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Research paper

Even in the era of congenital hypothyroidism screening mild and subclinical sensorineural hearing loss remains a relatively common complication of severe congenital hypothyroidism

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ABSTRACT

Only few studies have focused on neurosensory hearing function of patients with congenital hypothyroidism (CH) identified by CH screening programs and treated early and, therefore, this issue remains still controversial.

The aim of this study was to ascertain whether an early and adequate replacement treatment may be able to prevent sensorineural hearing loss in 32 screened children with CH and no associated risk factors for neuro-otologic alterations. These patients were recruited according to highly selective criteria aiming to preliminarily exclude the negative interference of both treatment variables and other underlying risk factors. All the selected patients underwent, at a median age of 15.4 years, an audiologic investigation, which evidenced a mild and subclinical hearing loss in 25% of them. The poorest hearing scores were recorded in the individuals with athyreosis and in those with absence of distal femur bony nucleus at CH diagnosis. The prevalence of hearing impairment was significantly higher in CH patients than in 32 age-matched control subjects with no CH ($\chi^2 = 6.3$, $p < 0.025$).

In light of these findings, we concluded that: a) 25% of CH patients detected by CH screening may show, at a median age of 15.4 years, a mild and subclinical hearing impairment, despite early and adequate replacement treatment; b) the risk of hearing loss is higher in CH young patients than in age-matched control subjects without CH; c) the risk of hearing loss is closely associated with the severity of CH; d) this risk is particularly relevant in the children with pre-natal onset of hypothyroidism.

1. Introduction

An association between thyroid function disorders and impaired auditory function has long been recognized in patients with either Pendred syndrome (Bizhanova and Kopp, 2010) or thyroid hormone (TH) resistance (Brucker-Davis et al., 1996) or endemic cretinism (DeLong et al., 1985). Such association has been sporadically reported also in children and adolescents with central hypothyroidism (De Luca et al., 1985; Wasniewska et al., 2002) and, more recently, in patients with TH monocarboxylate transporter 8 abnormalities (Dumitrescu et al., 2004). Permanent sensorineural hearing loss has also been described in children with unscreened primary congenital hypothyroidism (CH) whose replacement therapy began late and even in some CH individuals treated before the age of six months but outside the neonatal period (Crifò et al., 1989; De Luca et al., 1986; Vanderschueren-Ladeweyckx et al., 1983).

Neonatal screening programs of primary CH, which have been adopted over the last thirty years in most industrialized countries, have generally resulted in the prevention of severe cerebral damage and a large decrease of morbidity in these patients. Nevertheless, some mild hearing abnormalities were found to be still common

Abbreviations: CH, congenital hypothyroidism; dB, decibel; FT4, free thyroxine; Hz, Hertz; LT4, L-thyroxine; TH, thyroid hormone; TSH, thyrotropin; χ^2, chi-square

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even in screened and early treated children with primary CH, although these abnormalities were much less severe than those detected before CH screening era (Bellman et al., 1996; Rovet et al., 1996). Even in the last few years subtle hearing problems concerning high or very high frequencies have been reported to be possibly observed in screened patients with primary CH (Léger et al., 2011; Lichtenberger-Geslin et al., 2013; Léger et al., 2014) and these findings highlight the need for careful monitoring of sensorineural hearing function and treatment adequacy throughout childhood and adolescence (Léger et al., 2011). Other studies, in contrast, documented no hearing impairment in patients with screened CH (Francois et al., 1994; Hashemipour et al., 2012). However, only a few studies have focused on neurosensory function of CH patients identified by neonatal CH screening programs and treated early (Leger, 2014) and, therefore, this issue remains still controversial.

In the present study, in order to shed further light on this topic, we have cross-sectionally investigated hearing function in a CH selected population consisting of only screened and adequately substituted children with no underlying risk factors for sensorineural hearing impairment. The aim of our study was to ascertain whether an early and adequate replacement treatment may be able to prevent sensorineural hearing loss in CH patients with no associated risk factors for neuro-otologic alterations.

2. Material and methods

2.1. Study population

It includes 32 caucasian patients (21 females) who were diagnosed in many CH screening centers of two southern regions of Italy (Sicily and Calabria) during the period 1992–2006. From the time of diagnosis (median age 28 days, range 7–30) all these patients were provided with L-thyroxine (L-T4) replacement therapy and followed up as outpatients in our clinical center of pediatric endocrinology. The 32 recruited patients were members of a larger population of children with CH who were followed up during the same period in our center and were selected for this study according to the following exclusion and inclusion criteria.

Exclusion criteria: a) transient CH; b) family history of congenital or childhood onset sensorineural impairment; c) prematurity and/or low for gestational age birth weight; d) neonatal distress; e) congenital infections of toxoplasmosis, rubella, cytomegalovirus and herpes; f) severe neonatal hyperbilirubinemia; g) history of meningitis, recurrent otitis or ototoxic medications; h) craniofacial abnormalities and/or clinical findings compatible with either middle ear pathologies or syndromes including sensorineural hearing loss.

Inclusion criteria: a) age at L-T4 therapy onset $\leq$30 days; b) initial L-T4 dose between 10 and 14 μg/kg/day; c) availability of both thyroid scanning and knee X-rays at the time of L-T4 treatment initiation; d) no thyrotropin (TSH) determination outside the normal limits of our laboratory reference range (0.3–5.0 mU/l) during the overall follow-up period, from L-T4 therapy start to the time of this study.

2.2. Study design and methods

At confirmation of CH diagnosis thyroid scanning had been performed by 99 m Technetium, whilst skeletal maturation had been evaluated by X-ray assessment of the distal femur epiphyseal ossification center.

During the last months of 2014 all the selected children and young adults underwent, at the median age of 15.4 years (range 8.0–22.0), an audiologic investigation that was conducted in the entire cohort by the same conventional pure tone audiometry and was carried out by the same audiologist (R.B.). Before the audiometric evaluation each patient received a routine otologic examination aiming to identify any abnormalities that may interfere with hearing, such as a perforated tympanic membrane or other middle ear pathologies. At the same time the patients underwent also a re-evaluation of serum TSH and free thyroxine (FT4) levels under L-T4 therapy.

All hearing tests were carried out, in a double walled sound-insulated chamber fulfilling ANSI 2004 criteria, using a Plus model Bell audiometer (Inventis, Padova, Italy) and TDH-39 earphones.

In each audiogram, the hearing loss in decibels (dB) was recorded, for both ears, for the frequencies 125, 250, 500, 1000, 2000, 4000, 6000 and 8000 Hertz (Hz). Normal hearing sensitivity was defined as hearing acuity within 20 dB Hearing Level (HL), whereas hearing was considered as abnormal when hearing loss exceeded 20 dB HL in at least one ear. If hearing impairment degree differed between the two ears, then the category assigned was that for the ear for which the poorer results were obtained. Hearing loss was classified as mild when it ranged between 20 and 40 dB HL, whilst it was considered as moderate or more severe when it exceeded 40 dB HL. Hearing loss was classified as conductive or sensorineural, but only the cases with a sensorineural defect were taken into consideration in this study.

Audiometric results were correlated with CH severity (etiology, TSH levels and bone maturation delay at diagnosis) and treatment variables (age and L-T4 dose at therapy start).

The same investigation protocol was also applied in a sex- and age-matched control population consisting of 32 healthy children and adolescents (22 females) aged between 9.1 and 21.0 years (median age 13,5). These control subjects were recruited according to the following inclusion criteria: a) no personal history of CH screening positivity; b) no clinical evidence of perforated tympanic membrane or other middle ear pathologies at the time of the routine otologic examination which preceded audiometric evaluation.

2.3. Statistical analysis

Results are expressed as mean ± SD or median and range values. Comparisons between groups were performed by Student's unpaired t test (normally distributed data) or Mann–Whitney U test (non-normally distributed data), as appropriate. Frequency rates were compared by chi-square (χ^2) test. The level of significance was set at 0.05.

The study design was approved by the ethical committee of our hospital and the children' parents gave informed consent.

3. Results

CH etiology, as assessed by the thyroid scanning performed before treatment start in all the cases, was: athyreosis in 9 children, ectopic gland in 15 and eutopic gland in 8.

The distal femur bony nucleus was absent in 14/32 patients (43.7%) and the prevalence of children with absence of this nucleus was significantly higher in the subgroup with athyreosis than in that with either ectopic or eutopic gland (77.8% vs 30.4%; $\chi^2 = 5.9$, $p < 0.025$).

Eight patients (25%) exhibited, at audiometry, a mild sensorineural hearing impairment (between 25 and 40 dB HL), which was bilateral in 5 cases and unilateral in the remaining 3 cases (Table 1). Including all the right and left ears tested, the percentage of ears for which hearing loss was recorded was 20.3%. Assessments of

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