

Neuro-developmental Deficits in Early-treated Congenital Hypothyroidism

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Abstract

This paper summarises the current evidence on neuro-developmental deficits in the early (< 1 month of age) treated congenital hypothyroid and the influencing factors. A literature search revealed only few citations that compared outcome with matched controls. In all but one, the median age of treatment onset was >2 weeks. Mean Global IQ scores are about 10 points lower and remain identifiable in adulthood. Verbal and performance scores are usually similar. Deficits persisting into adolescence and adulthood involve the visuomotor, memory, attention and posture domains. Lower academic performance is common in the early years. Prenatal factors associated with a worse prognosis are aetiology (dysgenesis), low birth weight, associated complications and severity of hypothyroidism. Postnatal factors are age at onset of treatment (>1 month), lower thyroxine dose at onset (<8 mcg/kg/day), late normalisation of thyroid function (>2 weeks after treatment), and a lower socio economic family status. The author proposes the evaluation of a multi centre cohort with a median age of treatment onset <1 week, TSH normalisation by <3 weeks with treatment thyroxine levels maintained in the 3rd quartile for age. The outcome of this cohort should indicate if current targets in management need to be revised.

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Background

About half a century ago, it was documented that severe neuro-developmental deficits were present in children with hypothyroidism started on treatment after 7 months of age.¹ An IQ above 90 was obtained in only 10 of 22 children treated before that age. Almost a decade and half later, it was reported that if treatment was started before 3 months of age, 85% had an IQ >85.² Newborn screening for congenital hypothyroidism was thus initiated about 35 years ago with the primary goal of preventing the severe deficits found in treated hypothyroids. The outcome of the earliest cohort of patients diagnosed by screening was reported by Quebec Network who found that none had an IQ <85 and that the mean IQ at 12 and 18 months of age were 113 and 105 respectively.³ At 18 months of age the mean was significantly lower (105) than that of the controls (111).

Since then there has been a constant stream of publications documenting the practically normal development of

hypothyroids detected by screening and treated within 1-3 months of age. In this group of babies, IQs though in the normal range are lower than the population mean; in addition specific learning disabilities have been reported. Data also suggest that epidemiological characteristics and treatment onset and goals do influence the outcome. This paper summarises the current evidence on developmental deficits in the early (<1 month of age) treated congenital hypothyroid and the influencing factors.

Methods

A literature search yielded many citations describing the outcome of babies treated at less than 1 month of age. The majority were descriptions of the short term outcome of small cohorts. Only 8 of these were described as clinical trials with a control arm of healthy children against which the outcomes were compared. Only 1 study was randomised. There was also only 1 among all the citations, that reported a median age of 2 weeks for treatment onset.

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Results

In the only RCT, 31 children from Oregon, USA with severe and moderate congenital hypothyroidism and 3 different initial thyroxine doses had their neuro-developmental outcomes compared.⁴ The age at evaluation was wide, ranging from 2 to 8 years. Also studied was the effect of the time taken to normalise thyroid function. Higher (50 mcg) and lower (37.5 mcg) dose groups were separated by about 11 points on the full scale IQ. Verbal, performance and achievements scores however did not differ. Subjects taking longer than 2 weeks to normalise thyroid function had significantly lower cognitive, attention and achievement scores.

Connelly and associates from Victoria, Australia were among the earliest to report on the long term outcome of a large cohort with age matched controls.⁵ Their cohort of about 152 cases had median age of onset of treatment of 14 days. At 2, 5 and 8 years, their mean composite scores were 8.5 to 10.2 points lower than the 60 age matched controls. Very low scores at the same ages were 10.1%, 3.9% and 6.8% respectively. A lower socio economic status and maternal education of less than 10 years in school were associated with about a 10 point lowering of verbal but not performance scores.

The outcome at adulthood of hypothyroids in the Netherlands has been documented.⁶ Their median age at treatment onset was 28 days and they were divided into 3 severity groups based on the screening T4 value. In those with severe hypothyroidism, the full scale, Verbal and performance intelligence quotients were 91.3, 92.9 and 90.4 respectively. In those with moderate disease, the respective scores were 99.1, 97.8 and 101.3 respectively. The scores were 101.3, 101.8 and 100.4 respectively in those affected mildly. The severely, moderately and the mildly affected had from the Movement Assessment Battery for Children, motor scores of 9.8, 4.3, and 6.7 respectively. In the controls, it was 3.2. Their conclusion was that Global IQ and motor scores correlated with severity rather than the age of commencement of therapy.

Similar results were obtained from the 49 Norwegian cases of the 1979-81 cohort who were assessed at the mean age of 20 years and compared with 41 sibling controls of mean age 21 years.⁷ The cases had lower scores than controls: Global IQ 102.4(13) and 111.4(13). Secondary schooling was not completed in 24% of cases and 6% of controls. Motor outcome was associated with severity of the hypothyroidism while verbal and arithmetic scores correlated with initial thyroxine dose and second year T4 levels and, arithmetic score with only second year T4 levels.

The subgroup of severe hypothyroids from the Dutch 1992-1993 cohort with median age of treatment at 20 days

had at 10 years of age, significantly ($P < 0.05$) lower scores (Full scale 93.7, Verbal 94.9 and Performance 93.9) than the normative population.⁸ Moderate and mild hypothyroids and the normative population had similar scores. The 1981-1982 cohort with a median age of 28 days at the onset of treatment showed a similar outcome with that of the 1991-1992 cohort. Reducing the age of onset of treatment also appeared not to have a benefit in the severely affected hypothyroid.

The effect of initial and post initial treatment factors on outcome at 5 to 7 years was recently reported. The cohort comprised 45 Dutch patients (19 severe and 26 mild hypothyroids) and 37 controls. The global IQ was similar between the groups. However, the visual-motor scores and verbal scores were lower.⁹ The TRF scores (teacher report form) were also higher. The authors concluded that suboptimal initial and post initial treatment would lead to abnormalities in IQ and in behavioural problems. They recommended that TSH concentrations be maintained within the normal range.

A Toronto cohort of 83 hypothyroids in grade 3 when compared to 80 classmates scored lower in reading, comprehension and arithmetic.¹⁰ They, however, did not differ on word recognition, writing or spelling. By Grade 6 the differences were not present. However, cognitive problems in memory, attention and visual-spatial processing areas have persisted into adolescence. The impact of these deficits on future educational accomplishments needs further investigation. A subgroup of this cohort comprising 42 cases was compared at 6 to 9 years of age to their 42 unaffected siblings.¹¹ The cases scored lower by about 8-6 points on the McCarthy/WISC-R. Factors contributing to the effect were only aetiology (dysgenesis vs. dyshormonogenesis) and starting dose (above or below 8.2 mcg/kg/day).

Deficits in postural control have also been observed in those where TSH normalisation took more than 3 months.¹² In a Japanese cohort of 129 cases, the intellectual outcome was similar except in a subgroup of unfavourable cases (LBW, complications and a high TSH) whose scores were less than 100.¹³ A French cohort of 131 cases from 1979-94 and 30 controls were studied to determine the importance of age of treatment versus the initial dose of thyroxine.¹⁴ Treatment onset before 15 days produced global IQ scores of 119 (1.8). Below and beyond 3 weeks the scores were 117.1 (1.2) and 107.7 (2.4). Initial doses above and below 6 mcg/kg/day were associated with performance scores of 117.3 (1.8) and 112.8 (1.2).

Summary

Newborns treated early in infancy for hypothyroidism still appear to have mild cognitive and learning deficits.

The factors predicting deficits include those originating prenatally – aetiology (dysgenesis), low birth weight, associated complications and severity of hypothyroidism. The postnatal factors are age of treatment onset >1 month, low thyroxine dose at onset, late (>2 weeks), normalisation of the TSH/ft4 and lower socio economic strata.

It is now time to ascertain if this gap between the healthy child and the early treated hypothyroid can be narrowed further. This will require the establishment of a large multi national collaborative in which congenital hypothyroids are treated with a target of median age of treatment onset <1 week, TSH normalisation by <3 weeks and thyroxine levels maintained in the 3rd quartile. The outcome of this cohort should indicate if current treatment targets need to be revised.

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