Long-term follow-up of children born with sporadic congenital hypothyroidism

J. Rovet
Department of Pediatrics, University of Toronto Senior Scientist, The Hospital for Sick Children, Toronto, Canada.

Congenital hypothyroidism (CH) is a pediatric endocrine disorder of newborns caused by a failure in the production of thyroid hormone (TH), an essential hormone for early brain development. Formerly a leading contributor of mental retardation due to delayed diagnosis and treatment, CH is now identified at birth through screening programs and so has much milder consequences. In my presentation, I will describe:

a) the persisting neuropsychological sequelae despite screening,
b) related mechanisms,
c) four systems that account for the present phenotype.

THE CURRENT STATUS OF CONGENITAL HYPOTHYROIDISM

Sporadic congenital hypothyroidism affects between 1 and 3000 to 4000 newborns due to a loss of thyroid tissue. This can result from an absent gland or athyrosis or a gland that is ectopic or hypoplastic, known as thyroid dysgenesis. It can also result from a gland that does not function properly or thyroid dyshormonogenesis. Some of the genes contributing to dysgenesis and dyshormonogenesis have recently been identified.

CH is well noted for its characteristic facial dysmorphism (i.e., the cretinoid appearance), poor growth, and mental retardation. Such characteristics arise if treatment is delayed for several months after birth, which was a common occurrence due to the delayed appearance of the outward physical symptoms of CH. As a consequence of late treatment, the majority of children with CH suffered permanent and extensive brain damage. However over the past several decades, newborn screening for CH has allowed for much earlier diagnosis such that affected children are now treated shortly after birth, within the critical period to prevent mental retardation. As most children now attain normal physical development and IQ levels within the normal range, newborn screening for CH represents one of the most significant medical achievements of the 20th century.

Nevertheless, children with CH-treated early due to screening are still at risk for subtle and selective intellectual impairments. A recent meta-analysis of the principal CH follow-up studies found a 7-point decline in IQ compared to unaffected controls. Generally, the best outcome occurs in children who:

a) have the least severe presentation of this disease,
b) received prompt and adequate treatment,
c) are compliant with therapy. Their deficits are as a rule not global but rather selective for skills within the visuospatial, sensorimotor, and language domains.

These deficits also contribute to mildly poorer school achievement and, reportedly, less adequate educational accomplishments ultimately. In addition, the children with early-treated are also at increased risk for a variety of mild nonspecific behavioural problems.

The nature and severity of the cognitive deficits in children with CH reflect the complex interplay of factors associated with this disease and its management. These include:

a) fetal hypothyroidism,
b) disease etiology,
c) disease severity,
d) age at initiation of therapy,
e) starting and subsequent dose levels of thyroxine,
f) frequency and quality of subsequent management. In addition, some test results appear to be directly affected by the child’s ambient level of TH at time of testing.

Since 1981, we have been studying several groups of children with CH in Toronto, Canada. Our original cohort consisted of over 100 children born between 1976 and 1986 who were closely monitored by endocrinologists at The Hospital for Sick Children. We evaluated these children over a 15-year period extending from infancy to adolescence at regular, usually annual, intervals. Assessments included multiple age-appropriate neurodevelopmental examinations, detailed studies of psychoeducational functioning, and a thorough neuropsychological evaluation at adolescence. Siblings, classmates, and age- and gender-matched children from the community served as controls.
The findings revealed:
I. reduced IQ and a greater decline in IQ with age in CH than control participants,
II. poorer arithmetic abilities during the early school grades,
III. a pattern of neuropsychological deficits reflecting problems in visuospatial, language, and sensorimotor processing. The CH group also indicated selective problems within attention and memory domains and their attention difficulties reflected problems in focusing and shifting attention and their memory problems, difficulties with short-term memory and verbal encoding.

We have subsequently conducted a number of hypothesis-driven studies on children with CH born after 1986. In these studies, issues derived from our former longitudinal project were systematically evaluated. CH participants were typically recruited through the community where they were managed by local physicians and pediatricians and seemed to receive an inferior level of care compared to those originally followed in our hospital. The particular studies, some of which are still ongoing, include:
I. examining multiple components of attention assessed using experimental tasks,
II. evaluating children’s memory using clinical and experimental memory tasks,
III. an electrophysiological study of memory in pre- and early adolescent children,
IV. a study of infant attention and memory,
V. an electrophysiological study of infant visual processing.

Our findings to date suggest that infants and children with CH show selective deficits in attention, memory, and visual domains. As a rule, their visual deficits correlate with parameters of prenatal hypothyroidism, memory deficits with parameters of postnatal hypothyroidism, and attention problems with concurrent TH levels.

**MECHANISMS UNDERLYING SPECIFIC BRAIN IMPAIRMENTS**

To identify the mechanisms contributing to the specific deficits in children with CH, we have turned to the animal and basic science literatures, which have shown that TH is essential for a variety of fundamental neurobiological processes. These processes include neurogenesis, neuronal migration, axon and dendrite formation, synaptogenesis, and myelination. TH functions by regulating essential brain genes, which vary as to type of function and age in pregnancy or postnatally when they need TH. For example, genes that are involved in neurite outgrowth need TH in the third trimester, whereas those that control the production of myelin need TH postnatally.

Of the two thyroid hormones manufactured in the thyroid, T4 is much more abundantly produced than T3. However, because T3 is the active hormone in the brain, this requires local conversion of T4 to T3 via the action of the deiodonase enzymes. As these enzymes are temporally and spatially regulated in the brain, this means that some structures will be protected from early TH loss, while others will be vulnerable. This suggests the potential for selective deficits in children with CH.

The action of TH on genes involves formation of a receptor complex between a thyroid-specific receptor and T3. There are four TH receptors, two with alpha subunits and two with beta. Generally, beta receptors up-regulate genes while the alpha receptors down-regulate them. These receptors are localized in different neural substrates at different times in ontogeny. Of relevance for children with CH, the beta-1 receptor is expressed prior to and shortly after birth in neural substrates important for visual processing, memory, and attention.

In addition to its role in structural brain development, TH is also critical for the development and functioning of neurotransmitter systems, which are important for the regulation of attention. This too has important implications for children’s cognitive functioning because abnormal TH levels at time of testing may lead to poor attention.

**MECHANISMS CONTRIBUTING TO DEFICITS IN CHILDREN WITH CH**

We propose that the pattern of deficit in children with early-treated CH reflects disturbances in four systems, which are each affected by a TH loss at different times in development. The first disturbance arises from a basic deficit in visual processing and is caused by a prenatal loss of TS. The second involves selective memory deficits and arises from developmental abnormalities in specific subregions of the hippocampus. The third reflects slow processing speeds due to reduced myelin production while the fourth concerns selective attention problems caused by abnormal TH levels at time of testing.

**The Visual System Deficit**

It is proposed that a disturbance in the visual system in children with CH arises from impairment in one of the two primary visual pathways, namely the magnocellular or dorsal visual pathway. This pathway involves a circuit that includes the thalamus, striate or occipital cortex,
and posterior parietal lobe, all of which are TH-dependent. Studies with both monkeys and patients with focal brain lesions as well as normal individuals tested with fMRI have shown that this pathway is responsible for such basic visual processes as contrast sensitivity as well as the processing of spatial, movement, and configural information. Disturbances along this pathway not only disrupt basic processes but also higher-order cognitive processes such as indexing, number skills, and global processing that depend on the integrity of this pathway. We hypothesize that in children with CH, this disturbance is manifested during prenatal life.

The evidence in support of this mechanism is based on several recent studies in our lab. In one study, contrast sensitivity development was assessed in infants at 3, 4.5, and 6 months using a procedure known as “the sweep VEP (visual evoked potential)”. In this procedure, infants fitted with electrodes over the occipital cortex watch the computer monitor as a series of striped bars that change rapidly in contrast (low to high) or spatial frequency (bar width) are shown. Using the Power Diva system, which deploys electrical activation data to identify the minimal level of contrast to see the bars (contrast sensitivity) or the highest spatial frequency before they no longer see the bars (visual acuity), we found that some 3-month old CH infants had a definite contrast sensitivity deficit. Affected children were those with the athyrotic etiology and most likely experienced TH insufficiency in utero.

In another study from our lab, adolescents with CH were given a variety of visuospatial tasks categorized as to involving dorsal pathway processes or ventral pathway processes. We found that the CH group performed significantly below controls on dorsal- but not ventral-pathway tasks and furthermore dorsal-task performance (but not ventral) was correlated with initial severity of hypothyroidism.

Overall then, these findings support the view that children with CH have a basic visual deficit in contrast sensitivity and that this deficit is associated with, if not causes, a deficit in visual spatial processing on tasks presumed to invoke the dorsal pathway. Furthermore, this deficit appears to be prenatal in origin.

System #2: Selective Memory Deficits
Animal studies suggest the hippocampus, which is integral for memory, requires TH for its proper development in the early postnatal period. Recent studies also indicate that expression of a gene important for synapse formation is reduced in certain regions of the hippocampus. Affected regions include the CA1 nucleus, which animal studies show is important for event learning, and the dentate gyrus, important for place learning. In contrast, the CA3 nucleus, which is important for associative learning, develops normally in hypothyroid rodents. Our research asked whether place and event memory deficits would characterize the memory problems of children with CH while associative learning would be unaffected. A supplementary goal was to determine whether deficits would be most evident in children whose hypothyroidism lasted the longest in infancy.

Using two memory tests, we compared 7-12 year old children with CH to normal controls. One test, the Children’s Memory Scale (CMS) assessed a wide range of memory functions, while the other, Everyday Memory Scale, involved a rating scale completed by parents. Children with CH scored significantly lower than controls on the General Memory Index of the CMS and differed most from them on the Dot Locations subtest, a measure of place memory, and Word Pairs, a measure of associative learning. In contrast, groups did not differ in recognizing faces or remembering story details. Furthermore, children with the lowest scores were those whose TSH levels took the longest to normalize. On the Everyday Memory Scale, children with CH indicated a significantly greater number of problems and their particular problems reflected their tendency to forget recent events, where things are kept, what they were told, and to do something. Thus, these results suggest that children with CH have selective memory impairments in areas of the hippocampus that are vulnerable to TH loss in the postnatal period.

System #3: Slow Processing Speeds
In rats, hypothyroidism is associated with reduced production of myelin, the sheath that surrounds neurons and is responsible for efficient neural transmission. This reduction reflects TH’s critical role in regulating two genes (myelin-basic-protein and myelin-associated-glycoprotein) that underlie myelin formation. Several brain structures including the cortex appear to need TH for myelination in the postnatal period.

We have observed that children with CH show sensorimotor deficits and these deficits are due to their slow processing speeds. Furthermore, the ability most sensitive to postnatal duration of hypothyroidism is sensorimotor performance. These findings therefore support a role for TH postnatally in the formation of myelin in the cortex.

System #4: Poorer Attention reflects Abnormal Thyroid Levels at Time of Testing
The fourth disturbance reflects TH’s activational role in brain function. It has been posited that TH acts as a “cotransmitter” to affect neurotransmitter regulation. We have found that children’s performance on atten-
tion tests does correlate with TH levels at time of testing and that both very high and very low TH levels are associated with poor attention.

CONCLUSION

In conclusion, early-treated CH results in far improved outcome from that seen in the prescreening era. However, affected children are still at risk for a variety of specific subtle neurocognitive impairments. Their particular impairments appear to reflect different neural systems, which are affected by a loss of TH at different critical times before and after birth. As these reflect different disease and treatment-related factors, our research suggests that in managing CH, it is imperative to start treatment as soon as humanly possible, use a dose of thyroxine that normalizes hormone levels as fast as possible, and follow the children regularly and closely throughout childhood and adolescence to ensure that TH levels are always in the normal range. Although some deficits are prenatal in origin, and so fixed, it is nevertheless critical to identify and remediate these deficits. This necessitates performing detailed evaluations on all children with CH, particularly those with athyrosis, and implementing programs to facilitate all areas of weakness. Close and mindful care of these children everywhere is necessary to ensure their best possible school attainments and life outcome.

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E-mail : Marie-Françoise.Tahon@pasteur-lille.fr