Congenital hypothyroidism: a clinical update of long-term outcome in young adults

Juliane Léger1,2,3,†
1Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Service d’Endocrinologie Diabétologie Pédiatrique, Centre de Référence des Maladies Endocrinienes Rares de la Croissance, F-75019 Paris, France, 2Université Paris Diderot, Sorbonne Paris Cité, F-75019 Paris, France and 3Institut National de la Santé et de la Recherche Médicale (Inserm), Unité 1141, DHU Protect, F-75019 Paris, France
†J Léger is now at Paediatric Endocrinology Department, Centre de Référence Maladies Endocrinienes de la Croissance, INSERM U 1141, Hôpital Robert Debré, 48 Bd Sérurier, 75019 Paris, France

Abstract
Congenital hypothyroidism (CH) is the most common congenital endocrine disorder. The early treatment of CH patients has successfully improved the prognosis and management of this disorder. Optimal treatment and management throughout the patient’s life, beginning in the neonatal period, are required to ensure long-term health. Affected patients should be offered assessments of associated medical conditions and provided with accurate information about their condition throughout their lives, but particularly during the transition from pediatric to adult services. This review provides a summary of current knowledge about the long-term outcomes of these patients and appropriate management into early adulthood. We carried out a systematic search of the Medline database to identify relevant articles. Despite major improvements in prognosis, the impact of CH is clearly not uniform, and management should take into account a broader range of relevant indicators, including CH severity, associated comorbid conditions and the adequacy of treatment during childhood and adulthood. The early diagnosis and management of associated medical conditions, and better educational strategies to improve compliance with treatment, should improve the long-term prognosis. Further studies are required to explore changes with aging.

Introduction
Neonatal screening programs for congenital hypothyroidism (CH), resulting in the early treatment of patients with CH, have been introduced over the last 40 years in most industrialized countries and have markedly improved neurologic and health outcomes. Primary CH is the most frequent congenital endocrine disorder. Central CH is much less frequent and not detected by most screening programs based on thyrotropin (TSH) determination. Permanent primary CH affects about one in every 3500 live births in most industrialized countries (1). Over the years, lower cutoff points for TSH levels have been adopted in screening programs, to make it possible to detect
additional mild forms of the disease, essentially with the gland in situ, and this has led to an increase in the reported incidence of CH (2). Thyroid dysgenesis is the most frequent cause of CH. It may take several forms, with some patients displaying ectopic thyroid tissue, which is frequently found at the base of the tongue, whereas other patients present athyreosis or hypoplasia of the thyroid gland. CH with a normally located thyroid gland is a heterogeneous group of conditions, currently accounting for 30–40% of all CH cases (3, 4). Hormone synthesis defects, due to genetic mutations generally inherited in an autosomal recessive manner, are usually associated with goiter development, whereas normal or hypoplasic glands classically result from a developmental defect, resistance to TSH acting at the level of the receptor or its signaling pathway, or unknown causes (5). In addition, hypothyroidism may be permanent or transient in about 30% of patients with a normally located thyroid gland. In such patients, the most common causes are iodine deficiency (the frequency of which varies considerably across the world), iodine overload, particularly in premature newborns treated in intensive care, and the transplacental passage of antithyroid antibodies or anti-thyroid drugs during pregnancy. TSH levels normalize rapidly in such cases, and most have normal TSH levels at recall examination. These newborns are frequently identified as false-positives during CH screening and they do not require L-thyroxine treatment. However, the half-life of maternal antibodies is 4–6 weeks, extending beyond the recall period, and the effects of iodine overload may last for over a month (1). L-thyroxine treatment is initiated if hypothyroidism is confirmed at the recall examination. Transient CH has also been linked to genetic defects, such as heterozygous DUOX2 mutation (6). Infants with such defects have a normally located thyroid gland and a heterogeneous clinical and biochemical syndrome. There is currently no way to distinguish infants with mild, transient hypothyroidism from those with true permanent hypothyroidism requiring life-long treatment; a re-evaluation of thyroid function is therefore required early in life (3, 4, 7, 8).

Isolated thyroid dysgenesis is generally a sporadic disease. However, three observations suggest a possible but as yet undetermined genetic basis: a higher rate of familial cases than would be expected by chance alone (>15 times higher) (9); minor morphological abnormalities of the thyroid gland in euthyroid first-degree relatives of patients with thyroid dysgenesis (10); and a high incidence of associated extrathyroidal malformations (11, 12, 13). Specific genetic forms of syndromic and non-syndromic thyroid dysgenesis and TSH resistance may be associated with mutations in the NK2 homeobox 1 (NKKX2-1 (OMIM 610978), brain–lung–thyroid syndrome), Forkhead box E1 (FOXE1, Bamforth-Lazarus syndrome), Paired box gene 8 (PAX8), NK2 homeobox 5 (NKKX2-5), TSH receptor (TSHR), and Gs alpha (GNAS, pseudohypoparathyroidism type 1A) genes (14).

Many studies carried out since the introduction of neonatal screening programs have described the outcome of patients during early childhood. However, little is known about the outcomes of these patients in adolescence and adulthood. We review here current knowledge about long-term outcome in young adult patients treated early for CH, and its impact on the clinical management of CH in individuals.

Cognition, behavior and socioeducational attainment

Severe cognitive impairment has long been known to be associated with persistent disease in patients with CH who are treated late or not at all. In series of patients studied before the introduction of neonatal screening, major differences in clinical characteristics were found between patients with different degrees of intellectual disability (15, 16, 17, 18) and about one-quarter of children with clinically diagnosed CH have overt neurodevelopmental deficits (19).

The prevention of neurological deficits through the early initiation of treatment during the neonatal period is one of the chief justifications for the screening of newborns and has greatly modified disease prognosis. With early and adequate treatment, intellectual disability has largely become a thing of the past and the mean intellectual quotient (IQ) is now about 20 points higher than in patients born before the screening (1, 19). However, several studies of patients born since the introduction of screening have reported subtle neurological deficits in some patients, reflecting subnormal cognitive and motor development during childhood and into early adulthood. Some children of school age have displayed minor deficits in psychomotricity, reaction time, memory and attention, and a delayed acquisition of language, but have progressed normally through the school system (20, 21, 22, 23, 24). By contrast, others have achieved lower levels of educational attainment during childhood and adulthood, mostly due to CH severity and treatment inadequacy (25, 26, 27, 28, 29). A subtle social disadvantage has been described in early adulthood (Table 1). However, this impairment has been found to
have little impact from a public health standpoint, as most patients are well integrated into society, and are either still in education or employed at least part time (29). The association between poor educational attainment, high disease severity, and inadequate treatment during childhood is consistent with a severe impairment or the absence of thyroid hormone (TH) action during specific time windows in brain development, including the late fetal and early postnatal period, leading to profound brain damage, with lower levels of neural cell migration and differentiation, synaptogenesis, and myelination (30). Such an association is also consistent with experimental studies showing the effects of chronic hypothyroidism on development (31). Overtreatment should also be avoided (32, 33). These results highlight the need for careful monitoring of treatment adequacy throughout childhood and adulthood.

Only minor behavioral differences between patients and the reference population have been reported (34, 35, 36). The higher percentage of CH patients than of their healthy peers still living with parents may reflect lower patient maturity and autonomy, as reported for young adult patients with chronic conditions of childhood onset (37). It may also reflect parental stress or the association of particular types of social behavior with personality disorders (38). For example, some young adults with CH present depressive moods or anxiety (39, 40), requiring psychological support and counseling.

The impact of CH is clearly not uniform, and decisions about the support required during childhood and adulthood should therefore take into account a broader range of relevant indicators, including CH severity, associated comorbidity, and treatment adequacy, together with the socioeducational status of the parents (8). A recent study of patients displaying a more rapid normalization of thyroid function during the neonatal period than reported during the first two decades following the introduction of screening has shown normal intellectual and motor development in the children at the age of about 10 years, with no subtle deficit (41). Further studies are required to explore changes with aging, to determine whether socioeducational disadvantages persist to the same extent if serum TH levels are normalized earlier and whether long-term thyroxine therapy can be optimized by better educational strategies.

In summary, despite the normal neurodevelopmental outcome observed for most patients with CH treated early, careful monitoring of cognitive, motor, and behavior development is crucial, particularly during childhood, to ensure the detection of any developmental disability requiring early intervention, thereby optimizing neuro- and sociodevelopmental outcomes.

### Neurosensory development

Hypothyroidism has long been recognized as a cause of hearing impairment. About 25% of patients with acquired hypothyroidism and 30–50% of patients with CH identified before the introduction of screening programs and treated late are thought to display hearing loss, which is partially reversed by TH replacement treatment (42, 43, 44, 45, 46). Hearing loss has also been reported in cases of endemic cretinism (47), in patients with TH resistance (48), and in patients with TH monocarboxylate transporter 8 (MCT8) abnormalities (49).

Permanent sensorineural hearing loss has been reported in patients with unscreened CH, whose treatment began late, and even in some patients treated before the age of 6 months but outside the neonatal period (44, 50, 51). Hearing impairment has been associated with...
all etiologies of CH, including thyroid dysgenesis and dyshormonogenesis (50, 51). Only a few studies have focused on CH patients identified since the start of screening programs and treated early, other than those with Pendred syndrome, who have the Mondini-type malformation of the cochlea typically resulting in severe hearing impairment (52). Conflicting results have been reported for these patients during childhood, with some studies reporting hearing impairment (53, 54, 55, 56, 57) and others reporting no such impairment (54, 58). One study investigated 12 older patients, at the age of 20 years, and suggested that auditory processing abnormalities persisted in these patients (59).

In our nationwide study of 1202 young adult patients, we have recently shown that, at a median age of 23.4 years, a significantly larger proportion of the CH population than of the general population reported having hearing impairment (9.5 vs 2.5%) and that the risk of developing hearing impairment was more than three times higher in these patients than in the reference population (29, 60). Hearing loss was mostly detected during childhood, at a median (23–75th percentile) age of 7.0 (3.4–19.0) years and 17% of the patients who declared hearing impairment at a median age of 23.4 years had required a hearing aid since a median age of 10 years. Hearing loss was mostly bilateral, mild to moderate, of the sensorineural type and concerned principally high frequencies. Hearing loss was associated with the type of CH, patients with athyreosis and gland in situ being more frequently affected than those with an ectopic thyroid gland. It was also associated with disease severity, as assessed by bone maturation delay at the time of diagnosis. The patients with comorbid conditions or visual impairment were more frequently affected by hearing loss (Table 2).

Several experimental studies have shown that the induction of CH in utero results in impaired maturation of the sensory epithelium of the inner ear, and that there are periods of sensitivity to THs during the later stages of cochlear development (61, 62). The severity of the lesions was found to depend on the timing of antithyroid drug treatment initiation in the pregnant animals. Extrapolation from experimental studies suggests that this critical period corresponds to the period between the end of the first trimester of pregnancy and the end of the first month of life in humans (63, 64, 65). It has been shown that the complex process of cochlear differentiation is regulated by the amount of T3, which is locally controlled by type 2 and type 3 deiodinases and by TH transporters (66, 67, 68, 69). However, middle ear defects (immature ossicles, otitis) may also be involved (70), albeit to a lesser extent, together with cochlear defects, in the hearing loss observed in developmental thyroid disorders, potentially accounting for the occurrence of conductive or mixed hearing loss in some cases (60).

### Table 2

Hearing loss according to the type and severity of CH (adapted from reference (60)).

<table>
<thead>
<tr>
<th>Etiology of CH</th>
<th>No hearing impairment</th>
<th>Hearing impairment</th>
<th>Crude RR* (95% CI)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic gland</td>
<td>601 (95%)</td>
<td>34 (5%)</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Eutopic gland</td>
<td>136 (85.5%)</td>
<td>23 (14.5%)</td>
<td>2.70 (1.64–4.45)</td>
<td></td>
</tr>
<tr>
<td>Athyreosis</td>
<td>293 (86%)</td>
<td>47 (14%)</td>
<td>2.58 (1.69–3.93)</td>
<td></td>
</tr>
<tr>
<td>Bone maturation at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at knee epiphyseal ossification centers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both present</td>
<td>324 (94%)</td>
<td>21 (6%)</td>
<td>1</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>One present/one absent</td>
<td>267 (91%)</td>
<td>27 (9%)</td>
<td>1.51 (0.87–2.61)</td>
<td></td>
</tr>
<tr>
<td>Both absent</td>
<td>253 (86%)</td>
<td>41 (14%)</td>
<td>2.29 (1.39–3.79)</td>
<td></td>
</tr>
<tr>
<td>FT4 at diagnosis (pmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>597 (90%)</td>
<td>69 (10%)</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>≤ 5.0</td>
<td>357 (93%)</td>
<td>27 (7%)</td>
<td>1.47 (0.96–2.26)</td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>487 (94%)</td>
<td>31 (6%)</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Present</td>
<td>563 (88%)</td>
<td>76 (12%)</td>
<td>1.99 (1.33–2.97)</td>
<td></td>
</tr>
<tr>
<td>Associated chronic moderate to severe disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1008 (92%)</td>
<td>89 (8%)</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Present</td>
<td>43 (70.5%)</td>
<td>18 (29.5%)</td>
<td>3.64 (2.35–5.62)</td>
<td></td>
</tr>
<tr>
<td>Neurologic or mental disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1026 (91%)</td>
<td>100 (9%)</td>
<td>1</td>
<td>0.023</td>
</tr>
<tr>
<td>Present</td>
<td>25 (78%)</td>
<td>7 (22%)</td>
<td>2.46 (1.25–4.87)</td>
<td></td>
</tr>
</tbody>
</table>
Late-onset and progressive mild congenital hearing loss should therefore be considered in this population, because, with the exception of Pendred syndrome, hearing impairment is currently undetectable in neonates with the screening methods available (71). Some of the hearing loss observed in patients with CH is probably mild congenital progressive hearing loss that does not become severe enough for detection until early childhood.

In summary, hearing loss remains a significant problem, particularly in patients with severe CH, in whom predominantly sensorineural but also conductive deficits are frequently reported. These findings illustrate the need for early and regular evaluations of hearing acuity, beginning before the child starts school and continuing throughout childhood and early adulthood, and for careful follow-up, taking the child’s individual risk indicators into account (8). Indeed, hearing loss may be one of the many factors hindering normal psychomotor development, particularly as it may impair the understanding of speech and language development and hinder social interactions (55, 72). Parents, patients, and primary care providers should be aware of this risk, as early diagnosis and intervention could improve the long-term prognosis of these patients. Additional longitudinal studies are required to determine whether hearing deteriorates further later in adulthood.

In our French nationwide study of 1202 young adult patients, the proportion of subjects reporting visual impairment was higher for the population of CH patients than for the general population. However, such deficits appeared to be a less pronounced problem than hearing deficits in this population, with 55% of patients declaring visual problems, vs 48% of the general population (29). Visuospatial problems have also been suggested in some small series of patients (73, 74). The careful assessment of patients for visual problems is therefore suggested (8).

Associated malformations, chronic diseases, and cardiovascular health

Reviews of several databases have shown that CH is associated with an increase in the risk of associated malformations, with high proportions of renal and heart abnormalities, including septal defects, potentially accounting for some of the associated chronic diseases (11, 12, 13, 75, 76, 77).

Comorbidity with associated chronic diseases has been little investigated in children and young adult patients with CH and in older unscreened patients, in whom CH management focused principally on mental retardation. However, cardiovascular abnormalities have long been known to occur in patients with untreated hypothyroidism. A slight increase in cardiovascular risk factors was found in a small group of young adult patients with CH and impaired diastolic function, low exercise capacity, and a larger than normal intima-media thickness. However, few studies have focused on cardiovascular changes, and most of the existing studies concerned treatment inadequacy (78, 79).

We have recently shown that, at a median age of 23.4 years, a significantly larger proportion of the CH population than of the general population reported having other moderate to severe chronic diseases (5.7 vs 2.9%), and that patients with CH had a risk of developing a chronic disease twice that of the reference population (29, 77). Half of the health problems reported were due to neurodevelopmental disorders, which were diagnosed at various ages, from the neonatal period to late adolescence. They were heterogeneous and mostly described as encephalopathy, epilepsy or, psychiatric disorders associated with a moderate to severe psychomotor delay. Brain imaging data were available for only a few patients, which showed abnormal demyelination lesions and brain atrophy. The malformations and chromosomal abnormalities observed in this cohort included congenital heart defects, cleft palate, Down’s syndrome, and Di George syndrome. Congenital malformations were found to be more frequent in patients with athyreosis than in the other patients (77). Several chromosomal or gene abnormalities have been reported in such patients before, highlighting the heterogeneity of the developmental abnormalities observed in CH, which remain unexplained in most cases (11, 80, 81, 82). However, factors known to be associated with disease severity at diagnosis or inadequacy of treatment during follow-up were not found to be the risk factors for the disorders characterized by abnormal neurodevelopment (77). TH transporters are required to facilitate the cellular uptake and efflux of TH and are, therefore, essential for correct TH metabolism and function, at several sites of action in the brain. The devastating neurological symptoms of humans with inactivating mutations of the gene encoding MCT8, the TH transporter, are well known (83). None of the patients we studied had the typical biological profile of this rare disease, which is observed only in male patients, but there may be other as yet unknown molecular mechanisms facilitating TH access to the developing central nervous system (84, 85). It also remains possible that currently unknown underlying diseases associated with CH and increasing the risk of neurodevelopmental disorders will...
be identified in the future. Despite the severity of these disorders, the underlying cellular mechanisms remain largely unexplored. Experimental studies, based on TH deprivation in specific areas of the brain, for example, may make it possible to dissect the molecular mechanisms underlying the neurological symptoms of human TH deficiency.

In summary, although the prognosis of patients with CH has improved considerably over time, mostly due to early neonatal management, unfavorable outcomes are still observed in a small subset of patients born in the first decade after the introduction of the screening program and evaluated into early adulthood. The mechanism underlying the increase in the risk of neurodevelopmental disorders in these patients remains unclear. However, the small proportion of severely affected CH patients with major neurological abnormalities, status epilepticus, or severe cognitive impairment remains a matter of concern. A thorough physical examination should be carried out for all neonates and children with CH, to identify any underlying malformations/dysmorphic syndromes or neurodevelopmental disorders (8). Additional careful analyses of the phenotype presented are required for the definition of possible new syndromes, at least in some cases, and for the development of appropriate guidelines for the care and management of these patients throughout their lives.

**Growth, puberty, and fertility**

TH influences bone maturation during fetal development, but has no effect on fetal growth. However, it becomes essential for both normal growth and normal bone maturation during the postnatal period. Hypothyroidism decreases growth velocity, retards bone maturation, and compromises height growth if left untreated. Early and appropriate treatment during childhood and adolescence prevents the deleterious effects of TH deficiency on growth and bone maturation (86). Several studies on patients treated early for CH have reported normal height growth during childhood and normal adult height, with no effect of initial CH severity on adult height in either sex (87, 88, 89).

Hypothyroidism has long been recognized as a cause of impaired puberty and fecundity. Some affected children display precocious puberty, with macro-orchidism in boys, without excessive virilization, and bilateral ovary enlargement with multicystic ovaries in girls. This is consistent with a role for TSH in the pathophysiology of hypothalamic–pituitary axis activation, probably through interaction with the FSH receptor (90). Another pathogenic mechanism has also been proposed, involving the regulation of TH receptors’ mRNA expression by T3 observed in both testicular and ovarian cells (91). However, most of these abnormalities either improve or normalize with L-thyroxine treatment, after the restoration of a euthyroid state (92, 93). In the population-based study of CH patients in France treated early in life, mean age at menarche was similar in the CH and control groups (13.1 and 13.0 years respectively), and consistent with national data for the general population. There was also no difference between the two groups in terms of the pattern of menstruation in patients not using hormonal contraception. There was also no evidence of generally lower fecundity in a cohort of patients treated early through the CH screening program. However, disease severity was found to be associated with slightly lower fecundity in women, suggesting a possible impact of severe hypothyroidism on the reproductive tract during fetal development (94).

In summary, optimal treatment is essential for normal growth, puberty, and fecundity. The possibility of mild subfertility in women with severe CH may have clinical implications and investigations of ovarian function should be offered to this subgroup of patients.

**Table 3** Summary of studies on BMI in patients with CH.

<table>
<thead>
<tr>
<th>References</th>
<th>Year of birth</th>
<th>Median age (years) at the time of the study</th>
<th>Number of patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(88)</td>
<td>1981–1984 (Italy)</td>
<td>17</td>
<td>55</td>
<td>More frequently overweight</td>
</tr>
<tr>
<td>(95)</td>
<td>1983–1994 (UK)</td>
<td>10</td>
<td>53</td>
<td>Mean BMI: 1.1 SDS</td>
</tr>
<tr>
<td>(97)</td>
<td>1984–2001 (Greece)</td>
<td>At various age</td>
<td>152</td>
<td>BMI significantly higher than Greek reference population during the first 4 years of life</td>
</tr>
<tr>
<td>(29)</td>
<td>1978–1988 (France)</td>
<td>21.5</td>
<td>1012</td>
<td>Overweight or obese: 22.8 vs 15.7% (CH vs French reference population)</td>
</tr>
<tr>
<td>(96)</td>
<td>1990–2005 (Taiwan)</td>
<td>7</td>
<td>90</td>
<td>Overweight or obese: 32.2 vs 21.4% (CH vs Taiwanese reference population)</td>
</tr>
</tbody>
</table>

www.eje-online.org
**BMI, body composition, and bone health**

Early adiposity rebound has been reported in children with CH, and the proportion of overweight or obese subjects is greater for CH patients during childhood and young adulthood than for the general population (Table 3) (29, 88, 95, 96, 97). Lifestyle interventions, including diet and exercise, should be encouraged in individuals with CH (8).

THs have major effects on bone remodeling. Patients overtreated with thyroxine display higher levels of bone resorption than of bone formation, leading to progressive bone loss. Bone mineral density and body composition in children and young adults with CH seem to be within the normal range (41, 98, 99, 100). However, more long-term data are required for patients treated with the doses in current use.

**Metabolic and cardiovascular health**

Patients with CH have a higher risk of being overweight and, thus, of metabolic complications, than the general population. In addition to the higher risk of congenital heart malformations (12, 13), young adults with CH have a slightly higher cardiovascular risk, which may be related to inadequate treatment (79).

**Treatment adequacy**

In our observational study, we showed that only about 70% of patients with CH have adequate treatment in early adulthood. This inadequacy of treatment, with non-optimal follow-up or poor compliance with treatment in young adults, is reflected in uncontrolled hypothyroidism or, less frequently, subclinical hyperthyroidism (29). These results are consistent with the findings of several studies on adult patients treated for hypothyroidism, including, in particular, women in the period around conception and during pregnancy (101, 102). It should also be borne in mind that TH requirements increase during pregnancy, and most women on l-thyroxine treatment therefore require an increase in the dose administered during early pregnancy (103, 104). It is widely accepted that the optimal treatment of maternal hypothyroidism is important for successful pregnancy outcomes and good neurodevelopmental outcomes in the offspring (105). These findings for patients highlight the need for more appropriate thyroid disease management, and for vigilant monitoring and adherence to treatment, to decrease the impact of the disease on both mother and child.

Slightly negative consequences for the patients’ health-related quality of life, with concerns about mental performance and ‘vitality’, have been reported for young adult patients with inadequate treatment (29). This is an important point, given that abnormal thyroid function can influence mood, emotional and/or behavioral functioning, neurosensory, and metabolic and cardiovascular functions, thereby having a long-term effect on health and social functioning (106).

These relationships highlight the need for careful monitoring of treatment adequacy throughout childhood and adulthood. Educational strategies should therefore be used to improve long-term compliance with treatment and medical care, particularly during the transition from pediatric to adult services.

**Conclusion**

The successful newborn screening program for CH introduced almost 40 years ago has been shown to be the best way to prevent the deleterious impact of TH deficiency on the developing brain of affected individuals, and should be implemented worldwide. The optimization of care for CH patients treated early in life involves regular medical follow-up, with particular attention paid to related comorbid conditions and treatment adequacy. Differences in risk factors for some health and educational outcomes, such as CH severity at diagnosis, the presence of other chronic health conditions, and treatment adequacy throughout childhood and adulthood, have been shown, but further studies are required to explore changes with aging and to improve our understanding of the mechanisms underlying the full spectrum of the disease and associated medical conditions.

**Declaration of interest**

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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