

# Congenital hypothyroidism – correlation between radiographic appearances of the knee epiphyses and biochemical data

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**Summary:** Plain knee radiographs of 20 neonates with congenital hypothyroidism, were reviewed. The size and appearances of the epiphyses were compared with the biochemical data at the time of referral. Fifteen infants had unequivocal evidence of delayed bone maturation based on absence of the distal femoral epiphysis or small epiphyseal size. Seven cases had fragmentation of at least one epiphysis.

A positive correlation was found, at diagnosis, between the thyroxine and triiodothyronine levels and the size of the knee epiphyses. All 14 infants with thyroxine levels of less than 70 nmol/l had small epiphyses with a combined mean diameter of the proximal tibial plus distal femoral epiphyses of 7 mm or less. Conversely, of the 6 infants with thyroxine levels of 70 nmol/l or above, 5 had combined epiphyseal diameters of greater than 10 mm.

We suggest that in infants with no clinical symptoms and only moderately raised screening thyroid stimulating hormone, a knee radiograph showing the described radiological changes should prompt institution of thyroxine treatment before awaiting biochemical confirmation of the diagnosis.

## Introduction

Early diagnosis and adequate treatment of congenital hypothyroidism is essential in preventing long term mental retardation or neurological dysfunction.<sup>1</sup>

As clinical features in the neonatal period are often absent or minimal, many countries have introduced neonatal dried blood spot screening programmes. Thyroid stimulating hormone (TSH) is most commonly estimated, with later confirmation of the diagnosis by full thyroid function testing.<sup>2,3</sup>

The biochemical confirmation of congenital hypothyroidism in a large district hospital can take up to 10 days and may result in a delay in initiating treatment. This delay could be reduced if a more rapidly available investigation, such as a knee radiograph, could also be used as a means of assessing thyroid deficiency.

Despite the absence of demonstrable clinical signs in the newborn, it has been recognized for many years that skeletal abnormalities may be present and may be of clinical value in the initial diagnosis of thyroid deficiency.<sup>1,4</sup>

The aims of this study were to assess quantitatively the value of plain radiography of the knee in providing supportive evidence for the initial diagnosis of congenital hypothyroidism, and to explore the relationship between delayed skeletal maturation and severity of thyroid deficiency.

## Material and methods

In Leicestershire, dried blood spot TSH screening for congenital hypothyroidism, (Neonatal Screening Laboratory, The Children's Hospital, Sheffield), is carried out on all infants at 5 or 6 days of age. All infants with a screening TSH level over 60 nmol/l are referred for further investigation. The diagnosis is confirmed at the first clinic visit by measurements of serum TSH thyroxine (T4) and tri-iodothyroxine (T3) levels, when a supine anterior-posterior radiograph of one knee is also obtained. The film is placed directly below the infant with the tube focal spot to film distance set at 100 cm in order to reduce magnification. The radiograph is made immediately available in the clinic.

Our study comprised of 21 infants with treated primary congenital hypothyroidism between 1980 and 1988. One preterm infant was excluded from the study since the normal values used refer to full term infants. In all 20 infants the knee radiographs

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were reviewed retrospectively by C.J.N. and A.C.L.

The appearances of the distal femoral and proximal tibial epiphyses were noted and compared with normal reference values in term infants previously reported by Senecal,<sup>5</sup> using the  $\chi^2$  test for significance.

The greatest and smallest diameter of each epiphysis was measured. The mean value of these 2 measurements was calculated, as described by Von Harnack,<sup>6</sup> and the distribution of these mean epiphyseal diameters compared to his reported normal values.

The values for the mean epiphyseal diameter were compared with T4 and T3 levels using Pearson's correlation coefficient to assess the strength of a positive relationship. Furthermore, the mean diameter of the distal femoral and proximal tibial epiphyses were added together and these combined mean epiphyseal sizes compared with thyroid hormone levels. In 3 infants the initial T3 level was not available.

The presence of epiphyseal abnormalities, in particular fragmentation or irregularity, were noted.

## Results

The 20 infants were born at a mean gestational age of 40 weeks, (range 36 to 43 weeks), all were over 40 weeks by gestational age at the time of diagnosis.

Initial knee radiographs were obtained at a mean postnatal age of 21.3 days, (range 13 to 39). In 5 infants the distal femoral epiphysis was absent. This is significantly abnormal ( $P < 0.025$ ) when compared to the normal values in term infants reported by Senecal.<sup>5</sup> The proximal tibial epiphysis was absent in 9 cases, but used in isolation is not a statistically significant abnormal finding.

The range in size of both the distal femoral and proximal tibial epiphyses was between 0 and 8 mm (Table I). In 14 cases (70%), the distal femoral, and in 13 cases (65%), the proximal tibial epiphyses, were below the average size for term infants (Figure 1) reported by Von Harnack.<sup>6</sup>

The 5 infants with an absent distal femoral epiphysis showed a mean T4 level of 34 nmol/l (range 17–70), this compared with a mean T4 level of 98 nmol/l (range 70–141) in the 5 infants whose epiphyseal sizes were within the normal range.

A highly positive correlation was shown when either the individual epiphyseal diameter or combined mean epiphyseal size was compared to thyroid hormone levels. R values correlating epiphyseal size to T4 levels varied between 0.7 and 0.8, the highest figure correlating combined mean epiphyseal size to T4 (Figure 2). These r values being significant with a  $P$  value of less than 0.001.

**Table I** Epiphyseal diameter in each infant recorded with initial thyroxine and triiodothyronine level

T4	T3 (nmol/l)	Mean epiphyseal size (mm)	
		Distal femur	Proximal tibia
17	0.6	0	0
19	1.4	3.5	1
21	0.9	0	0
25	0.6	0	0
30	0.4	3	0
30	1.3	4.5	1.5
30	–	4	2.5
38	1.2	0	0
42	1.4	4.5	0
46	1.7	3.5	0
47	–	4	3
48	2.2	3.5	0
52	2.7	4	3
61	–	6	0.75
70	2.0	0	0
70	1.9	6	5
84	2.4	8	8
91	1.9	6.5	5
103	2.7	6	5.5
141	3.1	8	7

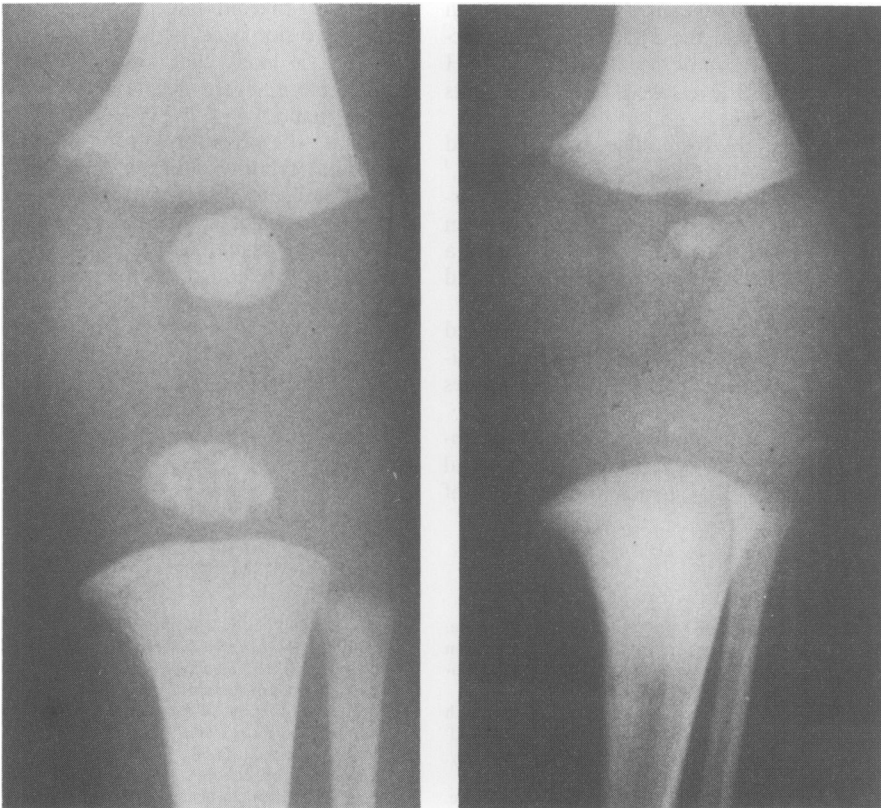
Correlating epiphyseal size with T3 levels the r value ranged from 0.7 to 0.73, this being significant at a  $P$  value of less than 0.01.

Five of the 15 (33%) infants in whom the distal femoral epiphysis was present showed minimal fragmentation or irregularity. Similar abnormalities were seen in 4 (36%) of the 11 infants whose proximal tibial epiphyses were present and a lucent line in the distal femoral metaphysis was noted in five.

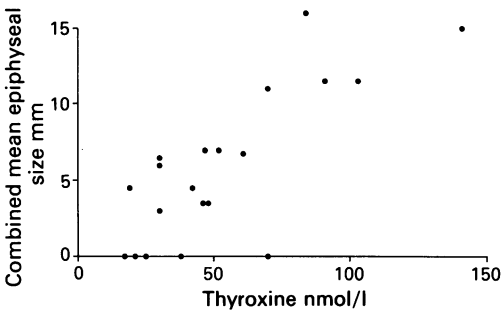
## Discussion

This study shows that delayed skeletal maturation was present in 75% of infants with raised neonatal TSH levels. Delayed maturation was confirmed by absence of the femoral epiphysis in 5 cases and by small epiphyses in 10 cases, when compared to the normal range of Von Harnack.<sup>6</sup> Fragmentation of the epiphyses was also present in 5 of these infants. The measured epiphyseal size was within the normal range in 5 cases and of these 2 had evidence of fragmentation or irregularity. These appearances, however, are found in other conditions and occasionally in normal infants and cannot be used in isolation as evidence of congenital hypothyroidism.<sup>7,8</sup>

We found a significant correlation between the measured epiphyseal size of the femoral and tibial epiphyses and the thyroid hormone levels. All 14 infants with T4 levels less than 70 nmol/l had a



**Figure 1** On the left is shown a normal neonate with both knee epiphyses present. On the right a neonate with congenital hypothyroidism in whom both epiphyses are small.



**Figure 2** Graph showing combined mean epiphyseal size compared to thyroxine levels.

combined mean femoral plus tibial epiphyseal diameter of 7 mm or less. Conversely, 5 out of 6 infants with T4 levels of 70 nmol/l or more had a combined epiphyseal size greater than 10 mm. Thus a combined epiphyseal size of 7 mm or less implies a T4 of less than 70 nmol/l with a sensitivity of 100%, specificity of 83% and a positive predictive value of 93%.

There was no correlation between the epiphyseal size and screening TSH levels which ranged from 69–325 mU/l.

Of the 5 infants with normal epiphyseal measurements 3 had recognizable early symptoms of hypothyroidism and were treated immediately. Two appeared normal. Their treatment was withheld until radioisotope scans confirmed an ectopic gland in each case and later thyroid function tests confirmed unequivocal persistent hypothyroidism.

One infant had absent epiphyses and early symptoms of hypothyroidism when seen and treated in clinic. Her T4 of 70 nmol/l might be considered to be just within the normal neonatal range. However, the very high TSH (325 mU/l) and a scan showing a small unilobar gland justified early treatment.

Retarded bone age in 40–73% of neonates with congenital hypothyroidism has been described in previous papers.<sup>2,9</sup> A few have attempted to correlate biochemical tests with skeletal maturity, where maturity was assessed in relation to gestation age, using the method of Senecal *et al.*<sup>5</sup> or to birth weight using the method of Caffey.<sup>10</sup>

Illig<sup>2</sup> reported a significant difference between biochemical values and the extremes in the spectrum of size of the ossification centres. Higher TSH and lower T4 and T3 levels were found in infants with absent epiphyses.

In a similar study from The New England Congenital Hypothyroidism Collaborative,<sup>3</sup> significant correlations were reported between hormonal concentrations and retarded bone age, when they grouped infants into 2 classes – those with a bone age equivalent to 40 weeks gestation, and those with a bone age less than gestation age.

No previous studies, however, have correlated the biochemical results with the measured epiphyseal size using the method and reference values of Von Harnack.<sup>6</sup>

The delay in skeletal maturation at birth probably depends upon the severity of the prenatal thyroid deficiency,<sup>11</sup> and hence the amount of

functioning thyroid tissue.<sup>4</sup> Although radioisotope scans have not been performed in many of our infants it is likely that lower T4 and T3 levels suggest more severe dysplasia or aplasia of the thyroid gland.

Despite the prenatal maturational influence of congenital hypothyroidism in many infants, recent studies indicate that most show no long term detrimental effect on mental development when early adequate treatment is instituted.<sup>3,9</sup>

This study demonstrates that when there is likely to be a delay of several days in the biochemical confirmation of suspected congenital hypothyroidism in an asymptomatic neonate, an immediately available X-ray of the knee showing a combined mean epiphyseal size of 7 mm or less confirms the diagnosis and the need for thyroxine treatment.

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