Diagnosis and treatment of subclinical hypothyroidism detected by neonatal screening

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Original article

Background: **This study was undertaken to explore the clinical outcome and prognosis of subclinical hypothyroidism detected by newborn screening.**

Methods: **Newborn screening was conducted at 1156 health care institutions in Zhejiang Province from October 1999 to September 2006. Included were (1) infants who had thyroid-stimulating hormone (TSH) ≥20 mU/L, and normal or lower normal levels of triiodothyronine (T_3) and thyroxine (T_4) and (2) infants with TSH between 5.6 mU/L and 20 mU/L at a confirmatory examination and follow-up showing TSH levels ≥20 mU/L or delayed reduction in T_4 levels. These infants were considered as having subclinical hypothyroidism and levothyroxine (L-T_4) at an initial dose of 3-5 μg/kg per day was administered. The levels of TSH and T_4, developmental quotient (DQ), and index of growth were evaluated.**

Results: **A total of 204 infants met our criteria for subclinical hypothyroidism, with an incidence of 1/8809. After 2-4 weeks of standard therapy, serum TSH level dropped to normal and T_4 reached a higher normal level in all the 204 infants. Evaluations of 60 patients after 2 years of therapy showed that their average DQ was 101±14.61, and body weight and height were within the normal ranges. Bone age test for 54 patients revealed normal development in 44, slightly retarded development in 7, and advanced development in 3.**

Conclusions: **Newborns with high TSH levels should be given particular attention to ensure early diagnosis. A L-T_4 dose of 3-5 μg/kg per day was effective in the initial treatment of subclinical hypothyroidism.**

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Key words: **congenital hypothyroidism; diagnosis; L-thyroxine; newborn screening**

Introduction

Congenital hypothyroidism (CH) is one of the most important causes of mental retardation. It may be worsened and become irreversible if not treated timely. Neonatal screening ensures early detection and therapy of children with permanent CH.[1] Subclinical hypothyroidism, also referred to as latent hypothyroidism, is characterized by elevated levels of thyroid-stimulating hormone (TSH) and normal thyroid hormone in the absence of clinical symptoms of hypothyroidism.[2-6] Subclinical hypothyroidism is uncommon and its symptoms are not obvious. A small number of reports have focused on subclinical hypothyroidism in infants in the past decades.[7-9] However, we found that subclinical hypothyroidism in infants is more common than reported.

Between October 1999 and September 2006, we screened 1 797 115 newborns for CH in Zhejiang Province, China. A total of 204 patients with subclinical hypothyroidism were identified. The available diagnostic criteria and therapy for children with subclinical hypothyroidism were evaluated and the outcome of these newborns were reported.

Methods

Participants

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Hospital, Zhejiang University School of Medicine has established a screening network in the province by coordinating all 83 local screening centers covering 10 municipalities and 73 counties and cities. All 1156 health care institutions in the province can offer screening services to all live-born neonates. Informed consent was obtained from the parents whose infants participated in the screening. The procedures of the screening were approved by the local institutional ethics committees.

Methods

Screening tests were performed using the dissociation enhanced lauthanide fluoroimmunoassay (DELFIA) method. Only TSH was measured at the screening with a cut-off value of 9 mU/L. All samples with a spot TSH above the cut-off value would be rechecked, and repeat analysis was performed on the blood spot.

All infants with TSH >9 mU/L at the screening were recalled to the hospital for further examination. To confirm the diagnosis of hypothyroidism in those suspected cases, serum levels of triiodothyronine (T_3), thyroxine (T_4) and TSH were measured with an enzyme-amplified chemiluminescence assay (confirmatory examination). Reference ranges were 1.2-3.4 nmol/L for T_3, 54-174 nmol/L for T_4, and 0.34-5.5 mU/L for TSH. The lowest detectable value of T_4 was 12.8 nmol/L, and the upper limit for TSH was 75 mU/L.

The diagnostic criteria for subclinical hypothyroidism were defined as follows: either (1) TSH ≥20 mU/L, and normal or lower normal T_3 and T_4 levels at a confirmatory examination; or (2) infants with TSH levels between 5.6 mU/L and 20 mU/L at the confirmatory examination, and follow-up showing TSH levels ≥20 mU/L or delayed reduction in T4 levels.

Once the infants were confirmed as having subclinical hypothyroidism, imaging studies were performed. Radioisotope scanning was performed and later it was changed to ultrasonography for less side-effects. Meanwhile, oral levothyroxine (L-T_4, Merck, Germany) was administered at a dose of 3-5 μg/kg per day. After 2 to 4 weeks, serum levels of TSH and T_4 were measured again and L-T_4 dosage was adjusted to reach normal TSH and high-normal T_4 levels. Patients with stable hormone levels were followed up every 3 months in the first year and then every 3-6 months. Ultrasonography or radioisotope scanning of the thyroid gland was performed at intervals. In addition, mental development, bone age assessed by a single X-ray examination of the left wrist and hand, and general physical condition were evaluated regularly.

Hormone replacement was discontinued in patients with stable TSH, T_3 and T_4 levels after 2 years of standard therapy. Thyroid function was measured during the follow-up at 1, 2, 6, and 12 months after hormone withdrawal. If laboratory parameters remained in the normal range, hormone replacement was discontinued.

Permanent hypothyroidism was defined as marked reduction of T_4 and TSH levels beyond the normal ranges with additional abnormal findings of the thyroid gland (agenesis, dystopia, and dysplasia) shown by ultrasonography or radioisotope scanning.[10,11] Hypothyroidism was seen as temporary in normally developing children with diagnosed hypothyroidism, normal bone age development, normal findings in ultrasonography and radioisotope scanning and with successful discontinuation of hormone replacement after 2 to 3 years of L-T_4 substitution.

Statistical analysis

Statistical analysis was performed with the SPSS 13 software package for Windows. Data were presented as mean ± standard deviation. Inter-group differences were tested by independent sample *t* test (2 groups). *P* values less than 0.05 were considered statistically significant.

Results

In the 7-year study period, there were 2 696 461 registered live births in Zhejiang Province. Among them 1 797 115 neonates took part in the screening program, with a coverage rate of 66.6%. There were 11 157 patients suspected of having congenital hypothyroidism, and 10 471 patients were subjected to a confirmatory examination (93.9%). A total of 204 infants with subclinical hypothyroidism were confirmed.

Measurements of TSH and thyroid hormones

In the 204 infants, the TSH level at the initial screening was 25.93±23.42 mU/L. Age of the infants at the confirmatory examination was 36.55±11.16 days, and TSH level was 31.91±27.23 mU/L. At the definite diagnosis, TSH level was 36.64±15.29 mU/L. In 143 infants, TSH level was higher than 20 mU/L and it was kept in the normal range after L-T_4 administration. In 61 infants, TSH levels were less than 20 mU/L during the follow-up. One infant with a TSH level of 6.7 mU/L at the confirmatory examination had 10 visits during a follow-up of 14 months. The TSH levels of the patient fluctuated between 11.5 and 15 mU/L, and T_4 levels maintained at 104 nmol/L. Ultrasonography of the thyroid gland revealed maldevelopment of the right lobe, and the patient continued to receive hormone substitution. In the 61 infants who had TSH levels less than 20 mU/L, 23 had a TSH level below 20 mU/L at the time of diagnosis. Five of these infants showed a

delayed reduction in T_4 levels at follow-up, and another 3 infants suffered from maldevelopment of the thyroid gland determined by ultrasonography. TSH levels of the other 38 infants were higher than the cut-off value (20 mU/L) during the follow-up. Infants diagnosed with subclinical hypothyroidism showed an increasing tendency of TSH levels between the first screening and the definite diagnosis.

Among the 204 patients with subclinical hypothyroidism, 60 patients had complete information on the time trend of TSH and therapeutic outcome measured with the Gesell score[12,13] (Table 1). Physical examination showed that their body weight and height were within the normal ranges. Bone age determination revealed normal development in 44 (81.5%) of 54 infants, slowly retarded development in 7 (12.9%), and advanced development in 3 (5.6%). Gesell score was determined at age of 25.42±9.35 months with an average developmental quotient (DQ) of 101.10±14.61.

Table 1. Time trend of TSH and therapeutic outcome measured with the Gesell score in 60 infants with subclinical hypothyroidism

Variables	Subclinical hypothyroidism
Cases (*n*)	60
Male	36
Female	24
First screening spot TSH (mU/L)	28.11±23.36
Age at recall (d)	36.33±13.57
Recall spot TSH (mU/L)	35.12±20.02
Definite diagnosis serum TSH (mU/L)	40.83±18.59
Definite diagnosis serum T_4 (nmol/L)	85.14±24.57
Gesell score	
Age (mon)	25.42±9.35
Adaptive behavior	99.73±15.48
Neurological-motor growth	101.91±14.95
Language development	97.90±18.94
Personal-social behavior	106.00±18.83
Development quotient	101.10±14.61

TSH: thyroid-stimulating hormone; T_4: thyroxine.

Morphological examination of the thyroid gland

Data of therapy and follow-up were recorded in 77 infants with subclinical hypothyroidism for at least 2 years, and 75 infants were examined by ultrasonography (57 patients) or radioisotope scanning (21 infants, 3 of them took both examinations). Normal results of thyroid imaging were obtained in 53 infants, while abnormalities of the thyroid gland were observed in 22 infants: right and left lobe hypoplasia in 11 infants (including 1 infant with cystic lesions) (volume of the right lobe: 0.307±0.176 mL; left lobe: 0.298±0.172 mL); right lobe hypoplasia in 1 (volume: 0.048 mL); right lobe hypoplasia and left lobe enlargement in 1 (volume of the right lobe: 0.475 mL; left lobe: 9.288 mL); and right and left lobe enlargement in 9 (volume of the right lobe: 4.904±1.036 mL; left lobe: 4.942±1.172 mL).

Evaluation of mental and physical development

Despite different TSH levels (<20 mU/L *vs.* >20 mU/L) at the first screening, no significant difference was observed in TSH levels between the two groups at the time of definite diagnosis (P=0.866), nor a different DQ after substitution therapy (P=0.105). In infants with different TSH levels measured at recall examination (<20 mU/L *vs.* >20 mU/L), the significantly different TSH levels persisted at the time of definite diagnosis (P=0.002), but DQ was not different between the two groups after substitution therapy (P=0.647) (Table 2). The 60 infants were re-examined at our hospital at the age of 36.33±13.57 days. Thirty-seven infants were diagnosed as having subclinical hypothyroidism with a TSH level of >20 mU/L, and the treatment was initiated

Table 2. Gesell score and corresponding factors in 60 patients with subclinical hypothyroidism

Variables	*n*	TSH (mU/L) at definite diagnosis	Adaptive behavior	Neurological motor growth	Language development	Personal-social behavior	Development quotient
First screening TSH							
<20 mU/L	31	34.69±18.73	96.34±12.46	97.62±11.33	99.51±19.02	103.83±18.29	98.14±12.92
>20 mU/L	29	35.58±21.64	103.36±17.66	106.48±17.07	101.52±18.49	108.33±19.45	104.26±15.84
P value		0.866	0.079	0.023	0.153	0.360	0.105
Recall TSH							
<20 mU/L	19	30.01±17.47	98.80±12.67	101.06±14.29	97.91±20.00	106.98±20.32	99.82±12.92
>20 mU/L	41	45.84±17.06	100.16±16.75	102.29±15.40	97.89±18.68	106.01±18.37	101.69±15.42
P value		0.002	0.754	0.768	0.997	0.996	0.647
Start of therapy							
<2 mon after birth	37	48.31±17.09	99.36±13.63	100.89±16.09	97.10±20.85	107.55±21.25	101.28±16.07
>2 mon after birth	23	28.78±12.98	100.33±18.38	103.57±13.09	99.19±15.73	103.51±14.21	100.82±12.20
P value		0.001	0.814	0.502	0.681	0.423	0.907

TSH: thyroid-stimulating hormone.

within the first 2 months after birth. The remaining 23 infants with a TSH level of <20 mU/L were diagnosed after monitoring for 2-10 months, thus the treatment was started later than 2 months after delivery at a mean age of 5.59 months. Although TSH was significantly higher in the former group at the definite diagnosis (P=0.005), DQ did not show any significant differences between the two groups after 2 years of treatment (P=0.907).

Discussion

Although neonatal screening has been conducted in China for more than 20 years, subclinical hypothyroidism has rarely been reported. Staub et al[14] reported three different levels of subclinical hypothyroidism. Subclinical hypothyroidism appears as an asymptomatic condition that is difficult to evaluate and requires TSH determination. Subclinical impairment of thyroid function precedes hypothyroidism. Thyroid dysfunction appears in infants with CH in three stages. Initially, subclinical dysfunction is characterized by slightly elevated TSH level but normal levels of T_3 and T_4.[2-4,6] Subsequently, mild symptomatic hypothyroidism develops with moderately elevated TSH, normal T_3 and lower T_4 levels. Finally, patients present with clinically overt hypothyroidism, high TSH level and reduced blood levels of T_3 and T_4.[15] Longitudinal studies showed that 20%-50% of infants with subclinical thyroid dysfunction developed hypothyroidism between 4 to 8 years of age.[16,17] It has been reported that infants with a TSH level higher than 20 mU/L and normal or low normal T_4 level shown by a confirmatory examination can be diagnosed as having subclinical hypothyroidism. These infants need to be treated and followed up to determine their outcome (temporary, permanent hypothyroidism or hyperthyrotropinemia).[18,19] The updated guidelines for neonatal CH screening by the American Academy of Paediatrics described that children with elevated TSH and normal T_4 levels at re-examination and an elevated TSH level of >10 mU/L after a follow-up for 2-4 weeks should be treated with L-thyroxine.[19] According to the diagnostic criteria of our study, the patients with subclinical hypothyroidism require immediate treatment after a definite diagnosis. The majority of newborns with high TSH levels at the first screening showed normal development of thyroid function; however, infants with functional compensation of latent hypothyroidism are at risk of developing symptoms, and those with subclinical hypothyroidism need a long-term follow-up.

There are many reports on the treatment regimen of CH,[10,11,18-23] but few on the treatment of subclinical hypothyroidism.[24] Moore[17] believed that most infants with subclinical hypothyroidism maintain functional compensation despite elevated TSH levels, while a few develop permanent hypothyroidism. TSH >20 mU/L is thought to indicate a higher risk of developing hypothyroidism, whereas TSH <10 mU/L represents a low-risk population who needs TSH monitoring in regular intervals, but without obligatory hormone substitution. Most strategies for the treatment of subclinical hypothyroidism are based on the data from adult populations.[17,25-27] Calaciura et al[16] considered the high level of TSH in the initial screening as a high risk factor for developing subclinical hypothyroidism. They proposed that infants with two TSH measurements >5 mU/L within the first 3 months of life and normal or reduced T_4 level should be treated with L-T_4 so as to maintain the levels of TSH and T_4 within the normal physiological range. In our study, an initial dose of 3-5 μg/kg L-T_4 per day was adopted with a close follow-up visit for 2-4 weeks to make necessary adjustments on an individual basis. We aimed at controlling the TSH level between 0.34 mU/L and 5.5 mU/L and maintaining a normal to higher normal T_4 level. Regular follow-up visits and evaluations helped to optimize hormone replacement and ensure a satisfactory therapeutic outcome.

The analysis of Gesell score on 60 infants showed that TSH levels at the first screening, recall examination, and the time of definite diagnosis did not predict therapeutic outcome. The infants had a comparably high score on all four dimensions of the DQ. This shows that normal mental development could be ensured by close monitoring, timely diagnosis, and adequate treatment, despite delayed definite diagnosis of subclinical hypothyroidism in some infants with a slightly elevated TSH level at the initial screening.

Presently, there is a paucity of data concerning newborns and infants with subclinical hypothyroidism. Some studies only reported infants with a prolonged elevation of serum TSH level. Further investigations with a long-term follow-up, covering school age children and adolescents, are needed to determine whether the criteria for diagnosis and treatment of subclinical hypothyroidism in our study are correct and sufficient. A limitation in our study is the low coverage rate (66.6%), which demands further investigation and better epidemic data.

In conclusion, newborns with subclinical hypothyroidism deserve particular attention to ensure early diagnosis and adequate treatment, combined with a regular long-term follow-up. L-T_4 dosage of 3-5 μg/kg per day is effective in the initial treatment of subclinical hypothyroidism.

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Ethical approval: This study was approved by the local institutional ethics committee.

Competing interest: The authors declare that they have no competing interests.

Contributors: Chen XX and Qin YF conceived the study, participated in its design and supervision and in the drafting of the manuscript. Chen XX, Zhou XL and Yang RL participated in the design of the study and performed the statistical analysis. Mao HQ, Qin YF and Wang X participated in the analysis and interpretation of data, and drafting of the manuscript. Zhao ZY contributed to conception, design and drafting of the manuscript. All authors read and approved the final manuscript.

References

1 Kohler B, Schnabel D, Biebermann H, Gruters A. Transient congenital hypothyroidism and hyperthyrotropinemia: normal thyroid function and physical development at the ages of 6-14 years. J Clin Endocrinol Metab 1996;81:1563-1567.

2 Paoli-Valeri M, Maman-Alvarado D, Jimenez-Lopez V, Arias-Ferreira A, Bianchi G, Arata-Bellabarba G. Frequency of subclinical hypothyroidism among healthy children and those with neurological conditions in the state of Merida, Venezuela. Invest Clin 2003;44:209-218.

3 Reiterer E, Borkenstein MH. Disorders of the thyroid gland in neonates and youth: latent hypothyroidism and hyperthyroidism. Acta Med Austriaca 2003;30:107-109.

4 Teofoli F, Camilot M, Tato L. Lack of association between thyrotropin receptor gene polymorphisms and subclinical hypothyroidism in children. J Endocrinol Invest 2007;30:163-166.

5 Motta RM, Gullio D, Fichera G. Children with neonatal short lasting hyper-TSH frequently have subclinical hypothyroidism in early infancy. 4th Meeting of the International Society for Neonatal Screening. Stockholm, Sweden: 1999, 82.

6 Paoli-Valeri M, Guzman M, Jimenez-Lopez V, Arias-Ferreira A, Briceno-Fernandez M, Arata-Bellabarba G. Atherogenic lipid profile in children with subclinical hypothyroidism. An Pediatr (Barc) 2005;62:128-134.

7 Waldhauser F, Frisch H, Schober E. Subclinical hypothyroidism in infancy (author's transl). Monatsschr Kinderheilkd 1981;129:364-366.

8 Clemens PC. Subclinical hypothyroidism in the neonate: not to treat. Am J Med Sci 1989;297:132-133.

9 Alemzadeh R, Friedman S, Fort P, Recker B, Lifshitz F. Is there compensated hypothyroidism in infancy? Pediatrics 1992;90:207-211.

10 American Academy of Pediatrics AAP Section on Endocrinology and Committee on Genetics, American Thyroid Association Committee on Public Health. Newborn screening for congenital hypothyroidism: recommended guidelines. Pediatrics 1993;91:1203-1209.

11 American Academy of Pediatrics, Section on Endocrinologyan, Committee on Genetics, American Thyroid Association, Committee on Public Health. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-2303.

12 Voigt RG, Jensen CL, Fraley JK, Rozelle JC, Brown FR 3rd, Heird WC. Relationship between omega3 long-chain polyunsaturated fatty acid status during early infancy and neurodevelopmental status at 1 year of age. J Hum Nutr Diet 2002;15:111-120.

13 Knobloch H, Stevens F, Malone AF. Manual of Developmental Diagnosis. Hagerstown: Harper & Row, 1980.

14 Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, et al. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med 1992;92:631-642.

15 Teng WP. Subclinical hypothyroidism. Foreign Med Sci Sec Endocrinology 2003;23:370-372. [In Chinese]

16 Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, et al. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab 2002;87:3209-3214.

17 Moore DC. Natural course of 'subclinical' hypothyroidism in childhood and adolescence. Arch Pediatr Adolesc Med 1996;150:293-297.

18 Chen XX, Yang RL, Shi YH, Cao LP, Zhou XL, Mao HQ, et al. Screening for congenital hypothyroidism in neonates of Zhejiang Province during 1999-2004. Zhejiang Da Xue Xue Bao Yi Xue Ban 2005;34:304-307. [In Chinese]

19 Tian GL, Cao X, Dong QY. Neonatal screening and clinical analysis for congenital hypothyroidism. Chin J Endocrinol Metab 2001;17:90-92. [In Chinese]

20 Ehrlich RM. Thyroxin dose for congenital hypothyroidism. Clin Pediatr (Phila) 1995;34:521-522.

21 He YF, Zhang LQ, Yu SY, Xu N, Liu ML, Song Y. A study on initial L-T_4 dose application in congenital hypothyroid children. J Clin Pediatr 2003;21:410-412.

22 Bongers-Schokking JJ, de Muinck Keizer-Schrama SM. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. J Pediatr 2005;147:768-774.

23 Rovet JF. In search of the optimal therapy for congenital hypothyroidism. J Pediatr 2004;144:698-700.

24 Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, et al. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol 1998;138:141-145.

25 McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001;86:4585-4590.

26 Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med 2001;345:260-265.

27 Alberti L, Proverbio MC, Costagliola S, Romoli R, Boldrighini B, Vigone MC, et al. Germline mutations of TSH receptor gene as cause of nonautoimmune subclinical hypothyroidism. J Clin Endocrinol Metab 2002;87:2549-2555.

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