IODINE DEFICIENCY AND NEUROLOGICAL IMPLICATIONS

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I-GENERAL INTRODUCTION ON MENTAL HANDICAP

Some 5-15% of children aged 3 to 15 years in both developing and developed countries suffer from mental handicaps. There may be as many as 10-30 million severely and about 60-80 million mildly or moderately mentally retarded children in the world. The conditions causing mental handicaps are largely preventable through primary health care measures in developing countries.

Birth asphyxia and birth trauma are the leading causes of mental handicaps in developing countries where over 1.2 million newborns die each year from moderate or severe asphyxia and an equal number survive with severe morbidity due to brain damage. The other preventable or manageable conditions are: infections such as tuberculosis and pyogenic meningitides and encephalopathies associated with measles and whooping cough; severe malnutrition in infancy; hyperbilirubinaemia in the newborn; iodine deficiency; and iron deficiency anemia in infancy and early childhood.
In addition, recent demographic and socioeconomic changes tend to deprive both infants and young children of stimulation for normal

development. To improve this situation, the primary health care approach involving families and communities and instilling the spirit of self-care and self-help is indispensable (1).

II-NEUROLOGICAL MANIFESTATIONS OF IODINE DEFICIENCY

A-HISTORY

Two hundred years ago, V. Malacarne, pathologist and surgeon, published a booklet entitled "Su i gozzi e sulla stupidita che in alcuni paesi gli accompagna". Malacarne was born at Saluzzo, a town at the foot of the Cottian Alps, in Western Piedmont. Goiter and endemic cretinism were prevalent at the time (1789) in the countryside. On the basis of his own observations on autopsy material, he suggested that the main cause of cretinism was brain damage due to impeding of the blood circulation by the neck swelling, and invited the pathologists of the Po and Aosta valleys to send him the head and the neck of these goitrous idiots for his researches.

B-IDD A PREVENTABLE MAJOR HEALTH PROBLEM

Brain development in humans is remarkably resistant to permanent damage from protein-energy malnutrition. However, specific nutrients have crucial roles. Iodine deficiency is the most important and widespread nutrient deficiency. **Iodine deficiency during pregnancy causes both maternal and fetal hypothyroxinemia resulting in irreversible impairment of brain development at a critical stage. Neuropathological data place this after 14 wk, perhaps continuing through the third trimester (2).**

Disorders caused by iodine deficiency continue to be a major health problem in many underdeveloped areas of the world. The most significant is the impaired mental and physical development which occurs as a result of iodine deprivation early in life. Individuals in affected communities show a spectrum of abnormalities which can be attributed to two interacting pathological processes.

Fetal hypothyroidism in the first and early second trimester predominantly affects the developing nervous system causing deaf-mutism and mental

retardation. If hypothyroidism occurs in the early postnatal period the main abnormalities are growth stunting and related somatic abnormalities.
Sub-clinical deficits of intellectual and motor development may also be found in apparently normal individuals living in affected areas.
Although dietary iodine deficiency is clearly the major etiological factor in both endemic goiter and cretinism, cofactors such as goitrogens, other trace element deficiencies and immunological mechanisms may greatly modify the expression of these disorders.

C-NEUROLOGICAL SIGNS IN CONGENITAL IODINE DEFICIENCY

There was a distinct and readily identifiable pattern of neurological deficits. These included, to varying degrees:

1-Deaf-mutism or lesser degrees of bilateral hearing-loss or dysarthria; spasticity, particularly involving the proximal lower extremities;
2-Mental deficiency of a characteristic type; and rigidity and bradykinesia.
3-Less common features were:
Strabismus, Kyphoscoliosis, Frontal-lobe signs, Exceptional cases with hypotonia.

In contrast, cerebellar function was largely spared, as were functions of emotion and attention, vegetative and autonomic functions, social interaction, and probably memory, except in the most severely involved (3).

D-INFLUENCE ON HUMAN RESOURCES

Studies using specific and sensitive techniques to assess the functional status of thyroid in areas with iodine deficiency and endemic goiter, show large scale prevalence of functional failure among neonates, children and adults. As thyroxin deficiency can impair quality of human resource, poverty and socio-economic backwardness in endemic areas may have a causal nexus with nutritional iodine deficiency. Eradication of NID, therefore, is an essential first step in the socio-economic transformation, through human resource development, of goiter endemics in developing countries.
In iodine-deficient areas, lower intelligence-quotient scores showed a relationship with the detection by audiometry of nerve deafness and with

the presence of abnormal neurological signs. Iodine deficiency imposes a further suppressive effect on the intellectual performance of these areas inhabitants, and results in a shift of the entire population distribution of cognitive skills to a lower level.

III-COMPARATIVE STUDIES OF NEUROLOGICAL and MYXOEDEMATOUS CRETINISM

A-CHINA: It was found that categorization of the cretins into the conventional types did not reflect the pathophysiology of the condition, since an identical pattern and intensity of neurological, intellectual, and audiometric deficits were common to and equally present in all three types of endemic cretins regardless of their thyroid function.

The differing clinical manifestations of cretinism could be explained by the length and severity of thyroid hormone deficiency. Myxedematous cretins were severely thyroid hormone deficient and as a result sexually immature, dwarfed, and had retarded skeletal maturity. They had clinical and sonographic thyroid atrophy, rather than goiter. Although neurological cretins were euthyroid, linear growth arrest lines (demonstrated radiologically) in the long bones of these cretins suggested previous hypothyroidism. Furthermore, all cretins were growth retarded when compared with peers of similar age and race. These data suggest that the different clinical types of endemic cretinism are in fact the same disorder phenotypically modified by the length and severity of postnatal hypothyroidism. The neurological manifestations are interpreted as reflecting the effects of maternal and fetal hypothyroxinemia, secondary to severe iodine deficiency, on the developing nervous system (4).

B-ALGERIA: Although some overlap did exist, proximal spasticity and rigidity were characteristic of neurological cretinism (NC). The hormonal profiles of the two groups, including TRH tests, were clearly different. The two groups were similar with regard to the percentage of palpable thyroids, the absence of anti-microsomal and anti-thyroglobulin antibodies, seropositive viral antibodies and thiocyanate concentrations in serum and urine. Thus it is unlikely that these factors have any significant etiological role in NC. The data collected in the general population in this area and those obtained in the mothers of the myxoedematous and neurological cretins support the hypothesis **that the neurological signs are the result of hypothyroxinaemia in the mothers and the fetus at different periods of pregnancy. They could be aggravated by neonatal hypothyroidism, which may be transient in NC and permanent in MC (5).**

C-Two forms of cretinism are traditionally described: neurological and myxoedematous. Although this classification highlights the important neurological sequelae of the disorder it implies that myxoedematous cretins have an alternative mechanism. Further, the nature of the neurological deficit associated with both types of endemic cretinism has received scant attention in recent times considering that it remains a common disorder in many parts of the world. Similar pattern of neurological involvement was found in nearly all cretins from both endemias, regardless of type (myxoedematous or neurological), and of current thyroid function. Hallmarks of the neurological features included mental retardation, pyramidal signs in a proximal distribution and extrapyramidal signs. Many patients exhibited a characteristic gait. This probably reflected pyramidal and extrapyramidal dysfunction, although joint laxity and deformity were important contributing factors. Other frequently encountered clinical features were squint, deafness, and primitive reflexes. Cerebral computerized tomography (CT) revealed basal ganglia calcification in 15 of 50 subjects. The presence of basal ganglia calcification was confined to cretins with severe hypothyroidism. Otherwise, cerebral CT scanning demonstrated only minor abnormalities which did not contribute to the localization of the clinical deficits. We conclude that the same neurological disorder is present in both types of endemic cretinism reflecting a diffuse insult to the developing fetal nervous system. These clinical findings support the concept of maternal and fetal hypothyroxinaemia, arising from severe iodine deficiency, as the primary pathophysiological event in endemic cretinism. Differences between the two types of cretinism may be explained by continuing postnatal thyroid hormone deficiency in the myxoedematous type, which results in impaired growth, skeletal retardation and sexual immaturity (6).

D-Endemic infantile hypothyroidism in a severe endemic goiter area of central Africa

Multivariate analysis showed that both iodine deficiency and thiocyanate overload were explanatory factors of the serum levels of T4, FT4 and TSH in children. Results showed that infantile hypothyroidism was is much more frequent at 5-7 years of age than at birth or during the first year of life.

The deterioration in thyroid function during and after weaning is likely linked to persistent iodine deficiency accompanied by an increase in thiocyanate overload. The variability in the age of onset, the severity, and the duration of infantile hypothyroidism might explain the wide range of psychomotor and physical abnormalities observed in a large proportion of subjects in that area (7).

IV-OTHER UNIDENTIFIED FACTORS IN EC

1-Maternal iodine deficiency has been established as the major cause in EC (endemic cretinism), whereas a genetic predisposition has not been well-documented. Genetic data on 70 families with EC from Highland Ecuador were reported. A segregation analysis of 49 fully classified families yielded an estimate of P = 0.245 (var [P] = 0.00167). Half-sibs were all unaffected and no significant birth order effect was observed among 101 probands. **The data indicated an autosomal recessive predisposition as a major etiological factor. Because the neurological type of EC represents a defined section of the spectrum of iodine deficiency disorders (IDD), the term fetal iodine deficiency disorder (FIDD) rather than cretinism was suggested (8).**

2-A study of four successive siblings, age 9, 12, 14 and 16 years with cretinism associated with congenital central hypothyroidism (central cretinism), born to a mother in the endemic goiter region of the Jos Plateau, Nigeria, was reported. Biochemically, the defects were characterized by abnormally low basal thyroxin, triiodothyronine and thyroid stimulating hormone, as well as refractory TSH response to thyrotrophin releasing hormone and gross hyperlipidaemia. **Clinically, the intellectual, physical and neurological impairment varied from moderate in the youngest to very severe in the oldest**. Contrasting clinical pictures of cretinism, which appeared related to age and previous treatment were found with a spectrum ranging from predominantly myxoedematous in the youngest to predominantly neurological in the 16 year old male. Response to adequate treatment was dramatic, with restoration of severe gait disturbance occurring almost completely, but the imprints of thyroid hormone deficiency on mental defects and intellectual performance remained almost unaltered. The parents and two older sisters were normal with normal thyroid function (9).

V-NEUROMOTOR AND COGNITIVE DISORDERS

1-In order to detect somatic and psychomotor disturbances in children and adolescents residing in areas of iodine deficiency, school children from three areas with different degrees of iodine deficiency were studied. In Randan, the prevalence of severe endemic goiter was accompanied by alteration in thyroid function, increased thyrotropin levels and retardation of both bone and psychomotor age and decreased intellectual quotient. In Tehran, where iodine deficiency is mild, visible goiter was present in 15% of school children but no alterations in thyroid function, serum thyrotropin, somatic or psychomotor development could be detected. In Zagoon, where the prevalence and severity of goiter was less than Randan but more than Tehran, thyroid function was normal but slightly decreased as compared to Tehran; somatic development was unaltered, but retardation in psychomotor development was evident and the mean intellectual quotient was less than that of Tehranian school children. **These findings indicate the occurrence of physical and psychomotor disturbances in apparently normal school children from areas of iodine deficiency. Alteration in psychomotor development may occur in children with normal physical growth, due to iodine deficiency (10)**.

B-The effects of mild/moderate iodine deficiency during the fetal/neonatal life on neuropsychological performances are still poorly defined. Some parameters of cognitive performance with sensitive psychometric tests in children living in an area with moderate iodine deficiency were analyzed. Each subject was submitted to the following neuropsychological tests: 1) a reaction time (RT) session, 2) the block design subtest of the WISC-R, 3) the coding subtest of the WISC-R. No significant difference was found between children with mild iodine deficiency and controls, for block design and coding tests. On the other hand controls had significantly faster RTs.

Data showed that **exposure to mild iodine deficiency in fetal/neonatal life does not affect general cognitive performance but influences the velocity of motor response to visual stimuli, which may be due to an alteration of the efficiency of the information processing mechanism (11)**.

C-The results of tests of intellectual and psychomotor performance and school performance in a group of school children from a rural impoverished

and iodine deficient Andean community whose mothers received injections of iodinated oil prior to the end of the first trimester of pregnancy have been compared with results in children from a neighboring comparable community whose mothers had received no iodinated oil. Subjects between ages 8 and 15 were studied. Statistically significant differences were not observed between the two groups in tests of intellectual function, but children of mothers who had received iodinated oil performed better on tests of psychomotor maturation. The group whose mothers had received oil performed distinctly better when assessed in terms of school drop-out rates, grades achieved, grades repeated, and in overall performance as judged by teacher notes in school records. Performance of both groups on standard tests of intellectual and psychomotor function was lower than standard scores. This may be a result of social and cultural deprivation, the general malnutrition prevailing in the region or other unidentified factors. The improved scoring and school performance exhibited by the children of mothers who received iodinated oil underlines the importance of prophylaxis with iodine in iodine deficient regions as one important contributor to community development (12).

VI-HEARING DISORDERS

1-There is no general impairment of hearing associated with mild to moderate iodine deficiency. It is suggested that **the most likely cause of the poorer hearing level among the ostensibly normal schoolchildren in endemic areas is sub-clinical hypothyroidism due to prolonged severe iodine deficiency**.

2-Hearing acuity was measured either by conventional mono-aural pure-tone audiometry or **by binaural free field testing depending on the child's age. Hearing loss at 4000 Hz and average hearing impairment at speech frequencies (500, 1000 and 2000 Hz) were more severe among children at risk of mild to moderate iodine deficiency (less than 10 micrograms/100 ml) compared with those with urinary excretion above 10 micrograms/100 ml (13).**

VII-IMAGING and MORPHOLOGIC BRAIN MODIFICATIONS IN IDD

A report on the clinical and magnetic resonance imaging brain scan findings of 3 adult Chinese cretins showed that **all had an apparent magnetic resonance imaging abnormality in the globus pallidus and substantia nigra, with hyperintensity on T1-weighted images and hypointensity on T2-weighted images**. The motor abnormality, characterized by truncal and proximal limb-girdle rigidity and spasticity, with relative sparing of the hands and feet, is analogous to other extrapyramidal disorders (14). Brains of therapeutically aborted fetuses from cretinism endemic region after a supplement of iodized salt for ten years were studied under both light and electron microscopes. Serum T3, T4 and TSH of the fetuses and their mothers were coincidentally assayed. **The brain development of fetuses from the endemic region was noticed to be still retarded as compared with those from the non-endemic region, despite that the serum hormones of the fetuses and their mothers in the endemic region showed no more significant difference from those in the non-endemic region. The retardation of the brain development could be evidenced by the increase of cellular density, decrease of the average volume of neurocytes, increase of the volume ratio between nucleus and cytoplasm per neuron, as well as decrease in number and average surface area of the mitochondria, and all of these were obtained in the cerebral cortex, hippocampus and the layer of Purkinje's cells of the cerebellum**. A pathological examination on the hippocampus of brain was carried out on 5 cases of endemic cretinism. Computer image analysis was focused on the pyramidal and granular cells. **There was a wide distribution of hypoplasia, and changes of the parameters involved in the pyramidal and granular cells were remarkable, which indicated that a development disorder existed in the hippocampus. Besides, a correlation was noticed between the**

weights of the thyroid gland and the brain as well as the parameters of the hippocampus. It is also noticed that changes of the thyroid gland correlated with the change in the CNS. Since lesions in the hippocampus were known to be closely related to dementia, it is considered that lesions found in the hippocampus constitute one of the morphologic bases of dementia in endemic cretinism.

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