INVITED COMMENTARY

Iodine and the brain: evidence from the mountains of Thailand

Steven C Boyages

Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, Sydney, New South Wales 2145, Australia

(Correspondence should be addressed to S C Boyages, Department of Diabetes and Endocrinology, Westmead Hospital, Hawkesbury Road, Westmead, Sydney, New South Wales 2145, Australia)

Endemic cretinism is one of the earliest recorded ecological disorders of mankind. The first recorded description of endemic cretinism and goitre is pictorial, a Buddha frieze (second century A.D.) from Gandara, India, which depicts a short, goitrous, deaf subject with the typical physiognomic features of cretinism (1). Yet, after so many years, as we stand on the threshold of a new millennium, debate still continues as to the pathogenesis of this disorder. The remoteness of most endemias has been one of the major factors which has hindered progress in the understanding of this complex disorder and, as a consequence, modern clinical methods using multidisciplinary teams have, until recently, rarely been applied to its investigation. Rajatanavin et al. in this issue (2) provide the most recent evidence, from an iodine deficiency endemia in a remote, moutainous area of Thailand, which helps to further unravel the puzzle of endemic cretinism. This new evidence supports the two-step hypothesis of the pathogenesis of endemic cretinism, as well as highlighting the important contribution of prenatal thyroid hormone from maternal sources to normal brain development (3).

The current descriptive classification of endemic cretinism is based upon McCarrison’s original report of endemic cretins from the Himalayan valleys in 1908, which classified cretins into myxoedematous and neurological types (4). Heterogeneity of presentation is not only found between different endemias, but also within the same endemia. This geographic and clinical diversity has led many researchers to suggest that two distinct forms of the disorder exist. Alternatively, others have suggested that endemic cretinism is a bipolar disorder, with myxoedematous and neurological types representing different ends of a continuous spectrum.

Neurological cretinism is the commonest form of the disorder and is encountered in all endemias. These cretins are typified not by signs of hypothyroidism, but by a well defined neurological deficit which includes mental disability, deafness and pyramidal and extrapyramidal signs, as well as a characteristic disturbance of gait (5). They are usually goitrous and biochemically euthyroid. By contrast, myxoedematous cretinism is less common and predominates in the endemias of central Africa, Nepal and western provinces of China. The basis for this geographic clustering is unknown. The clinical appearance of myxoedematous cretins is dominated by mental disability as well as signs of thyroid hormone deficiency, shortness of stature, pubertal delay and, paradoxically, by atrophy of the thyroid (3). Until recently, the absence of neurological features in these myxoedematous cretins was used as the major argument to support a different pathogenesis for the two types of the disorder.

Rajatanavin et al. report the results of an extensive multidisciplinary study of a large cohort of people with endemic cretinism who had been traditionally classified as neurological, myxoedematous or mixed type (2). Despite this physiognomic classification they found that a specific pattern of neurological damage, including audiometric and intellectual damage, was present in all types of endemic cretin. Gait disorder and pyramidal and extrapyramidal signs were the commonest neurological manifestations, reflecting damage to the cerebral cortex and basal ganglia. The findings from these studies are similar to our studies from China and Indonesia which have also found that a synonymous pattern and intensity of neurological, intellectual and audiometric deficits is common to and equally present in all types of endemic cretin (3, 5). Reports from northern Italy have also demonstrated similar findings, indicating that the pathogenesis of endemic cretinism is similar in different geographical areas of the world (6).

The significance of these findings is that endemic cretinism provides a critically important clinical model for elucidating the thyroid hormone-dependent events in the development of the human central nervous system. The nature of these neurologic and auditory deficits points to an intrauterine insult to the developing fetal nervous system around the time of the mid-trimester. Based upon the present observations and the work of others showing that placental transfer of maternal thyroxine does occur (7), particularly in the first trimester, prenatal thyroid hormone deficiency, from both maternal and fetal sources (secondary to severe iodine deficiency), can be postulated as the pathogenic mechanism responsible for the neurological damage of endemic cretinism. None of the neurological features of
Endemic cretinism have been described in children with sporadic congenital hypothyroidism if maternal thyroid function is normal. The limited distribution of the β2 thyroid hormone receptor in the central nervous system may explain the predilection of certain areas of the brain to thyroid hormone deficiency (8).

Whereas previous workers had attributed the differences in the clinical presentation of endemic cretinism to the presence or absence of neurological features (i.e. prenatal hypothyroidism), Rajatanavin et al. (2) confirm that the distinction between the types of endemic cretin could be related to the length and severity of postnatal thyroid hormone deficiency. Endemic cretins with predominant neurological features appeared to have had only transient hypothyroidism in the postnatal period, evidenced by their near normal thyroid function and by a lack of hypothyroid clinical features. By contrast, those cretins with predominant myxoedematous features were characterised by permanent and severe thyroid hormone deficiency, with its clinical effects being reflected well past the early postnatal period. These cretins, in addition to the signs of neurological damage, were typically dwarfed and sexually immature, with marked clinical features of myxoedema.

Iodine deficiency is well established as the cause of the endemic cretinism and its correction always results in the prevention of endemic cretinism. McCarrison, whose original report is the basis for the current classification, was the first to have recognised that ‘both types of the malady may be combined in the same individual’ (4). Based upon current evidence from several endemias, it can be reasonably concluded that the clinical picture of endemic cretinism results from an interaction of two pathophysiological events, both resulting from iodine deficiency, but occurring at different times in the development of the fetus and neonate. The first event follows a lack of thyroid hormone in utero, resulting in the neurological manifestations (including the intellectual and auditory aspects) of the condition. The second determines the duration and severity of continuing hypothyroidism after birth, which is reflected clinically as growth retardation, sexual immaturity and persistent signs of thyroid hormone deficiency. Both components play a role and explain the frequent overlap of clinical signs.

References