



Iodine deficiency, thyroid function and hearing deficit: a review

Alida Melse-Boonstra^{1*} and Ian Mackenzie²

¹Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands

²World Health Organization Collaborating Centre for Prevention of Deafness, Child and Reproductive Health, Liverpool School of Tropical Medicine, Liverpool, UK

Abstract

Iodine deficiency affects an estimated 241 million school-aged children in the world. Little is known about iodine deficiency in relation to auditory function, except for the fact that deaf–mutism is one of the features of cretinism. In the present review, we documented the scientific knowledge on the role of iodine and hypothyroidism in the auditory system. We found that ear development and hearing function depend on thyroid hormones. Multiple pathways are involved in this, including both inner ear morphology as well as neurological processes. Conductive as well as sensorineural hearing loss is found in studies with animals that were rendered hypothyroidic. In humans, auditory impairment is reported frequently in relation to hypothyroidism, ranging from mild disturbances to severe handicap. Auditory impairment has been related more explicitly to congenital hypothyroidism than to acquired hypothyroidism. The critical period for thyroid function-related hearing maturation is the first and second trimesters of pregnancy. Although only a limited number of studies have directly investigated the relationship between iodine deficiency and auditory function, most studies point toward an association. However, evidence from good randomised controlled trials is lacking. Inclusion of auditory outcomes in iodine supplementation studies is therefore to be recommended, especially for trials in pregnancy. Hearing deficit is an invisible abnormality, but has major consequences for educational and social skills if not detected. In view of this, auditory impairment should be mapped in iodine-deficient areas in order to realistically estimate the magnitude of the problem.

Key words: Iodine deficiency: Thyroid function: Hearing deficit: School-aged children

Introduction

Iodine deficiency is still a significant public health problem in many countries throughout the world. It is estimated that in total 241 million school-aged children have some degree of iodine deficiency^(1,2), which forms a major threat to their developmental potential. It has been known for a few decades that an adequate iodine supply is particularly important during early life development^(3–5). Iodine deficiency, even when only mild to moderate, has repeatedly been found to be related to delayed or diminished cognitive development in children^(6,7). It has also been shown that the cognitive deficits related to mild-to-moderate iodine deficiency can still be reversed with iodine supplementation in children at school age^(8–10).

Impaired hearing function at an early age may well be linked to cognitive function and learning abilities in later life⁽¹¹⁾. A possible association between iodine deficiency and hearing function has not received much attention up until now, despite the fact that deaf–mutism is a

common characteristic of severe iodine deficiency in addition to mental retardation^(12,13). The fact that the auditory system is related to thyroid dysfunction was recognised over 100 years ago⁽¹⁴⁾. Increased prevalence of all forms of congenital deafness has been reported from areas that were renowned for a high prevalence of endemic goitre, such as the Alps, Himalayas and Andes⁽¹⁵⁾. An association between iodine intake and auditory function has been suggested by several authors^(16–19). Early studies have mostly focused on severe iodine deficiency in relation to deafness and deaf–mutism^(20,21). However, the effect of milder forms of iodine deficiency in the physiopathological mechanisms of hearing impairment is largely unknown.

With the present review we aim to document and critically review the scientific evidence for an association between mild-to-moderate iodine deficiency and hearing function. Since hypothyroidism is an important consequence of iodine deficiency and is the major mechanism of the iodine deficiency disorders, the role of the thyroid in the auditory system is included in this review.

Abbreviations: ABR, auditory brainstem response; Tg, thyroglobulin; TR, thyroid hormone receptor; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; UI, urinary iodine concentration.

*Corresponding author: Alida Melse-Boonstra, fax +31 317 483342, email alida.melse@wur.nl

Iodine and thyroid metabolism in a nutshell

Iodine is an essential component of the thyroid hormones triiodothyronine (T₃) and thyroxine (T₄). Iodine is taken up in the thyroid through the Na/iodide symporter. The thyroid of a healthy adult contains about 12–15 mg iodine, whereas in iodine deficiency this can drop to 20 µg⁽²²⁾. Iodine is oxidised by the enzymes thyroperoxidase and hydrogen peroxidase and then organified to tyrosyl residues in thyroglobulin (Tg). The hormone precursors iodotyrosine and di-iodotyrosine that are produced then couple to form T₄ or T₃, still bound to Tg. After Tg enters the thyrocyte by endocytosis, T₄ and T₃ are released into the circulation. Iodine uptake is regulated by thyroid-stimulating hormone (TSH), which is secreted at the pituitary. When iodine intake is low, increased TSH production stimulates expansion of the thyroid, resulting in goitre. Thyroid hormone receptors (TR), occurring as the two isoforms TR α and TR β , regulate thyroid hormone metabolism at the transcriptional level. TR genes encode nuclear receptors that can bind T₃, and transcription can be either activated or deactivated by TR⁽²³⁾. Both TR α and TR β are expressed in the cochlea⁽²⁴⁾, and both play a distinct role in auditory development^(23,25).

The auditory system

The anatomical and structural parts of the auditory system develop very early in pregnancy; the cochleae in the middle ear are largely ready by 15 weeks of gestational age and the auditory system becomes connected to the brainstem and temporal lobe of the cortex between 25 and 30 weeks of gestational age⁽²⁶⁾. The cochlea and the auditory cortex are most important in the developmental processes. Abnormalities in the hair cells of the organ of Corti result in sensorineural hearing loss. Conductive hearing loss is caused by obstructions in conducting sound waves; this can be anywhere along the route through the outer ear, tympanic membrane (eardrum) or middle ear (ossicles), for instance caused by the presence of ear wax or ear infections.

For the assessment of hearing loss, pure tone audiometry is the most commonly used method. It measures ear specific frequency thresholds and can distinguish between air and bone conductive hearing loss, the latter indicating a sensorineural cause. Since pure tone audiometry requires the cooperation of the individual assessed, it can only be used on adults and children that are old enough to understand the procedure and to respond. It requires careful calibration of the test environment and equipment. Over recent years, methods that measure hearing loss more objectively have been developed and are now widely used. Otoacoustic emission, which is a sound wave produced by the inner ear, can be measured non-invasively even in newborns. It is now used widely as a screening method for hearing loss in early life. Auditory brainstem

response (ABR) is another method used for screening and diagnostic testing of hearing that measures electric potentials in response to an auditory stimulus via electrodes placed on the head. Both methods are well tried and reliable. For otoacoustic emission, quietness is necessary and ABR testing takes time, but both tests are very accurate in establishing hearing thresholds. Event-related potentials, specifically the P300 wave, can be used to assess auditory information processing in the central nervous system and are also a reliable method for quantitative evaluation of auditory impairment.

Genetic factors, thyroid metabolism and auditory function

Various genetic disorders indicate that the auditory system is linked to thyroid metabolism. The most well known is Pendred's syndrome, an autosomal thyroid disorder that leads to goitre and sensorineural hearing loss caused by genetic factors^(27–29). Recent studies revealed that mutations in the solute carrier *SLC26A4* gene, which encodes for the protein pendrin, are responsible for Pendred's syndrome⁽³⁰⁾. An enlarged vestibular aqueduct has also been attributed to genetic mutations in the same gene^(31,32). Pendrin is an iodine transporter that is located on the apical cells of thyroid follicular cells, but also in the inner ear and the kidney⁽³³⁾. The functional change of the *SLC26A4* gene product has been suggested to result in abolished apical iodide efflux and organification⁽³⁴⁾, leading to a disturbance in thyroid hormone synthesis. However, the organification defect is only mild and only seems to result in hypothyroidism under iodine-deficient conditions⁽³⁵⁾. Therefore, it remains uncertain whether the sensorineural hearing loss associated with Pendred's syndrome is solely caused by hypothyroidism⁽²³⁾.

Another syndrome, characterised by resistance to thyroid hormone and also referred to as Refetoff syndrome, results in a high amount of circulating thyroid hormones and high urinary iodine excretion, due to the inability to take up hormones in target tissues. Deafness and hearing loss are among the many symptoms that have been reported in patients with Refetoff syndrome^(36–38). Mutations in TR β have been shown to be related to thyroid hormone resistance⁽³⁹⁾, and TR β has been found to be essential in auditory development⁽²⁵⁾. The thyroid β receptors localised in the cochlea are involved in auditory ontogenesis⁽⁴⁰⁾. Animal studies have revealed that TR α and TR β are not homogeneously distributed throughout the auditory system. Mice that are deficient in TR β (TR β ^{-/-}) have impaired evoked auditory brainstem potentials⁽²⁵⁾.

It has been found that the expression of mRNA of 5'-deiodinase type II, which is responsible for the conversion of T₄ to the active T₃ form, increases in the auditory pathways after induction of hypothyroidism in rats⁽⁴¹⁾. Later studies have revealed that the most important transcriptional factor for prestin, the motor protein of outer

hair cells in the cochlea, is regulated by thyroid hormones⁽⁴²⁾ and by TRP⁽⁴³⁾. In addition, it has been shown that *Kcnq4*, a gene encoding an outer hair cell K channel protein, is regulated by TRα1⁽⁴³⁾, and that thyroid hormone regulates the expression of genes related to outer hair cell function, such as *Tectb*⁽⁴⁴⁾. The *Duox2* gene is responsible for the production of H₂O₂, which is an essential cofactor in the production of thyroid peroxidase needed for the incorporation of iodine into Tg. Mice with the *Duox2* CV674G mutation have been shown to have dyshormonogenesis and 50–60 dB higher hearing thresholds in comparison with control mice⁽⁴⁵⁾. These findings indicate that thyroid hormones and their receptors are most probably involved in the auditory system through multiple pathways.

Congenital and acquired hypothyroidism, development of the auditory system and hearing function

Both non-genetic congenital and acquired hypothyroidism have been suggested to be causal to hearing loss^(46,47). In this section, the empirical evidence for this causality derived from animal and human studies is described.

Animal studies

In early studies in rats and chickens, *in utero* induction of hypothyroidism was shown to induce a delay in maturity and a degeneration of the sensitive epithelium of the inner ear, a distortion of the tectorial membrane, and the presence of acidophilic precipitates in the ductus^(48–53). For example, Meyerhoff⁽⁵⁰⁾ did a series of experiments in which guinea-pigs were experimentally kept hypothyroid during gestation in various ways. He found all hypothyroid animals to have elevated auditory thresholds using quantitative brainstem response as a physiological measure of auditory function. Morphologically, hypothyroid adult rats and their offspring showed alterations in the bone structure of the bullae, cochlea, as well as of the middle ear ossicles. The middle ear function relates to sound conduction, and morphological alterations can lead to conductive hearing loss. Other identified alterations included tectorial membrane distortion, inner and outer hair cell distortion, large dark staining lipid deposits of Hensen's cells, debris and acidophilic precipitate in the cochlear duct, and enlarged intracellular spaces in the stria vascularis. In general, Meyerhoff⁽⁵⁰⁾ found the audiological changes to be more severe in offspring than in the hypothyroid parent animals. Thyroid hormones and receptors were further shown to play an essential role in hearing maturation by others^(54–57), and it was demonstrated later that spiking activity of inner hair cells is under the control of thyroid hormones⁽⁵⁸⁾. In addition, thyroid hormones have been suggested not only to be necessary for the maturation of the cochlear organ but also of the central auditory areas^(24,59). It is also worthwhile

mentioning that exposure to polychlorinated biphenyl during fetal development impairs auditory function in rats⁽⁶⁰⁾. Polychlorinated biphenyls are pollutants that share structural features with thyroid hormones and can interfere with the endocrine system^(61–63).

Dussault & Ruel⁽⁶⁴⁾ found that experimentally induced gestational hypothyroidism in rats led to permanent auditory impairment as measured by ABR in offspring at age 200 d. Similarly, Goldey *et al.*⁽⁶⁵⁾ showed that gestational hypothyroidism in rats at various gradations led to diminished and delayed responses to noise stimuli in offspring, measured as startling response. Also, they found higher auditory thresholds with increasing severity of hypothyroidism which persisted even when rats reached adulthood. When hypothyroidism was induced postnatally beyond day 10, auditory impairment was no longer permanent as measured at the age of 120 d. Also, when T₄ treatment was given before day 10, permanent abnormalities were prevented⁽⁶⁴⁾. In contrast, Ritter⁽⁵¹⁾ reports an experiment in which 21-d-old chicks were exposed to propylthiouracil or radioiodine (¹³¹I). Only five out of 166 experimental animals had some degree of hearing loss ranging from 30 to 45 dB and all of these five animals had a middle ear infection that could explain the hearing loss⁽⁵¹⁾. It can also not be excluded that in these experiments findings were not due to hypothyroidism *per se* but to a secondary effect of the hypothyroidism-inducing agent (propylthiouracil) decreasing the conversion of T₄ to T₃.

In another experiment with rats, hypothyroidism was induced at various intervals during pregnancy and in the postnatal period, and distortion product otoacoustic emissions and auditory evoked brainstem responses were measured at regular timings⁽⁶⁶⁾. Results from this experiment showed that hypothyroidism from mid-pregnancy until the onset of hearing ability at postnatal day 12 led to elevated hearing thresholds (about 65 dB in offspring of hypothyroidic dams *v.* 25 dB in controls) and did not improve over time. Offspring of dams in which hypothyroidism was induced in early pregnancy (before the onset of the fetal thyroid gland) were not different from the offspring of dams with later induced hypothyroidism in terms of morphology of the cochlea and the organ of Corti, nor of hearing thresholds. This suggests that hearing impairment is not due to maternal thyroid hormone concentrations. Prolonged hypothyroidism up until postnatal day 28, however, resulted in morphological changes of the cochlea⁽⁶⁷⁾. Translation of these findings to the human situation would suggest that shortage of thyroid hormones due to iodine deficiency between 10 and 29 weeks of gestational age forms a critical time window for congenital hearing deficiencies⁽⁶⁶⁾.

Human studies

Various investigators have reported an association between thyroid hormone concentrations and hearing function in

humans. In 1956, Hilger⁽⁶⁸⁾ described various case studies in which hypothyroidism appeared to be related to hearing loss, which could be restored with T4 therapy. Bhatia *et al.*⁽⁴⁷⁾ found that of seventy-two hypothyroid patients, 43% had mild hearing loss as assessed by pure tone audiometry⁽⁴⁷⁾. Malik *et al.*⁽⁶⁹⁾ also report a higher degree of hearing loss in forty-five hypothyroid patients (age range 10–57 years) with decreasing concentrations of T3 and T4, or increasing concentrations of TSH. Based on a variety of auditory tests that their patients underwent, they conclude that hypothyroidism affects hearing function in various ways and may result in conductive as well as in sensorineural or mixed hearing impairment. Treatment with T4 resulted in improved hearing thresholds. In another study, four out of ten patients with mild congenital hypothyroidism had moderate or severe bilateral sensorineural hearing loss. The four patients with hearing loss were significantly older (22 *v.* 10 years) and had started later with levothyroxine treatment (17 *v.* 2.5 years) in comparison with the patients without hearing loss⁽⁵⁷⁾. Thornton & Jarvis⁽⁷⁰⁾ reported a higher frequency of hearing loss in a group of twenty-one hypothyroid individuals as compared with thirty-one controls. They speculate that the hearing loss may be caused by lower body temperature of the hypothyroid patients. However, they do not provide details on the body temperature measurements, nor did they control for thyroid hormone concentrations. Using event-related potentials, Ozisik & Arman⁽⁷¹⁾ found that the P300 latency was increased in twelve hypothyroid patients, indicating sensorineural hearing loss, as compared with twenty-seven controls.

Of forty-six patients with congenital hypothyroidism, half of the patients had loss of hearing function, of which five had severe or profound hearing loss⁽⁷²⁾. In a group of forty-five children with congenital hypothyroidism, nine were diagnosed with sensorineural hearing loss, and four of them were reported as having speech and language problems. After receiving a hearing aid, children were reported to improve in speech, language skills and behaviour⁽⁷³⁾. Debruyne *et al.*⁽⁷⁴⁾ reported that of forty-five paediatric patients with congenital hypothyroidism, 20% had some degree of deafness. Similarly, Rovet *et al.*⁽⁷⁵⁾ reported that among a group of seventy-five children with congenital hypothyroidism, 20% had persisting mild hearing impairment (either conductive, sensorineural, or both), whereas the prevalence was only 0.24% in the general paediatric population. Moreover, these children scored lower on various language tests until late in childhood, indicating delayed speech acquisition and difficulties in comprehension. In children with hearing impairment, L-thyroxine treatment had started somewhat later than in children with normal hearing function (day 22 *v.* day 13), indicating a critical window of thyroid hormone-dependent auditory development in the third week of life.

Hébert *et al.*⁽⁷⁶⁾ compared auditory function of thirty-six children with congenital hypothyroidism, who were

treated with T4 upon neonatal diagnosis, with twenty-four control children using ABR. They found significant auditory abnormalities in the treated hypothyroid children. François *et al.*⁽¹⁷⁾ did not find a difference in hearing thresholds measured by impedance audiometry between forty-two infants and children with congenital hypothyroidism on L-thyroxine treatment when compared with matched controls. Radetti *et al.*⁽⁷⁷⁾ compared the hearing function of nine children born to mothers who were treated with L-thyroxine for subclinical hypothyroidism early in pregnancy with that of nine control children at 9 months of age using ABR. They did not find any differences in hearing function between the two groups. Su *et al.*⁽⁷⁸⁾ found that hearing dysplasia was more prevalent among infants born to hyperthyroid mothers (5.6%; *n* 18) as compared with normothyroid mothers (0.5%; *n* 845) using ABR at 42 d and at 2 and 3 months of age. In the same study, no cases born to nine clinical or forty-one subclinical hypothyroid mothers were found.

Iodine deficiency and hearing function in children

Since thyroid hormones play such a critical role in various parts of the auditory system, it can be hypothesised that mild-to-moderate iodine deficiency may affect hearing function as well. In 1945, Wespi⁽⁷⁹⁾ described how the incidence of deaf-mutism in various Swiss cantons declined rapidly after the introduction of iodine prophylaxis in 1923⁽¹⁵⁾. Kochupillai *et al.*⁽⁸⁰⁾ found sensorineural hearing loss in eighteen out of ninety-three schoolchildren from a severely iodine-deficient village in Deoria district, India. Todd *et al.*⁽⁸¹⁾ report data on auditory function in mild-to-moderate iodine-deficient schoolchildren (*n* 43) living in Zimbabwe, not showing impairment of hearing thresholds. Valeix *et al.*⁽⁸²⁾ report data from French pre-school children (*n* 1222) aged 10 months, 2 years and 4 years. They found that hearing loss at 4000 Hz and at speech frequencies were more severe among children with urinary iodine concentration (UI) < 100 µg/l as compared with those with UI > 100 µg/l. The correlation between hearing thresholds and UI was *r* 0.10 (*P* < 0.02) at 4000 Hz and *r* 0.03 (*P* < 0.25) at speech frequencies. In a cross-sectional study conducted among schoolchildren in Iran (*n* 1045), Azizi *et al.*⁽⁸³⁾ showed that the prevalence of abnormal hearing function was 44 and 15%, respectively, in two villages where children had low UI, whereas the prevalence was 2% in a third village where children had close to normal UI. The mean hearing threshold was significantly increased in the village with the lowest UI (15.4 (SD 6.0) *v.* 13.2 (SD 3.2) dB (*P* < 0.005) and 12.4 (SD 2.1) dB (*P* < 0.001), respectively). A study in 381 Chinese children showed that iodine contents in hairs of children with perceptive nerve deafness were much lower than those of healthy children (*P* < 0.01)⁽⁸⁴⁾. A study among 150 Spanish schoolchildren showed an inverse relationship between the auditory thresholds at all frequen-

cies and UI in those with palpable goitre. Moreover, those with Tg values >10 ng/ml, a marker for possible iodine insufficiency, had higher auditory thresholds at all frequencies, and children with a thyroid size >95 th percentile had an OR of 3.86 (95% CI 2.59, 5.10) of having a threshold >20 dB⁽⁸⁵⁾.

Although an association between iodine deficiency and impaired hearing function has been found in most of the studies reviewed above, this does not provide sufficient evidence for causality. Only a few studies have directly investigated the effect of iodine supplementation on hearing function in humans. In 1985, Wang & Yang^(86,87) assessed hearing thresholds in a non-randomised controlled study among 120 schoolchildren living in either an iodine-deficient village or a non-deficient village in China. They found that 3 years after the introduction of iodised salt in the deficient village, hearing thresholds came down from 17.4 dB to 8.2% dB, which was almost similar to thresholds in the control village (7.5% dB). Azizi *et al.*, following up on their earlier study in which they found impaired hearing function in children from an iodine-deficient Iranian village⁽⁸³⁾, found that after iodised salt had been introduced in the area, the distribution of hearing thresholds made a clear shift towards lower values⁽⁸⁸⁾. Van den Briel *et al.*⁽⁸⁹⁾ reported auditory data from a randomised placebo-controlled trial (n 197) conducted in Benin, in which half of the children received an oral dose of oil with 540 mg iodine and the other half received placebo. After 11 months, auditory measurements were taken, which correlated with Tg concentrations at that time point (r 0.15; $P < 0.05$), but not with T4, TSH or UI. No comparison was made between treatment groups since iodised salt was introduced in the study area while the study was ongoing, thereby also exposing the placebo group to iodine.

Conclusion

In summary, the scientific literature indicates that ear development and hearing function depend on thyroid hormones through different pathways, including both inner ear morphology as well as neurological processes. Induced hypothyroidism in animals causes various auditory alterations, relating to both conductive as well as sensorineural hearing loss. In humans, auditory impairment is reported frequently in relation to hypothyroidism, ranging from mild disturbances to severe handicap. Congenital hypothyroidism has been related more explicitly to auditory impairment than acquired hypothyroidism. During critical developmental stages, shortage of T3 might fail to adequately stimulate hormone–receptor interaction in the corresponding auditory structures⁽²⁴⁾. In humans, the critical period for hearing maturation corresponds approximately to an interval ranging from the early embryonal period to the first year of postnatal life⁽²⁶⁾. Although the fetal thyroid is formed by 10–12 weeks of gestation, the

fetus remains dependent on maternal thyroid hormones through transplacental passage until the fetal thyroid starts to produce thyroid hormones at 16–20 weeks of gestation⁽⁶⁴⁾. Hypothyroidism occurring during this critical time window can lead to irreversible hearing impairment⁽⁶⁶⁾. However, when T4 therapy is begun early enough in life (<1 year), it might still successfully reverse hearing loss⁽⁵⁷⁾.

As described in the present review, only a few studies have evaluated associations between mild-to-moderate iodine deficiency and auditory function. The limited evidence does suggest that iodine deficiency is related to hearing loss, and that supplementation of iodine-deficient individuals may improve hearing thresholds. However, no solid randomised controlled trial was encountered in the literature to support this. Moreover, the effect of iodine deficiency on hearing function is likely to be largest during pregnancy. It would therefore be worthwhile to include auditory function as an outcome in studies investigating effects of iodine supplementation, especially during pregnancy.

Hearing deficit is a poorly reported disability as there is no physical abnormality⁽⁹⁰⁾. It is well recognised that the earlier hearing deficit is identified and managed, the more improved will be a child's educational and social skills⁽¹¹⁾. In areas of mild-to-moderate iodine deficiency, such as large parts of Europe, Asia and sub-Saharan Africa⁽¹⁾, auditory impairment due to hypothyroidism might exist. From a public health perspective, it would be helpful if the prevalence and severity of auditory impairment in relation to the degree of iodine deficiency were mapped in order to obtain a better view on the magnitude of the problem.

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