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Endocrinology

Congenital hypothyroidism

J H Lazarus

Commentary on the paper by Oerbeck *et al* (see page 132)

The introduction of neonatal screening programmes for congenital hypothyroidism in the 1970s is now regarded as a highly cost effective strategy to detect the commonest congenital metabolic disorder seen in the newborn (1 in around 4000 births).[1] There is no doubt that early diagnosis and treatment of the condition has led to the disappearance of mental retardation, which was the most dramatic long term sequel of congenital hypothyroidism.[2] However, it has been clearly recognised that persistent selective impairments may still occur in these children, such as language delays, minor motor problems, visuospatial defects, and attention problems.[3] Also, postnatal somatic abnormalities including an accelerated cranial growth[4] and delayed bone age[5] to 3 years have been observed, especially in children given high starting doses of levothyroxine. Initially, starting doses of thyroxine were in the range of 8–10 μg/kg/day,[6] but the dose was later revised upwards to 10–16 μg/kg/day.[7] There is clearly a need to define the optimal dose of T4 to initiate therapy as well as the desirable levels of serum T4 to be achieved during long term therapy.

This subject was recently discussed by Rovet,[8] who indicated that a number of studies (for example, Bongers-Schokking *et al*[9] and Dubuis *et al*[10]) have shown that a higher dose is beneficial in closing the IQ gap between moderate and severe forms of the disease. However, she has previously recorded a possible increase in neurobehavioural disorder in children who have received higher dose regimens of thyroxine.[11] Furthermore, hyperthyroxinaemia in rodents has been associated with adverse neurodevelopmental effects.[12 13] What current data are available to substantiate the practice of higher dose initial thyroxine therapy? Distinction must be made between the initial serum T4 at diagnosis, the starting dose of T4, and the maintenance serum levels of thyroid hormones in the outcome assessment. Two recent studies emphasise the importance of the initial serum T4. Ng and colleagues[14] found that the initial T4 was an independent factor (inversely related) in the control of head growth in the first three years in 125 subjects with congenital hypothyroidism (CH). In 31 CH subjects studied at 4 years of age, a higher baseline T4 was one of the main predictors of increased verbal IQ but, interestingly, levothyroxine dose at the beginning of treatment and thyroid hormone levels during treatment did not relate to IQ outcome.[15] In relation to the initial starting dose of T4, Gauchard and colleagues[16] showed in 17 patients that early normalisation of TSH (before 3 months) was necessary to allow for normal neurosensorial afferent pathway development (vestibular, proprioceptive), as well as pathways of central integration (cerebellum, vestibular nuclei). The Norwegian study of 49 patients[17] showed that the initial T4 dose predicted verbal IQ at age 20, but the authors have expressed concern at some negative associations between high dose treatment and developmental outcome.[18] Nevertheless, a recent Cuban study of 100 CH children studied at 8.2 years showed that total IQ was related to the initial T4 dose.[19] A careful study by Simoneau-Roy and colleagues[20] showed that children with severe CH treated early with a high dose (median 12 μg/kg/day) of levothyroxine had normal global development and behaviour at school entry. However, as these authors noted, the number of subjects was small, indicating the need for further studies. The Norwegian workers have now extended their study of the 49 subjects referred to above in an attempt to describe the psychological problems in these young adults and to evaluate any negative effects of high dose thyroxine replacement therapy.[21] The results indicate that the CH group, perhaps not surprisingly, had lower performance levels than their sibling controls for some aspects of memory, and attention, and had more behaviour problems. Importantly, a high T4 starting dose (⩾7.8 μg/kg/day) had no adverse effect on outcome at age 20. Furthermore, there was no deleterious effect of higher T4 levels during infancy, early childhood, or at assessment on the higher order cognitive skills. This study, which divided the initial treatment T4 dose into two groups similar to the Toronto workers,[8] adds significant evidence that a high starting dose of T4 in CH is not harmful in the long term and may be beneficial in some outcome measures.

There are other physiological factors to be considered in relation to thyroxine delivery to developing neural tissue. The fetus with CH derives its T4 mostly from the mother through gestation. Details of the transplacental passage of the hormone are certainly incomplete, but the role of the deiodinase enzymes, particularly type 3, in acting as ''a gatekeeper'' in this process is under intensive study.[22] Variations in the rate of different areas of brain development during gestation and their detailed response to T4 in marginally hormone deficient situations are further factors which cause abnormal brain morphology at birth.[23 24] In addition, the complexity of thyroid hormone action in the developing brain is compounded by temporal and regional variations in metabolism, receptor and gene expression.[25] On a practical level the maternal thyroid hormone supply to the fetus is dependent on the iodine supply which may be precarious.[26]

It is probable that the classification of CH into mild moderate and severe, for example, is too simplistic in relation to brain architecture and may account for variation in outcome in children with similar initial hormone levels. Hence it is not surprising that studies in children using psychological outcomes will have differing specificities and sensitivities. From the available clinical evidence, to which the study of Oerbeck *et al* has contributed significantly, it would appear that the starting dose of levothyroxine should be higher rather

than lower, and that the long term risks of adverse psychological performance are small. A large scale multicentre study is indicated to clarify the concerns of the ''low dose'' group of investigators. Meanwhile advances in our understanding of thyroid hormone action on the developing brain will improve our ability to make these important clinical judgements.

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Health care

The evolution of paediatric hospitals

R B Goldbloom

Commentary on the paper by Ogilvie (see page 138)

The words ''hospice'', ''hostel'', and ''hospital'' share the same etymological root. In ancient times, the aged and infirm were often admitted to a hospice as a place to die. Typically the physical environment was spartan—walls bare except perhaps for a crucifix, and help limited to prayer. The spirit was otherwise ignored. Most, but not all, hospitals have overcome their monastic provenance and have evolved into cheerier environments. More and more hospitals now encourage the support of family and friends as an aid to recovery. But in too many adult hospitals, the physical environment still betrays its monastic unicellular roots. In health care, as in life, old traditions die hard.

The mere idea of a hospital dedicated exclusively to the care of children is a relatively recent concept. In the mid-19th century, Charles Dickens was a vigorous campaigner for the support of such a hospital in London—specifically, for The Hospital for Sick Children, Great Ormond Street. In *Our Mutual Friend*, published in 1868, he provided one of the first literary references to an exclusively paediatric hospital.[1] He describes how Mrs Boffin persuades an elderly woman to seek good care for an ill child:

> ''We want to move Johnny to a place where there are none but children; a place set up on purpose for sick children; where the good doctors and nurses pass their lives with children, talk to none but children, touch none but children and comfort and cure none but children.
> 'Is there really such a place?' asked the old woman with a gaze of wonder.''

Dickens later describes how the child was permitted the comfort of bringing favourite toys to the hospital:

> ''At the Children's Hospital, the gallant steed, the Noah's Ark, the yellow bird and the officer in the Guards were made as welcome as their child owner.''

The early ancestors of the modern paediatric hospital (now, in many cases, wisely renamed health centres) included the foundling hospitals, best known for interminable stays, high mortality, and for being the sites where psychosocial deprivation, or ''failure to thrive'' was first identified as a clinical entity. The paediatric hospital's ancestry also includes isolation hospitals for