

## Congenital Hypothyroidism and Developmental Difficulties

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### The Story

A case was posted in internet by a distressed mother in the year 2008 who has a son with possible congenital hypothyroidism and possibly some underlying syndrome like Prader Willi Syndrome, was only picked up by 1 year of age. Her family moved from Middle East to India and then finally to Canada. The mother wondered how much damage could this delay in diagnosis make to his mental development.

The story of course, raises several questions and the “borderline hypothyroidism” may not be the son’s immediate underlying pathology where one is compelled to worry about Prader Willie Syndrome and the likes instead! But borderline hypothyroidism (mother is probably referring to ‘subclinical hypothyroidism’) may be one of those aspects which must be addressed immediately in her son’s management.

Her son is now getting the services that he needed as they have moved to Canada. But, for someone who is posting comments on an internet, it remains unacceptable that this borderline hypothyroidism was not picked up by Newborn Screening, be it in Middle East or in India. We cannot afford to keep missing congenital hypothyroidisms in the second decade of 21<sup>st</sup> Century. It has been proven amply by now that the Holy Grail of present day Pediatrics is Early Detection and Early Intervention [1,2]. To do so, we must ask ourselves the following questions, examining the existing evidence and weighing our interventional options with fine judgments based on the available evidence, as follows:

### Does congenital hypothyroidism cause developmental problems?

Let us review this question scientifically (Expert Review)

### History

#### Historically

“The various subgroups have grown up clinically since Gull, in 1873, first called attention to myxedema”.

Diseases of the nervous system by Smith Ely Jelliffe, William Alanson White (1917) Nervous and Mental Diseases by Archibald Church, Frederick Peterson (1914) myxedema. Under the generic term of myxedema it is proposed to bring together those clinical variations of nutritive disorder dependent upon partial or ...” The Medical Clinics of North America by Michael C. Fiore, Stephen S. Entman, Charles B. Rush (1922) “There are, however, some patients with early, mild, or atypical types of myxedema wherein the symptoms and signs may be very suggestive, ...” (Supplementary). The Thyroid Gland by Cleveland Clinic Foundation, George Washington Crile (1922) “myxedema may be congenital in origin, in which case it is due to the absence of the ... In cases of congenital myxedema the child fails to develop ...”

### What causes CH?

In the vast majority of patients, congenital hypothyroidism is (a) sporadic and associated with *thyroid dysgenesis*, a spectrum of organ developmental defects, e.g. (i) the absence of detectable thyroid tissue, (ii) ectopic tissue, and (iii) thyroid hypoplasia. Defects in one of the (b) multiple steps required for normal hormone synthesis account for

about 10% of cases with congenital hypothyroidism. They are typically recessive and therefore more common in inbred families.

### Currently—there is no doubt that CH causes DD—but what exactly does it affect?

Current Evidence of Congenital Hypothyroidism with Developmental consequences:

Congenital Hypothyroidism (CH) is one of the commonest (1 in around 4000 births in Caucasian populations [3], 1 in around 1800 in largest Indian study [4] and 1 in around 918 births in Asians in the UK) [5] and easily preventable causes of Developmental Difficulties (DD), if detected early and treated adequately.

Let us look at the current understanding of the developmental consequences of CH below:

### Deficits in IQ scores

The importance of thyroid hormone to brain growth and development is demonstrated by comparing treated and untreated children with congenital hypothyroidism [6]. The deficit in IQ score found at 3 and 5 years in children with severe hypothyroidism is still evident at the age of 10 years [7].

Thyroid hormone is necessary for normal brain growth, myelination and normal neuronal connections [6]. The most critical period for the effect of thyroid hormone on brain development is the first few months of life [6]. Profound mental retardation is the most serious effect of untreated congenital hypothyroidism, as was found by studying 128 cases in the year 1957! We hope to avoid such events today.

### Physical impact with developmental consequences

Severe impairment of linear growth and bone maturation also occurs [8]. Affected infants whose treatment is delayed can have neurologic problems such as spasticity and gait abnormalities, dysarthria or mutism, and autistic behaviour [9].

### Hearing

Pure tone audiometry, tympanometry, acoustic stapedial reflex thresholds (ASRTs), and auditory evoked brain stem responses (AEBRs) were carried out in 38 children with early treated congenital hypothyroidism aged 10-12 years, together with tests of vestibular function (electronystaggraphy, rotational, and calorimetric tests). Sensorineural hearing loss with thresholds of greater than 15 dB was detected in 18

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children (10 at 8 kHz only); only two children had more than 40 dB hearing loss, each in one ear. Raised ASRTs were found in eight children and two children had abnormal AEBRs. Of the 29 children tested, 12 had an abnormality of vestibular function. Although not significant at the 5% level, there was a tendency for the abnormalities to be more prevalent and severe in the children with more severe hypothyroidism, as judged by pretreatment plasma thyroxine.

It is concluded that (i) mild abnormality of hearing is still common in children with congenital hypothyroidism despite early treatment but this is much less severe than that found before neonatal screening and (ii) mild abnormalities of vestibular function may be common in early treated congenital hypothyroidism [10].

### Sensory impairment

Patients with congenital hypothyroidism showed a deviance in early auditory ERP (Event Related Potentials) components, tapping sensory processing, sensory gating and selective attention, compared to sibling controls. Deficits in these earlier and modality specific ERP components may be the result of delayed maturation of neural connections that possibly have influenced later cognitive development [11]. While study confirms earlier findings of normal P3 (third peak of the latent phase) latency and amplitude in early treated hypothyroidism, it found indication of a topographic pattern of amplitude distribution, indicative of a developmental delay. In the patient group, age at start of thyroxine treatment correlated with P3 latency and amplitude. Early treatment with hormone substitution may have thus assisted in the normalization of this component. Hormone levels at the time of the study in young adulthood were unrelated to ERP results.

Both clinical and experimental studies therefore indicate that a deficit in frontal lobe connectivity may cause changes in P1 (peak) and N1 (nadir) amplitudes consistent with the study results.

It is noteworthy that the frontal lobes mature during a long time-span reaching into young adulthood, and that myelination follows a similar protracted time course [6,11].

Thus, the findings in the CH group could be related to suboptimal maturation of frontal lobe connectivity in relation to the thalamus and temporal lobe.

### Learning deficit

A resulting problem in auditory sensory gating may then lead to a non-specific interference with educational achievement [7] which has been observed in the total congenital hypothyroidism cohort from which the present group is drawn (Oerbeck et al. [11])

### Newborn screening programme

Not only that, more recent researches from the west shows relevant findings, as overt manifestations of CH are swept away in the west by the stringent application of effective Newborn Screening programmes [12]. Therefore, some of the following findings make strong evidence for the need for increased vigil.

Patients with CH were significantly more likely than their peers to report associated chronic diseases (5.7 vs. 2.9%), hearing impairment (9.5 vs. 2.5%), visual problems (55.4 vs. 47.9%), and being overweight with a body mass index of at least 25 kg/m<sup>2</sup> (22.8 vs. 15.7%) ( $p < 0.0001$ ). Furthermore, fewer patients attained the highest socioeconomic category (14.6 vs. 23.1%) and were in full-time employment (39.9 vs. 44.8%) ( $p < 0.0001$ ). They were more likely to still be living with their parents and had a lower health-related quality of life than their healthy

peers, particularly for mental dimensions, with a mean difference for the mental summary component of 0.35 sd score ( $p < 0.0001$ ). CH severity at diagnosis, treatment adequacy, and the presence of other chronic health conditions were the main determinants of educational achievement and health-related quality of life scores.

### Conclusion

These findings highlight the need for careful monitoring of neurosensory functioning, weight, and long-term treatment adequacy throughout childhood and adulthood [13].

All children and adolescent with Congenital Hypothyroidism manifest Memory Deficiency [14-16]. Attention Deficiency is consistently observed in congenital hypothyroidism [17-19]. Behavioural problems were found in terms of activity regulation [20] and internalizing symptoms [21]. Therefore, the scientific world has been able to narrow down the developmental consequences of CH even in the era of Early Detection and Early Intervention.

There are some recent works on babies picked up by Newborn Screening as follows: Patients, particularly those with severe congenital hypothyroidism, had significantly higher (i.e. worse) motor scores (total score, 7.8; ball skills, 2.0; balance, 4.1) compared with controls (total score, 3.2; ball skills, 0.7; balance, 1.1), and lower full-scale (95.8), verbal (96.4), and performance (95.6) intelligence quotient (IQ) scores than the normal population. No significant change in IQ from childhood to adulthood was found, and for the majority of patients, motor score classification remained the same. The severity of congenital hypothyroidism, but not the starting day of treatment, was correlated with IQ and motor scores [22].

Paediatricians should be informed about the increased risk of the development of behavioral problems at primary school age in fully treated CH patients. At this age special attention should be paid to parental worries and anxiety. However, it can be reassuring for the patients and parents to know that the problems may be related to CH, and that they may spontaneously disappear [23].

Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism suggest that optimal treatment includes achievement of euthyroidism before the third week of life by initiation of therapy before 13 days with a levothyroxine dose above 9.5 µg/kg/d and maintenance of FT<sub>4</sub> (free thyroxine) concentrations in the upper normal range during the first year. Thus treated patients with CH can achieve normal psychomotor development at 10 to 30 months, irrespective of the severity of the disease [24].

### Back to History

Newborn Screening Programs started in the seventies to prevent mental retardation from congenital hypothyroidism (CH). If not promptly picked up at birth, follow up patients still showed residual mental retardation compared to the controls. Causes were thought to be delay in diagnosis, starting the treatment or non-optimal replacement therapy. From 2003, higher starting doses were recommended in the guidelines. In a systematic review [25], reviewers summarized outcome studies firstly, in CH vs. controls and secondly, in mild vs. severe cases of CH. Then, they reported results on the outcome differences between levothyroxine treatment variations and developmental outcomes. Six research groups reported on intelligence outcome with starting dose of levothyroxine, while eight reported that of the circulating thyroid levels. Most studies came up with higher doses and levels in the first year of life with improved later-life intelligence. As some studies also reported

negative associations with higher doses/levels, the jury is still out on what is the optimum starting and maintaining dose! However, high dose thyroxine replacement does not seem to affect somatic growth in any negative way at least between 3 months to 3 years of age [26].

Since its existence in the last 25 years, more than 150,000,000 newborns have been tested and around 42,000 are detected. Anecdotal estimate predicts that one million newborns are tested yearly and 2800 detected annually. New programs are being established regularly in developing countries. Mexican experience is a good one. The American Office of Technology Assessment concludes that screening for congenital hypothyroidism is one of the few programs in preventive medicine that has an impact on public health with a positive cost to benefit ratio (10:1). This is cited in the anecdotal history of screening for congenital hypothyroidism for the special issue of December, 1999 in the Journal of clinical Endocrinology and Metabolism by Dussault.

Early-treated CH is associated with mild delays in several basic achievement areas (reading comprehension and arithmetic) at the third grade level, with catch up by the sixth grade. However, as other findings indicate cognitive problems do persist into adolescence in memory, attention, and visuospatial processing areas, the implications of these deficits for other educational accomplishments needs additional follow-up. Congenital hypothyroidism, thyroid hormone, newborn screening, achievement, behavior, attention etc. [15] should all be focused during such long term developmental follow up of the early treated CH group.

The cognitive functioning, motor skills and behaviour of 5-year-old children with early-treated congenital hypothyroidism was assessed. In the North Thames Region in London, UK, they have studies 57 children between 1978 and 1881 comparing them with 51 non-affected controls. CH group had significant motor deficits, particularly in body balance and there was correlation with the severity of CH. These findings probably suggest early impairment of the vestibular system despite the early intervention [27].

Let us therefore, take a look at the evidences available to date on the relationship between fetal development, brain maturation and growth and thyroid hormones. Studies on the role of maternal thyroid hormone on early fetal brain, mostly done on the west, suggest maternal low thyroid hormone state is potentially neurodevelopmentally damaging throughout pregnancy! This effect is most pronounced during gestation. These studies suggest that many cases of learning disabilities may be prevented by the simple advice of iodine supplementation peri-conception [6].

Currently, although newborn screening programs can help minimize effects of cerebral damage, research shows that normal motor or cognitive skill attainment may still be a far cry from the irreparable *in utero* damages from CH. Even when some children started their thyroid replacement by a mean of 23 days of age, particularly children with thyroid agenesis as the underlying cause, showed significant motor problems and borderline intelligence levels by 9½ years of age. With adequate replacement, language and memory seem to be maintained, while balance and gross motor functions tended to decline between 7½ to 9½ years of age. But sooner the replacement was started, quicker the motor scores and performance IQ scores improved on [28].

For optimum neurodevelopmental outcome, the correlation with the faster time of normalization and initial levothyroxine dose must be noted. To achieve these goals, it is important to choose a higher initial dose in severe CH [29].

## Conclusion

Yasmin's son should have been picked up by Newborn Screening- at least his CH should not have been missed! But, we are acutely aware that we keep missing many such children. A look at all the Evidence painstakingly gathered by scientists throughout the globe shows amply that we cannot afford to miss CH. It is easily detectable, cheap and there is easy treatment for it. If adequately treated, the results are gratifying and of lifelong benefit. Despite of treatment, the intra uterine effects may be impossible to eradicate [6]. But we can eliminate most of the curses of a delayed diagnosis and inefficient handling with the available resources, to which we remain duty bound to strive.

## Key Learning Points

- CH must be picked up at birth or as soon as possible thereafter.
- Even Raised TSH should be protected with treatment and follow up for 2-3 years.
- Paediatricians should know about the developmental consequences of CH and should familiarize themselves with Early Detection of DD.
- Early Detection of DD has the potential to lead to desirable Early Intervention. Cognitive drop can be prevented, if treatment is started within 14 days of birth.
- Physicians must not relinquish their clinical judgment and experience in the face of normal newborn thyroid test results. Hypothyroidism can be acquired after the newborn screening. When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum free thyroxine and thyroid-stimulating hormone determinations should be performed [12].
- Until further evidence arrives, initial high dose replacement should be started based on the currently available evidence.
- Starting dose per kilogram of body weight should be clearly documented.
- Child should be monitored through the childhood to identify negative outcomes of a high dose replacement regime and expert help should be sought for early at that stage.
- Paediatricians should be aware of such expert centers in their locality and should access such facilities judiciously and rationally as otherwise, the consequences to the child could be life-long.
- Early detection CH is rewarding. Early detection of DD in CH is rewarding. Early Intervention and Expert Intervention in CH and DD in CH are both gratifying. But the price of acting in time by the professional may have to be borne by the subtly suffering child, for whom the suffering may not be so subtle and may be life-long.

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