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Treatment and follow-up of children with transient congenital hypothyroidism*

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Abstract: Objective: To study the clinical therapy and prognosis in children with transient congenital hypothyroidism (CH). Methods: Fifty-seven children with CH diagnosed after neonatal screening were treated with low-dosage levothyroxine (L-T4). Follow-up evaluation included the determination of TT3, TT4 and TSH serum levels and the assessment of thyroid gland morphology, bone age, growth development and development quotients (DQ). A full check-up was performed at age 2, when the affected children first discontinued the L-T4 treatment for 1 month, and one year later. Development quotients were compared with a control group of 29 healthy peers. Results: The initial L-T4 dosage administered was 3.21~5.81 μg/(kg·d) with an average of (16.25±3.87) μg/d. Mean duration of therapy was (28.09±9.56) months. No significant difference was found between study group and control group in the DQ test (average score (106.58±14.40) vs (102.4±8.6), $P>0.05$) and 96.49% of the CH children achieved a test score above 85. Bone age, 99mTc scans and ultrasonographic findings were all normal, and evaluation of physical development was normal too, as were the serum levels of TT3, TT4 and TSH after one year of follow-up. Conclusion: A L-T4 dosage of 3.21~5.81 μg/(kg·d) was found sufficient for the treatment of transient CH. The treated children showed satisfactory overall mental and physical development at age 2. So it is possible for CH children to stop taking medicine if their laboratory findings and physical development are all normal after regular treatment and 2~3 years of follow-up.

Key words: Transient congenital hypothyroidism, Levothyroxine, Development quotient, Follow-up
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INTRODUCTION

Congenital hypothyroidism (CH), one of the most common endocrinological paediatric diseases, results from the dysfunction of the thyroid gland and, if untreated, may lead to seriously impaired mental and physical development (Gu and Wang, 2004; Gruters *et al*., 1997; Peneva *et al*., 1997; Pasquier *et al*., 1997; Wang *et al*., 1998). Nationwide efforts to promote neonatal screening programs in recent years have also sparked the interest of researchers in CH. However, there is still a paucity of data on clinical treatment and follow-up of patients with transient CH. Two major misconceptions are still very common among young parents in China. First, many do not fully understand the seriousness of the disease, refuse to participate in the neonatal screening or otherwise show poor compliance in diagnosis, treatment and follow-up. Second, others believe that the treatment of CH implies a life-long dependency on drug administration and therefore feel highly distressed when confronted with their child's disease. There are different opinions on the initial dose to CH among experts. In this retrospective study, we analyzed treatment plans and follow-up data from 57 children with transient CH so as to formulate a general clinical approach to treatment and to study the clinical outcome in these patients.

SUBJECTS AND METHODS

Subjects

About 1112784 children took part in the neo-

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natal screening in Zhejiang Province between August 1999 and September 2004, and 764 cases were diagnosed as CH. Among these, 57 children were identified who recovered normal thyroid function after two to three years of thyroxin treatment. The diagnosis of CH in this group, including 34 boys and 23 girls, was made between ten days and three months post partum (average (33.28±9.94) d). Analysis of patient data shows an average gestational age of (39.44±1.58) weeks (ranging from 36 to 42 weeks) at the time of delivery, an Apgar score between 8 and 10 and a mean birth weight of (3.25±0.50) kg. Twenty-nine age-matched healthy peers who took part in a routine physical examination at our institution served as controls in our study.

Methods

All CH patients were first treated with 3~6 μg/(kg·d) of levothyroxine (L-T4, Euthyrox®). According to their gestational age at delivery, birth weight and clinical status, mature neonates received dose of 25 μg/d (half pill), and premature and low birth weight neonates received 12.5~16.67 μg/d (one fourth to one third pill). Adjustment of the initial dosage after one month of treatment was based on the results of a T3/T4/TSH laboratory check. Once normal hormone levels were reached, follow-up tests of the thyroid function were performed every three months in 6-month-old infants and every 6 months after age 1. Thyroxin treatment was discontinued for one month as the child reached age 2, followed by a determination of T3/T4/TSH and a comprehensive clinical check-up, including bone age, physical growth, evaluation with Gesell's test (Gesell's baby growth scale) and ultrasonography and a SPECT (single photon emission computed tomography) scan of the thyroid gland. T3/T4/TSH were then repeatedly checked at regular intervals as the children maintained normal thyroid function without oral hormone substitution.

The diagnostic criteria of CH: the level of TSH in serum rises to 0.34~5.5 mU/L, and the level of T4 decreases to 54~174 nmol/L, but the level of T3 may be normal or lower than normal (the normal level is between 1.2 and 3.4 nmol/L). Transient CH diagnosis of those whose thyroid function, physical and mental development were all normal after treatments was discontinued for one month and after 2 to 3 years of regular treatment.

The development quotient (DQ) was used to evaluate the overall mental development in children. A DQ score≥85 was considered as normal, the range from 76 and 85 as borderline, with a DQ<75 indicating impaired mental development. The ability assessment covers four areas: personal behaviour, language ability, motor behaviour and adaptive behaviour.

Statistical analysis

All values were analysed with SPSS Windows 10.0, with values shown as mean±*SD*. Comparison of T3, T4 and TSH levels were made with ANOVA one-way test and the DQ scores were tested in dependent sample *t* test. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

Physical development, bone age, 99mTc scans and ultrasonography findings on our 57 children with transient CH were all normal. Our 57 children with transient CH received L-T4 treatment for an average of (28.09±9.56) months with a mean dosage of (16.25±3.87) μg/d (equal to (3.21~5.81) μg/(kg·d)). More specifically, 15 children (26.32%) were given 12.5 μg/d and 8 children (14.04%) were given 25 μg/d over the whole course of therapy, while the initial dosage of 25 μg/d was reduced to 12.5 μg/d in 34 children (59.65%). T4 and TSH levels improved significantly after the first month of treatment ($P<0.01$), as shown in Table 1.

Results from the four areas of DQ assessment are listed in Table 2. Two children (3.51%) only reached a total DQ score between 76 and 85, 41 children (71.93%) ranged between 85 and 115 and 14 children (24.56%) achieved a total score of more than 115. Statistical comparison of CH group and control group showed a significantly higher DQ score of responsiveness to external stimuli for CH children (Table 2).

DISCUSSION

Congenital hypothyroidism is a common endocrinological disease. Early diagnosis and timely treatment are crucial for ensuring normal mental and

Table 1 Comparison of T3, T4 and TSH levels (mean±*SD*) before and after treatment

	T3 (nmol/L)	T4 (nmol/L)	TSH (mU/L)
Before treatment	2.46±1.32	46.01±37.46	66.81±15.83
After 1 month of treatment	2.49±0.56	119.83±42.42*	10.09±13.35*
After 1 month of discontinued therapy	2.60±0.26	147.20±35.58*	2.74±1.92*

*Compared with before treatment, $P<0.01$

Table 2 Comparison of DQ scores (mean±*SD*) in the CH group and in the control group

Groups	Cases (*n*)	Personal behaviour DQ score	Language ability DQ score	Motor ability DQ score	Adaptive behaviour DQ score	Total DQ score
CH group	57	103.5±14.6	103.6±18.3	106.9±17.8	111.2±18.7	106.6±14.4
Control group	29	101.3±9.6	101.4±7.8	102.1±7.4	101.7±7.8	102.4±8.6
t		0.73	0.62	1.38	2.61	1.46
P		>0.05	>0.05	>0.05	<0.05	>0.05

physical development of the affected children. Oral substitution of thyroxin is the standard therapy for CH.

CH can manifest itself as a permanent or as a transient pathological condition. Permanent dysfunction mainly results from maldevelopment, absence or dystopia of the thyroid gland, whereas the underlying causes of transient functional impairment are less clear and may include maternal factors, such as excessive iodine intake, anti-hyperthyroid medication or the presence of antibodies against thyroid tissue during pregnancy. Children with transient CH show normal mental and physical development under thyroxin treatment, which can be discontinued after two or three years (Wu *et al*., 1995).

The 57 children in our study were diagnosed as having CH at one month after birth on an average. Thyroxin substitution had an immediate therapeutic effect, as shown by a greatly improved T3/T4/TSH profile after one month of therapy. It took an average period of (43.40±18.99) d for the 57 children to get a normal level of TSH. The mean value of TSH was (3.32±1.99) mU/L.

There are different opinions on the proper initial dose of L-T4 to CH. Gruters *et al*.(1997) recommended 8~15 μg/(kg·d) as a suitable dosage. But Campos *et al*.(1995) reported that there was no significant difference between the DQ of two groups treated with low and high starting dose of L-T4 after 5 years of follow-up. Moreover long-term follow-up studies found that high starting dose of L-T4 might cause more behavior problems reflecting increased anxiety, social withdrawal, and poorer concentration (Rovet and Ehrlich, 1995; Oerbeck *et al*., 2003). The starting dose of L-T4 we used is in conformity with what Campos and Rovet reported, but is much lower than the commonly used dose of 8~15 μg/(kg·d) or the 10.1~15.0 μg/(kg·d) reported from previous studies (Gruters *et al*., 1997; Hrytsiuk *et al*., 2002; Salerno *et al*., 2002). Patients with permanent CH require long-term substitution with a large dose of thyroxin (Rovet and Ehrlich, 1995). But in our study, to transient CH patients, a daily hormone substitution of 12.5~25 μg to patients was sufficient to maintain a normal T3/T4/TSH profile and to support normal growth and development. In 59.65% of patients the substituted amount of thyroxin could eventually be reduced by one-half over the course of the therapy. This showed that thyroid function gradually recovered as the children grew up. Normal findings on SPECT and ultrasonography scans without signs of maldevelopment, absence or dystopia also suggest that the cause of the transient thyroid insufficiency was functional, rather than morphological in nature.

Evaluation of the mental development in children should cover four distinctive areas: first, personality behaviour reflecting the child's living and communication abilities; second, language ability including listening, comprehension and expressive skills; thirdly, motor ability, such as climbing, walking, standing and the manual skills; and finally, adaptive behaviour representing the child's analytical and comprehension ability in dealing with the environment. The standardized DQ includes all these aspects and thus summarises the state of neurological and mental development in children. Hypothyroidism

adversely affects neuronal biochemical processes and subsequently the mental capacity and the ability to think logically. Typical CH children develop severe mental and physical retardation, unless they receive timely and adequate treatment (Hsiao *et al*., 2001). Reports from earlier studies on CH patients show that a direct relation exists between the extent of hearing loss and the age at which treatment for CH was initiated (Wasniewska *et al*., 2002). Furthermore, delayed recovery of elevated TSH levels is considered a major indicator of impaired mental development (Rovet and Ehrlich, 1995; Salerno *et al*., 2002). Rovet and Ehrlich (1995) and Salerno *et al*.(2002) believed that large doses of thyroxin (>10 μg/(kg·d)) are needed in order to rapidly normalise the T3/T4/TSH profile and that higher doses lead to a more favourable outcome, compared with low-dose treatment (<9 μg/(kg·d)). Our data showed the rapid normalization of TSH after one month of low-dose treatment and a normal T3/T4/TSH profile after discontinued substitution and one year of follow-up, while physical and mental development were not different from that of healthy peers at age 2 to 3. We therefore think that low-dose thyroxin is an adequate treatment for CH children if early diagnosis and timely treatment soon after birth is possible, if fast normalization of T3/T4/TSH can be achieved and if these laboratory parameters can be maintained within the normal range on follow-up examinations. If evaluation after discontinued substitution at the age of 2 to 3 shows normal thyroid function, as well as normal physical and mental development, congenital hypothyroidism can be diagnosed as transient without the need for continuous therapy. This way, the psychological pressure and the economic burden for the affected children and their families can be reduced greatly and precious medical resources can be saved as well.

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