

Hearing Impairment in Congenitally Hypothyroid Patients

Mahin Hashemipour^{1,2}, MD; Silva Hovsepian^{*1,2}, MD; Mostafa Hashemi¹, MD; Massoud Amini¹, MD;
Roya Kelishadi², MD, and Somaye Sadeghi¹, MD

1. Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
2. Child Health Promotion Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Received: Dec 22, 2010; Final Revision: Mar 18, 2011; Accepted: May 06, 2011

Abstract

Objective: Thyroid hormone is necessary for normal development of the auditory system. The aim of this study was to investigate the rate of hearing impairment in congenitally hypothyroid (CH) patients, and its relation with factors such as CH severity and age at starting treatment, during CH screening program in Isfahan.

Methods: Hearing acuity was assessed in two groups of children with (94 patients aged 4 months – 3 years) and without CH (450), between 2000-2006. Otoacoustic emission (OAE) was performed by a two step method. After two tests without OAE signals bilaterally, they were referred for auditory brainstem response (ABR) test. Subjects with both OAE and ABR abnormal test results were considered to have hearing problem. Obtained data was compared in case and control group and also CH patients with and without hearing impairment.

Findings: Three (3.2%) of patients and 1 of control group (0.2%) were diagnosed with sensorineural hearing loss. The rate of hearing loss was not different significantly in two studied groups ($P>0.05$). There was no difference between age of starting treatment and first T4 and TSH level in CH patients with and without hearing loss ($P>0.05$). CH neonates with hearing impairment had thyroid dyshormonogenesis according to the follow up results.

Conclusion: The rate of hearing loss was low among our studied CH patients. It may be due to proper management of CH patients. In view of the fact that all CH neonates were dyshormonogenic and considering the relation between certain gene mutations and hearing impairment in CH patients, further studies with larger sample size, with regard to different etiologies of CH should be investigated to indicate the possible gene mutations related to hearing loss in CH.

Iranian Journal of Pediatrics, Volume 22 (Number 1), March 2012, Pages: 92-96

Key Words: Hearing impairment; Auditory Brain Stem Response; ABR; Oto Acoustic Emission; OAE

Introduction

Thyroid hormone is necessary for normal development of the auditory system [1-3] and the association between thyroid hormone and hearing development has long been recognized in patients with congenital hypothyroidism (CH), endemic

cretinism and thyroid hormone resistance [4-6]. Recent genetic studies confirmed the relation between thyroid hormone and hearing system development [7,8]. So, CH, the most common endocrine disorder with an incidence rate of 1/4000-5000 live births also increase the risk of hearing impairment in children [9].

* Corresponding Author;

Address: Isfahan Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

E-mail: silvahovsep@hotmail.com

© 2012 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

Although mental outcome of CH patients is improved if patients are treated early in infancy, during CH screening, but subtle neurological deficits such as fine motor coordination, attention deficient, speech delay, hearing impairment, and hearing problems may develop [10-12]. Many studies, both in animal models and human patients have identified auditory system dysfunction among cases with thyroid disorders [13-15]. The rate of hearing loss has been reported to be 20-36% in CH patients before Iranian national CH screening program, and reported hearing loss was bilateral and severe [16]. On the other hand, recent reports held after CH screening programs, indicate that mild hearing loss occurs in up to 20% of CH patients [17,18].

Hearing loss, specially its mild form in children may result in delayed speech and difficulties in comprehension and problems in receptive language, auditory processing and reading, which may persist, especially in those with delayed treatment [19,20]. Therefore, considering the consequences of CH and its related hearing loss and also the fact that CH was more prevalent in our community [21,22], the aim of this study was to investigate the rate of hearing impairment in CH patients, and its relation with factors such as CH severity and age at starting treatment. This was conducted during CH screening program in Isfahan.

Subjects and Methods

Hearing acuity was assessed in two groups of children with and without CH. Hearing profiles of CH patients, consisting of both transient and permanent CH patients, were studied in 94 patients aged >4 months, between 2000-2006 and diagnosed primarily during CH screening program in Isfahan [21]. The cases were all treated with thyroxine and followed up regularly at endocrine clinic of Isfahan Endocrine and Metabolism Research Center. Hearing profile of control group was studied in 450 non-CH neonates, from Sepahan hospital.

All clinical, biochemical (including TSH and T4 levels), dose of levothyroxine, and age at which treatment began, were recorded. Subjects with

history of familial congenital hearing loss, VLBW (<1500), hyperbilirubinemia, craniofacial abnormalities, history of bacterial meningitis, history of neonatal mechanical ventilation, otitis media and head trauma were excluded from the study. Hearing acuity tests were performed after informed consent was obtained from the parents of both case and control groups. Hearing examination was conducted by trained audiologist. In case group (4 months – 3 years) otoacoustic emission (OAE) was performed by a two step method using Madsen-Capella (Denmark) device. After two tests without OAE signals bilaterally, the patients were referred for auditory brainstem response (ABR) test using Amplaid-MK22 (Italy) device.

In control group, hearing screening of newborns was performed before discharging from hospital on the second day in nursery by the same methods. Subjects with both OAE and ABR abnormal test results were considered to have hearing problem.

Obtained data in case and control group and in CH patients with and without hearing impairment are analyzed using SPSS version 13 software and by univariate and t-test. *P*-value <0.05 was considered statistically significant.

Findings

In this study 94 CH patients aged 4 months - 3 years (mean 19.5 ± 7.2 months) were studied. Mean T4 and TSH level in the first estimation was 6.3 ± 3.85 $\mu\text{g/dL}$ and 117.1 ± 91.5 mIU/L respectively. Three (3.2%) cases were diagnosed as sensorineural hearing loss. In control group 450 healthy neonates with mean age 2.3 ± 1.1 days were screened for hearing loss and one (0.2%) had sensorineural hearing loss. Mean value of T4 and TSH in the first estimation was 10.52 ± 2.5 $\mu\text{g/dL}$ and 3.12 ± 2.94 mIU/L, respectively.

The rate of hearing loss was not different significantly in the two studied groups, using univariate test (3.2% vs. 0.2%, *P*>0.05). Characteristics of CH patients with and without hearing impairment are presented in Table 1.

During follow up, it had been determined that the etiology of CH among those who had

Table 1: Characteristics of CH patients with and without hearing impairment

Variable	CH patients with normal hearing (n=91)	CH patients with hearing impairment (n=3)	P
Female/male	49 42	2 1	NS
Mean (SD) age (months)	18.9 (7.0)	20.1 (7.4)	NS
Mean (SD) T4 value in screening (µg/d)	6.4 (3.8)	4.3 (5.7)	NS
Mean (SD) TSH value in screening (mIU/l)	116.5 (92.2)	133.7 (80.3)	NS
Age in which treatment initiated (day)	16.4 (8.0)	13.7 (8.3)	NS

sensorineural hearing loss was dyshormonogenesis.

Discussion

The findings of our study indicate that 3.2% of studied CH patients diagnosed in newborn screening and treated early and followed up regularly had sensorineural hearing loss, whereas 0.2% of healthy neonates had this problem. The difference was not significant.

The prevalence of hearing loss in control group was similar to that reported by other studies for the general population [23-25], but the prevalence of hearing loss among CH patients was lower than in many other studies in this field [11,26,27], though there were also studies with lower [28] or similar prevalence [28]. Chou et al in Taiwan, during 1996-98, have reported that 25% of CH patients aged 3-5 years, who received early treatment, had hearing impairment diagnosed by auditory brainstem evoked potentials [26]. Rovet et al in their study in Canada have indicated that hearing impairment was presented in up to 20% of children with CH diagnosed by newborn screening and treated early [27].

Vanderschueren-Lodeweyckx et al have found that in 45 children with sporadic CH with adequate long-term treatment, 9 (20%) had sensorineural hearing loss, particularly in higher frequencies [11]. On the other hand, Francois et al in France have reported that none of their 49 CH patients had a sensorineural hearing loss that required prosthesis [28], and similar to our study, according to the results of Bellman et al, 5% of their CH patients with early treatment had hearing

problem [29].

Parazzini and colleagues, indicated that there was not any significant difference in the prevalence of hearing impairment among untreated CH patients within the first month after birth and control group [30]. The differences between mentioned studies may be due to different hearing acuity screening tests, age of hearing examination or genetic factors.

All CH patients with hearing impairment had sensorineural hearing loss, which support the previous reports regarding the histological findings in congenital hypothyroid animals. According to these reports, immature development of the organ of Corti including hair cells and tectorial membrane was observed among cases with hypothyroidism [13]. Our studied population consists of CH patients younger than 3 years old, so they are younger than most studied patients in mentioned studies (3-16 years old). Moreover, we studied all CH patients preliminary diagnosed and treated during CH screening program. They consisted of both transient and permanent CH patients, as permanency of hypothyroidism can be determined after 3 years follow up [31]. The lower rate of hearing loss in our study could be explained by proper management of CH regarding the mean age in which treatment began or administration of appropriate levothyroxine dosage [31]. However, it seems that for more accurate conclusion this study should be continued with longer sample size.

There are different reports about hearing impairment and time of starting treatment. In some studies, there was association between hearing loss and delay in initiating therapy [27], whereas in others, there was no relation found between mentioned factors [28,32]. Wasniewska and colleagues have reported that sensorineural

hearing loss may be found in CH patients when the substitutive treatment starts many years after its presentation [33].

In current study, there was no difference between age of starting treatment in CH patients with and without hearing loss. Our results were in agreement with those of De Laca et al [32] and Francois et al [28], but Rovet et al have reported that hearing impaired children, differed from children with normal hearing in age of treatment onset (22 vs. 14 days) [27].

Our findings indicate that there was no difference between mean screening T4 and TSH level and hearing impairment, which is in accordance with the results of Rovet et al [27]. In their study, TSH level at diagnosis was not different in CH patients.

CH neonates with hearing impairment had thyroid dysmorphogenesis according to follow up results, which was in line with the results of Crifo et al. They indicated that dysmorphogenesis was associated with a higher risk of hearing loss among CH patients [16].

Unlike Crifo et al Vanderschueren-Ladeweyckx found hearing loss in some patients with an ectopic thyroid gland, too [11]. However, recent studies reported the relation between hearing impairment and certain gene mutations such as TPO and DUOX2 among CH patients [34,35]. So, regarding the fact that the most common etiology of CH in Isfahan was dysmorphogenesis [36], it seems that further studies in this field including genetic studies should be done.

Considering that there were only 3 CH patients with hearing loss, our results would be more conclusive with larger sample size.

Conclusion

In spite of lower rate of hearing loss among our studied CH patients, regarding the importance of early treatment of hearing loss in order to prevent speech and language development problems, it seems that physicians should look for hearing loss in any patient with CH and in addition, further studies with larger sample size, with regard to different etiologies of CH should be investigated to indicate the possible gene mutations related to hearing loss in CH.

Acknowledgment

Authors would like to thank Dr Moshir Fatemi, Head of Sepahan Hospital, Dr Salek, Dr Ziba Farajzadegan, Dr Rezvane Hadian, Dr Mahsa Hajrahimi, Mr Jafari and Mr Masiri for their contribution.

Conflict of Interest: None

References

1. Mra Z, Wax MK. Effects of acute thyroxin depletion on hearing in humans. *Laryngoscope* 1999;109(3):343-50.
2. Knipper M, Zinn C, Maier H, et al. Thyroid hormone deficiency before the onset of hearing causes irreversible damage to peripheral and central auditory systems. *J Neurophysiol* 2000; 83(5):3101-12.
3. Uziel A, Gabrion J, Ohresser M, et al. Effect of hypothyroidism on the structural development of the organ of Corti in the rat. *Acta Otolaryngeol* 1981;92(5-6):469-80.
4. DeLong GR, Stanbury JB, Fierro-Benitez R. Neurological signs in congenital iodine-deficiency disorder (endemic cretinism). *Dev Med Child Neurol* 1985;27(3):317-24.
5. Refetoff S, De Wind IT, De Groot IJ. Familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. *J Clin Endocrinol* 1967;27(2):279-94.
6. Brucker-Davis F, Skarulis MC, Pikes A, et al. Prevalence and mechanisms of hearing loss in patients with resistance to thyroid hormone. *J Clin Endocrinol Metab* 1996;81(8):2768-72.
7. Knipper M, Richardson G, Mack A, et al. Thyroid hormone-deficient period prior to the onset of hearing is associated with reduced levels of beta-tectorin protein in the tectorial membrane: implication for hearing loss. *J Biol Chem* 2001; 276(42):39046-52.
8. Forrest DC, Erway L, Ng L, et al. Thyroid hormone receptor β is essential for development of auditory function. *Nature Genetics* 1996;13(3): 354-7.
9. Bradley DJ, Towle HC, Young S. Alpha and beta thyroid hormone receptor (TR) gene expression during auditory neurogenesis: evidence for TR isoform-specific transcriptional regulation in vivo. *Proc Natl Acad Sci* 1994;91(2):439-43.
10. Bargagna S, Canepa G, Costagli C, et al. Neuropsychological follow-up in early-treated

- congenital hypothyroidism: a problem-oriented approach. *Thyroid* 2000;10(3):243-9.
11. Vanderschueren-Lodeweyckx M, Debruyre F, Doms L, et al. Sensorineural hearing loss in sporadic congenital hypothyroidism. *Arch Des Child* 1983;58(6):419-22.
 12. Thornton AR, Jarvis SJ. Auditory brainstem response findings in hypothyroid and hyperthyroid disease. *Clin Neurophysiol* 2008; 119(4):786-90.
 13. Debruyne F, Vanderschuerer-Landeweyckx M, Bastijns P. Hearing in congenital hypothyroidism. *Audiology* 1983;22(4):404-9.
 14. Withers BT, Reuter SH, Janeke JB. The effects of hypothyroidism on the ears of cats and squirrel monkeys: a pilot study. *Laryngoscope* 1972; 82(5):779-84.
 15. Li M, Rsoyages SC. Detection of extended distribution of beta2-thyroid hormone receptor messenger ribonucleic acid (RNA) in adult rat brain using complementary RNA in situ hybridization histochemistry. *Endocrinology* 1996;137(4):1272-5
 16. Crifo S, Lazzari R, Salabe GB, et al. A retrospective study of audiological function in a group of hypothyroid patients. *Int J Pediatr Otorhinolarygeol* 1980;2(4):347-55.
 17. Fracois M, Bonfils P, Leger J, et al. Audiological assessment of eleven congenital hypothyroidisms before and after treatment. *Acta Otolaryngol* 1993; 113(1):39-42.
 18. Hebert R, Laurea E, Nanasse M, et al. Auditory brainstem response audiometry in congenitally hypothyroid children under early replacement therapy. *Pediatr Res* 1986;20(6):570-3.
 19. Gordon N, Ward. Abnormal response to sound and central auditory processing disorder. *Dev Med Child Neurol* 1995;37(7):645-52.
 20. Baret KA. Hearing and immittance screening of school age children. In: Katz J, editor. *Handbook of Clinical Audiology*. 3rd ed. Baltimore: Williams & Wilkins, 1985; Pp: 621-41.
 21. Hashemipour M, Amini M, Iranpour R, et al. Prevalence of congenital hypothyroidism in Isfahan, Iran: results of a survey on 20,000 neonates. *Horm Res* 2004;62(2):79-83.
 22. Karamizadeh Z, Dalili S, Sanei-far H, et al. Does Congenital hypothyroidism have different etiologies in Iran? *Iran J Pediatr* 2011;21(2):188-92.
 23. Russ SA, White K, Dougherty D, et al. Preface: newborn hearing screening in the United States: historical perspective and future directions. *Pediatrics* 2010;126(Suppl 1):S3-6.
 24. Hull FM, Mielke PW, Willeford JA, et al. *National speech and hearing survey (final report, project no. 59078)*. Washington (DC): US Department of Health, Education and Welfare, 1976.
 25. Brookhouser PE. Incidence/prevalence. *NIH Consensus Development Conference, Early Identification of Hearing Impairment in Infants and Young Children*. Bethesda (MD). National Institutes of Health 1993.
 26. Chou YH, Wang PJ. Auditory brainstem evoked potentials in early-treated congenital hypothyroidism. *J Child Neurol* 2002;17(7):510-4.
 27. Rovet J, Walker W, Bliss B, et al. Long term sequels of hearing impairment in congenital hypothyroidism. *J Pediatr* 1996;128(6):776-83.
 28. Francois M, Bonfils P, Legar J, et al. Role of congenital hypothyroidism in hearing loss in children. *J Pediatr* 1994;124(3):444-6.
 29. Bellman SC, Davis A, Faggie PW, et al. Mild impairment of neurootological function in early treated congenital hypothyroidism. *Arch Dis Child* 1996;74(3):215-8.
 30. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics* 2006;117(6):2290-303.
 31. Parazzini M, Ravazzani P, Medaglini S, et al. Click-evoked otoacoustic emissions recorded from untreated congenital hypothyroid newborns. *Hear Res* 2002; 166(1-2):136-42.
 32. De Luea F, Muritano M, Mami C, et al. Hypacousie de type perceptif et hypothyroidie congenital. *Ann Pediatr (Paris)* 1986;33(1):35-7. (French)
 33. Wasniewska M, De Luca F, Siclari S, et al. Hearing loss in congenital hypothalamic hypothyroidism: a wide therapeutic window. *Hear Res* 2002; 172(1-2):87-91.
 34. Pfarr N, Borck G, Turk A, et al. Goitrous congenital hypothyroidism and hearing impairment associated with mutations in the TPO and SLC26A4/PDS genes. *J Clin Endocrinol Metab* 2006;91(7):2678-81.
 35. Johnson KR, Marden CC, Ward-Bailey P, et al. Congenital hypothyroidism, dwarfism, and hearing impairment caused by a missense mutation in the mouse dual oxidase 2 gene, Duox2. *Mol Endocrinol* 2007;21(7):1593-602.
 36. Hashemipour M, Hovsepian S, Kelishadi R, et al. Permanent and transient congenital hypothyroidism in Isfahan-Iran. *J Med Screen* 2009;16(1):11-6.