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Recovery of sensorineural hearing loss in congenital hypothyroidism

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Abstract. *Recovery of sensorineural hearing loss in congenital hypothyroidism. Introduction:* Congenital hypothyroidism (CH) may generate serious neurologic complications in children. Sensorineural deafness is one of them, but can be prevented with prompt hormonal substitution.
Case report: The unusual case of an infant with sensorineural hearing loss associated with severe CH is reported. The infant recovered after adequate hormonal substitution, with thyroid hormone (TH) administered as late as 8 months after birth. The role of TH in auditory function and the underlying mechanisms that can lead to hearing loss in CH are discussed.
Conclusion: This case illustrates the possible association between sensorineural hearing loss and severe CH. Systematic checks of thyroid dysfunction in newborns are important. Despite systematic screening, errors may occur in the transmission of the results, leading to severe complications. Fortunately, sensorineural hearing loss may be recovered after delayed but adequate hormonal substitution.

Introduction

Congenital hypothyroidism (CH) is defined as insufficient thyroid hormone (TH) at birth. It is the most common, preventable cause of mental retardation.[1] Hearing loss is another common and severe complication in humans.[2] In most cases, it is irreversible.[3]

An exceptional case of recovery of hearing in an infant with severe CH is reported. The infant received hormone replacement therapy with TH 8 months after birth. The literature about CH, TH deficiency associated with deafness, and mechanisms involved in CH is reviewed. To our knowledge, this is the first case where TH was started at 8 months and hearing was restored reported in the literature.

Case report

A 5-month-old girl was referred to the Ear Nose and Throat (ENT) department of Mont-Godinne at CHU UCL Namur for suspicion of moderate bilateral deafness.

Otoscopy revealed normal tympanic membranes bilaterally. Her tympanometry at 1000 Hz was normal (type A).

Behavioral audiometry (warble tone in free field for air conduction and with bone transducer for bone conduction, without masking) showed a response at 50 dB HL (decibel hearing level) in bone conduction for 0.5, 1, 2, and 4 kHz and between 60 and 80 dB HL in air conduction (Figure 1). Initially, we considered the possibility that her behavioral auditory response correlated to a neurological problem (she had poor interest and reaction to auditory stimuli) rather than to real hearing loss. But transient oto-acoustic emissions (OAEs) were absent on both sides, and auditory brainstem responses (ABR) confirmed moderate bilateral sensorineural hearing loss, with thresholds at peak V at 50 dB nHL (decibel normalized hearing level) on the left side and between 50 and 60 dB nHL on the right side (Figure 2).

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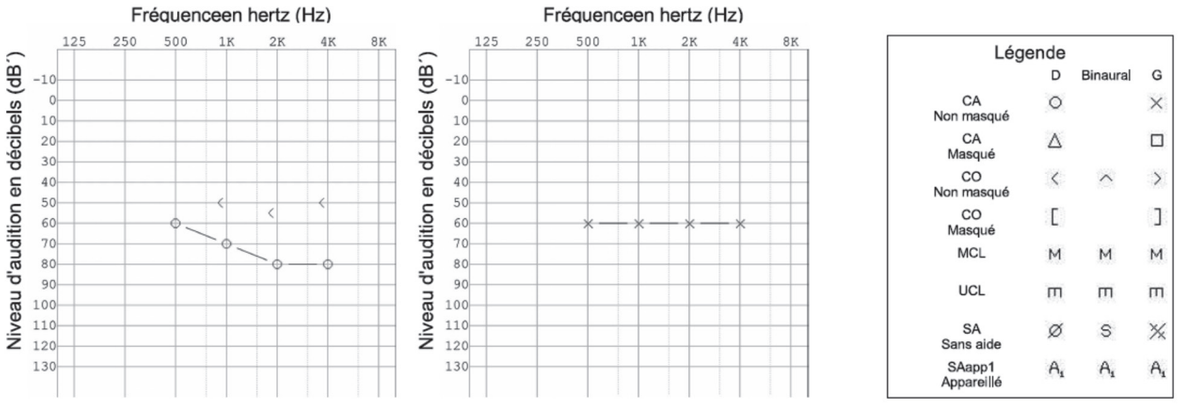

Figure 1

In pure tone audiometry at diagnosis, the unmasked bone conduction curve showed levels around 50 dB HL. In air conduction, at conversational frequencies, levels were situated between 60 and 80 dB HL on the right, and at 60 dB HL on the left.

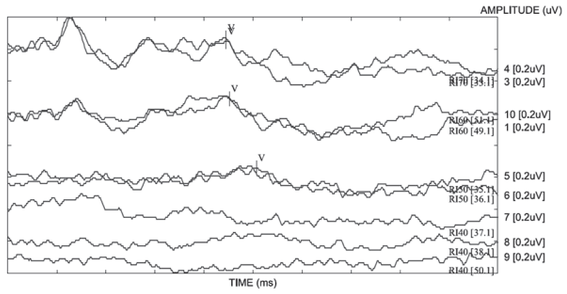

Figure 2

ABR at diagnosis confirmed moderate, bilateral sensorineural hearing loss, with thresholds at peak V at 50 dB nHL on the left side (L) and between 50 and 60 dB nHL on the right side (R).

Magnetic resonance imaging (MRI) that was ordered at the age of 6 months did not show malformation of the craniofacial joint, brainstem, or cerebellum or abnormal hemosiderin deposition. By comparison with the MRI performed at one week of age, the latter showed a lack of progress in the myelination of the internal capsule.

A trial with hearing aids was proposed (at 7 months of age) within a context of multidisciplinary rehabilitation in the Audiophonology Center of Mont-Godinne at CHU UCL Namur.

In the medical history, we noticed that the pregnancy was gemellary resulting from in vitro fertilization, with early death in utero of one of the two fetuses. The mother developed insulin-dependent diabetes of pregnancy and was hospitalized in the maternal intensive care unit for 1 month (at 32 weeks of pregnancy) for intra-uterine growth retardation diagnosed at 28 weeks of pregnancy.

The neonatal history of the girl was marked by birth at 41 weeks of pregnancy by planned cesarean due to a pathological stress test and lack of spontaneous labor. No neonatal instruments were used during the delivery and the baby was normal (Apgar score 9-10-10, weight 2.680 kg [P10], height 49.6 cm [P25-50], head circumference 32.6 cm [P10–25]).

At postnatal hour 10, the infant presented with hypotonia, metabolic acidosis, hypoglycemia, and cyanosis, requiring mechanical ventilation up to postnatal day 13 (P13). Her respiration evolved favorably thereafter.

Unfortunately, important neurological and digestive complications appeared, with major global hypotonia, encephalopathy, microcephalia, psychomotor delay, absence of sucking, as well as a marked digestive intolerance. Hirschprung disease was diagnosed and a colonosigmoidectomy was performed at P75.

A major arrest in her statural growth and head circumference was observed, while weight gain under enteral feeding was good. The fontanel remained wide and a myxoedema appeared.

Herneurologicalcheck-up(MRI,ultrasonography, and electroencephalogram) was unremarkable. Her cardiology check-up was reassuring, and her abdominal and urinary ultrasounds were normal as well as ophthalmoscopy. Her metabolic check-up demonstrated, amongst others, a normal CH neonatal screening (realized at P2) with a TSH level of < 15 µUI/ml.

Genetic testing was negative for Steinert's disease, Prader Willi Syndrome, and spinal

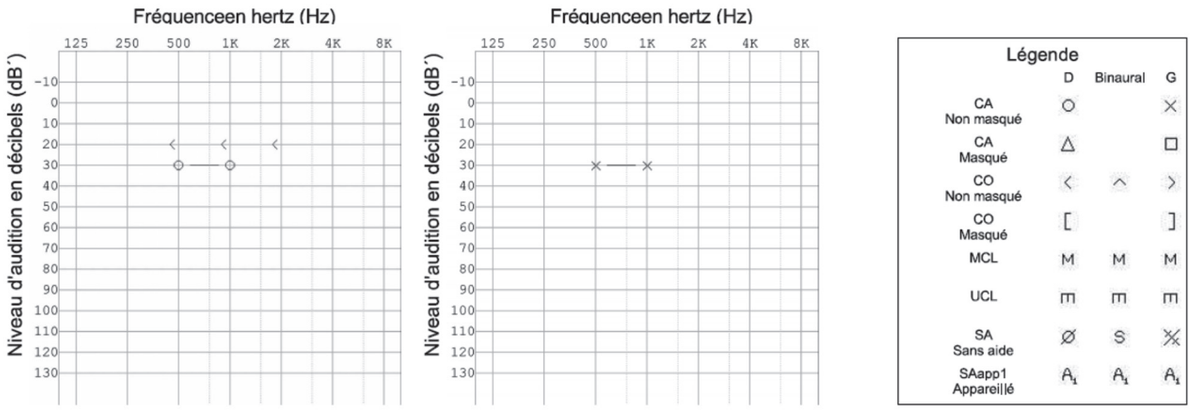

Figure 3
Hearing thresholds in pure-tone audiometry after 4 months of treatment were completely normalized.

amyotrophy. Array comparative genomic hybridization was normal. Searches for different gene mutations linked to severe encephalopathies, epilepsy, or mental retardation were negative.

The mother's medical history was marked by obesity treated with a gastric ring, hypercholesterolemia, and lactose intolerance. The father's history was marked by bicuspid aortic valve.

At 8 months, the child was transferred to the pediatric endocrinology department of Mont-Godinne at CHU UCL Namur, and a new thyroid function control was performed, which this time demonstrated severe CH, with levels of T4 of 0.7 pg/ml (8-20) and TSH of 384 µUI/ml (0.62-8.05). Consequently, TH replacement treatment with levothyroxine 50 µg per day (for 8 kg weight) was started immediately.

A check of the neonatal screening test with the laboratory charged with performing the analysis revealed a mistake in the written communication of the results; the TSH level had actually been 158 µUI/ml.

In the diagnostic workup of CH, thyroid ultrasounds demonstrated the absence of thyroid tissue in its normal position; this thyroid agenesia was considered the etiology of the severe CH.

After ten days of hormone substitution, the parents had already noticed marked behavioral changes. Globally, her neurological evolution became favorable with an improvement in psychomotor development, and the myxoedema quickly disappeared. An adjustment of the growth and head circumference were also observed. Concerning her digestive system, some difficulties remained that required continuing complementary enteral feeding and the implementation of a gastrostomy at 11 months.

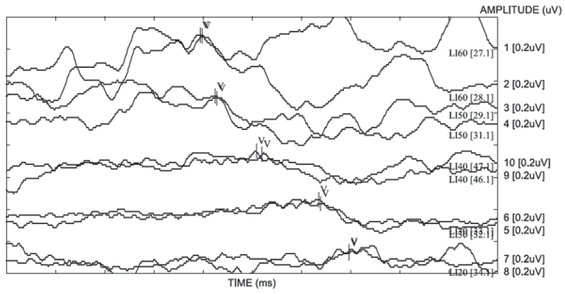

Figure 4
ABR after 4 months of treatment objectified a level of peak V at 20 dB nHL bilaterally (left [L] and right [R]).

As soon as hearing aids were installed at 7 months of age, the child's arousal and interest in sound was observed, and her babbling improved.

The child was then supported by a neurological daycare center and as a consequence, the multidisciplinary support in the Audiophonological Center was stopped after 2 months. Audiologic monitoring was, however, ensured by our ENT department.

After one and a half months of TH replacement treatment, hearing threshold testing in air conduction showed an improvement, with levels at around 50 dB HL. After 4 months of treatment (1 year age), her hearing thresholds were completely normalized in pure-tone audiometry (Figure 3). This was confirmed by ABR, which was reproducible and well structured, and objectified a peak V level

of 20 dB nHL bilaterally (Figure 4). The use of hearing aids was thus stopped. However, OAEs remained absent 2 months later. Unfortunately, they could not be controlled again later because the child was scared and agitated.

The little girl is currently 26 months old and is still being followed up in our ENT department. Her last hearing tests showed, in free field with an auditory orienting reflex method, thresholds in bone conduction at 20 dB HL and in air conduction at 30 dB HL (the tympanometry was type A). She still presents with a psychomotor development delay. Significant improvements, however, are observed in all fields.

Discussion

According to world-wide screening programs, permanent non syndromic congenital hypothyroidism has a rather constant incidence of 1:3000 to 1:4000 newborns, with a female predominance (2:1 to 4:1).[4] In most cases, this pathology results from abnormalities in thyroid gland development (2/3 ectopic thyroid, 1/3 athyreosis, and with hypoplasia being very rare), resistance to TSH binding or signaling, or a defect in thyroid hormone biosynthesis (normal or enlarged size of gland and normal position).[1,4,5] Some cases have a central origin caused by a pituitary or hypothalamic abnormality.[6]

Thyroid hormone deficiency at birth is sometimes transient due to transplacental passage of maternal medications or blocking antibodies or iodine rate disorders, but recovery is generally observed within the first few months of life.[1] Signs and symptoms are commonly underestimated and even unknown at birth, partly because of maternal TH transplacental passage during pregnancy. Typical signs and symptoms include prolonged jaundice, feeding difficulty, lethargy, distended abdomen with umbilical hernia, constipation, cold or mottled skin, hypothermia, hoarse cry, myxoedematous facies, large fontanels, macroglossia, and hypotonia. In 20% of cases, there is a history of prolonged gestation extending beyond 42 weeks.[6]

Most of the time, diagnosis is suspected via neonatal screening (systematically done in Belgium) including titration of TSH and an exhaustive thyroid assessment. The etiology is mainly ascertained by thyroid ultrasonography and sometimes by scintigraphy. Thyrotropin receptor-blocking antibodies are measured when there is a family history of CH to exclude a transient form of the deficiency.[1,5]

Syndromic CH or associated congenital malformations must be eliminated as well. Grüters *et al.* reported in 2002 that associated birth defects are significantly more common in CH compared to the general population. Half of them are cardiac abnormalities such as atrial and ventricular atrial defects.[4]

The recommended dosage for substitution starts with 10-15 µg/kg/day of levothyroxine by oral administration. The dose is then gradually increased depending on the serum measurement of T4 and TSH. The aim of this therapy is to normalize T4 within 2 weeks and TSH within 1 month, and to ensure normal growth and development by maintaining an optimal serum concentration of thyroid hormones.[1,4,5]

Nowadays, a relationship between the severity of CH and the start of treatment is clearly known with respect to the developmental outcome of the patient. The compliance of the patient or family is also essential for the maintenance of TSH levels and euthyroid status.[7,8]

Without an adequate replacement treatment or if substitution is delayed, long-term consequences are mainly neurodevelopmental deficits. Most of the time, retarded skeletal maturation is recovered after substitution, while those infants may still have a low-to-normal IQ or at least signs of minimal brain damage (impairment of arithmetic ability, speech or fine motor coordination).[1,5]

In addition to mental retardation, deafness is one of the long-term complications of CH. Rose *et al*. showed in 2006 that in 25% of the 27 children studied, auditory brainstem evoked potentials were abnormal, even in patients with CH who received early treatment.[1] In 1983, Vanderschueren-Lodeweyckx *et al*. showed that 20% of children with CH had sensorineural hearing loss to some degree, particularly those affecting the higher frequencies. The reasons for and outcome of this deafness are still under investigation.[2]

The importance of thyroid hormones in the development of the organ of Corti is clearly demonstrated. Indeed, a lack of TH leads to a defect in maturation of the tectorial membrane, with delayed differentiation of the inner sulcus; impaired nonlinear capacitance of the outer hair cells (OHC); reduced endocochlear potential; loss

of retarded expression of potassium current in the cochlear inner hair cells (IHC); and an altered neuronal connectivity to the IHC and OHC.[9,10]

A loss of distortion product otoacoustic emissions (DPOAEs, which reflects an active cochlear mechanism) is observed in animals with TH deficiency, which is explained by a reduction of β-tectorin in tectorial membrane proteins, which may cause the loss of active cochlear mechanisms.[11]

Thyroid hormone acts on gene transcription by binding to its nuclear receptors, TRα1 and TRβ, which are both expressed in IHC during critical periods of development of the organ of Corti.[12] In 2001, Rüsch *et al.* first confirmed the different roles of all TRs, but especially revealed the synergistic role of TRα1 and TRβ. In TRβ and TRα1 deficient rodents, the above-mentioned defects are more obvious than in only TRβ deficient mice.[9]

In 2015, Ng *et al*. demonstrated that through TRβ1, TH is also required in the maintenance of hearing after correct cochlear development.[13] Sundaresan *et al*.[10] (2016) demonstrated in a recent study the role of TH in pruning cochlear afferent innervation. Their study on mice with hypothyroidism focused on IHC afferent synapses. First, they concluded that the critical window of TH action is situated between P3 and P6 for presynaptic pruning, and up to P8 for postsynaptic pruning, which is preceded by presynaptic pruning. They also demonstrated that the excess synaptic puncta were not functional synapses, and that the subset of functional synapses was sufficient to generate normal calcium currents. They deduced from these data that TH was essential for pruning of synapses and activating the mechanisms involved in development of initial calcium current. Finally, they showed that TH was required for homeostatic maintenance of afferent synapses in adults, and that a lack of TH led to a reduction of GLAST protein expression in supporting cells, which could explain the glutamate excitotoxicity phenotype of the afferent nerve endings.[10]

Sohmer *et al.* (1995) as well as Sininger *et al.* (1997) have shown that in humans, the critical period for hearing maturation starts at the end of the first trimester of pregnancy and is over after one year of postnatal life.[14,15] Knipper *et al*. (2000) observed that short periods of TH deficiency in mice during the critical developmental period before the onset of auditory function resulted in permanent hearing impairment.[3] However, a recent study on rodents cast doubt on this interpretation; a TH-enriched diet improved the hearing deficits in mice with hypothyroidism and suggested that *"TH is not required for subsequent development of the organ of Corti but instead it determines the correct timing of the developmental progression. Thus, this feature seems unlikely to account for permanent hearing loss"*.[16]

We found no reports of similar cases in the literature. The recent study of Karoly, however, could provide some clues to explain why our case had a good result after thyroid hormone replacement treatment. TH determines the correct timing of the development of the cochlea rather than impacting the developmental steps per se. In this case, we can also consider that, on the one hand, the level of hearing loss (moderate) correlates with a partially functioning organ of Corti at birth. This is probably linked to the transplacental passage of the mother's TH (the development of the organ of Corti begins in utero). On the other hand, the recovery of hearing could be linked to the effect of TH on synaptic development and neuroplasticity (auditory maturation continues after birth). Finally, we can suppose there are perhaps some genetic factors that modulate the response of the auditory system to thyroid hormones.

Some questions remain to be clarified. We need to follow the evolution of this child and control the auditory tests, particularly those for pure tone audiometry at higher frequencies, speech audiometry, and OAEs. This will confirm and document the child's auditory recovery and perhaps, if anomalies are objectified, begin to answer questions concerning the role of TH in the auditory development of humans.

Conclusion

CH may generate serious complications in neonates. Because sensorineural hearing loss is part of these, all neonates with CH should have an appropriate hearing assessment and every child with unexplained sensorineural hearing loss should have a new titration of THs, even in countries were CH neonatal screening exists.

Hormonal substitution is the obvious treatment to prevent or decrease the severity of these complications. Its therapeutic effect and the patient's sustained compliance with this treatment must be closely monitored. Our case illustrates the

relationship between the levels of TH and hearing thresholds. Even hormonal substitution that is started late may normalize hearing thresholds that were pathologic at birth. Management of such patients by a multidisciplinary team as proposed in an audiophonology center is the best treatment option.

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