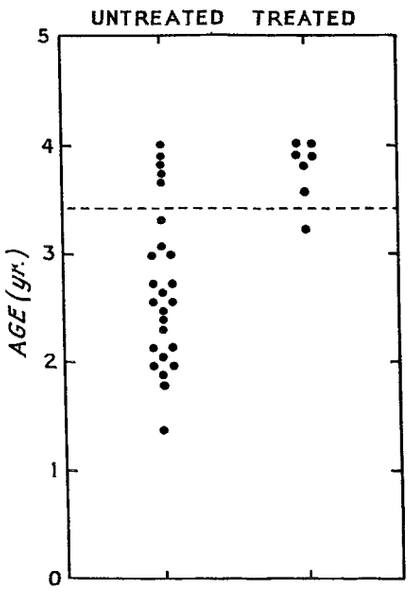

Fig. 1—Ages of neurologically damaged infants born since September, 1966.

Discussion

Endemic cretinism only occurs in geographic association with endemic goitre, though the reverse does not hold true. The effectiveness of iodine in the prevention of endemic goitre was first firmly established by the large-scale trials of Marine and Kimball in Ohio.[13] Subsequent salt iodinisation programmes or intramuscular administration of iodised oil have confirmed these findings.[8,12] Because iodine is an effective prophylactic for endemic goitre, it has been postulated that iodine deficiency is also responsible for endemic cretinism.

The disappearance of deaf-mutism in Switzerland following the introduction of iodised salt has been studied by Wespi.[14] However, Trotter [1] pointed out that in the Canton of Berne the incidence of deaf-mutism fell markedly even though iodination of salt remained uncommon. This was also a period of active social development, so that other factors may have been involved and a causal relationship between iodine deficiency and deaf-mutism cannot be assumed. Furthermore, a decline in the incidence of cretinism was noted by Malacarne as early as 1801, raising the possibility that factors other than iodine deficiency may play a part.

The results of this trial in the Highlands of New Guinea link the syndrome of endemic cretinism much more closely to iodine deficiency. The finding that 6 cretinous children were born to mothers who had had iodised oil but were pregnant at the time of treatment is of some significance. The uncertainty about the date

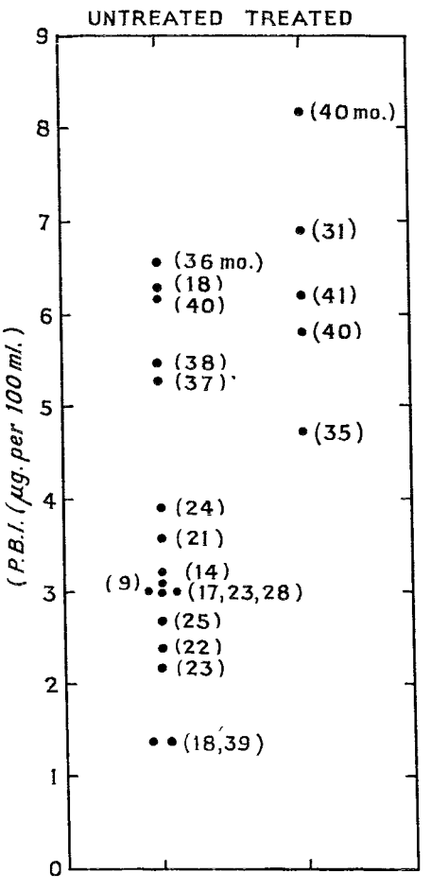

Fig. 2—Serum-P.B.I. values in mothers who have given birth to cretinous children.
The figures in parentheses give the time in months between the birth of a cretinous child and the P.B.I. estimation in the mother.

of birth of the 7th case makes it possible that this mother also had conceived before treatment. These data indicate that iodine deficiency in the mother during the first trimester is probably the main factor in the causation of endemic cretinism.

If iodine repletion prior to conception can prevent endemic cretinism, the mechanism by which it does so requires elucidation. Abnormally low P.B.I. values were found in otherwise normal adults in some areas of endemic goitre [9,12]; this was also found in most of the untreated mothers who had produced cretinous children. However, a normal P.B.I. was found in 5 untreated mothers (fig. 2), but as the blood had been withdrawn as long as 40 months after the birth of an affected child it is possible that the mother's iodine status had altered in the intervening period.

Maternal hypothyroidism has been postulated as a cause of endemic cretinism. In our series of cases there was no clinical evidence of this and their fertility precluded maternal hypothyroidism of any severity. It is rare for conception to occur in a myxœdematous female, or, if it does occur, for the pregnancy to proceed to term if the hypothyroidism is untreated.[15] An adaptation to severe iodine deficiency by the production of a proportionately greater amount of the metabolically more active triiodothyronine may occur. How this could affect the fetus is open to conjecture, and further investigations into triiodothyronine and thyroxine levels in pregnancy are in progress.

Fetal hypothyroidism as a result of the avidity of the maternal thyroid gland for iodine leaving insufficient iodine available for the fetus has been suggested as a possible ætiological factor in endemic cretinism.[1] This could be consistent with a normal maternal P.B.I.; fetal hypothyroidism should occur most severely in the sporadic congenital athyreotic cretin, yet in such cases deaf-mutism and congenital diplegia are not features of the syndrome.

It is possible that elemental iodine is necessary for the embryological development of the nervous system, quite apart from its role in the synthesis of the thyroid hormones. This must be considered in the light of the fact that other elemental deficiencies can produce neurological syndromes in animals—e.g., the role of copper deficiency in the ætiology of " swayback " in lambs.[16]

In conclusion, it appears that iodine deficiency is the primary factor in the causation of endemic cretinism, though other adjuvant factors may operate. Furthermore, the iodine deficiency appears to be critical in the first few months of pregnancy. Instances of insults during pregnancy producing fetal damage are well known—e.g., maternal rubella and thalidomide—whereas deficiencies producing similar irreversible damage in man are not recorded. If the exact role played by iodine in the ætiology of the deaf-mute, squinting, mentally deficient, congenital diplegia of endemic cretinism can be determined, this may indicate further lines of investigation in the ætiology of other congenital spastic diplegias.

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THIAMINE-RESPONSIVE MAPLE-SYRUP-URINE DISEASE

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Summary The rare inborn errors of metabolism are likely to be genetically heterogeneous. A new form of maple-syrup-urine disease in which the hyperaminoacidæmia is completely corrected by thiamine hydrochloride (10 mg. per day) without recourse to dietary restriction, illustrates this hypothesis. This trait is another example of vitamin-responsive hereditary metabolic disease.

Introduction

MAPLE-SYRUP-URINE disease (M.S.U.D.) or branched-chain ketonuria is typical of rare autosomal recessive traits in man. The abnormal gene product is one of the components of a large macromolecular aggregation concerned in the oxidative decarboxylation of the ketoacids of leucine, isoleucine, and valine. At least three different protein subunits and several low-molecular-weight cofactors are apparently involved in the enzyme complex.[1] Moreover, more than one specific decarboxylase serves branched-chain keto-acid decarboxylation in mammalian tissue.[1–3] Thus several genes presumably control this step in catabolism. As a result, one anticipates genetic and phenotypic heterogeneity for the M.S.U.D. trait, and it is not surprising that at least three phenotypic variants of M.S.U.D.—classical,[4] intermittent,[5] and intermediate [6] forms—are now known. We report here yet