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Monozygotic Twin Boys Concordant for Congenital Hypothyroidism: Two Cases

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Abstract Twins or multi-pregnancy is reported to have much higher risks for congenital hypothyroidism (CH), and most twins are discordant for CH. Monozygotic twins concordant for CH are rare. We describe two monozygotic twin-pairs concordant for CH. Filter paper screening was performed and a blood spot thyroid-stimulating hormone (TSH) value higher than 9 mU/L led to recall for whole blood evaluation. One of each twin pairs was normal at initial neonatal screening, while delayed TSH elevation and low T4 level were found in the diagnosis testing 2-3 weeks later. The L-thyroxine (L-T4) replacement therapy was initiated when the diagnosis was made. The initial dosage of L-T4 for the twins was 8 μg/d/kg. After 16 months of follow-up, thyroid function and development were all normal for the twin pairs.

Key words Congenital hypothyroidism; Screening strategy; Twins

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation.[1] Early diagnosis and treatment will benefit the good outcome of the patients and prevent them from severe mental retardation.[1-3] According to Devos et al's report, approximately 85% of CH cases in iodine-sufficient countries are due to defective differentiation or migration of the embryonic thyroid (thyroid dysgenesis), the cause of which is generally unknown.[4] Twins or multi-pregnancy are reported to have much higher risks for CH, and the majority of monozygotic twins are discordant for CH.[5,6] We recently encountered two pairs of monozygotic twin boys who are concordant for congenital hypothyroidism. In this case presentation, we describe the neonatal screening, diagnosis, treatment and follow-up for the twin boys.

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Case Report

First Twin-pair

These twin boys (A and B) were born at 37 weeks of gestational age after a normal pregnancy and with an uneventful delivery. Neonatal course was unremarkable, and family history of hypothyroidism was denied by the parents.

Mother's thyroid function and anti-thyroid autoantibodies were normal. Twin A had a birth weight of 3000 g and had mildly elevated thyroid-stimulating hormone (TSH) level (13.6 mU/L) at screening on postnatal day 4. According to our center's screening program, the blood spot TSH cut-off value is 9 mU/L. But for twins, both twins should be recalled even if only one of the twins has a blood spot TSH level above 9 mU/L. The twin boys were recalled and definitive testing was taken on day 23 after birth. Thyroid hormone testing and thyroid ultrasound were performed for the twins. Twin A had a high serum TSH level of more than 75 mU/L (reference range: 0.34-

5.6 mU/L) and a low free thyroxine (FT4) level of 6.6 pmol/L (reference range: 10.0-31.0 pmol/L). Twin B who although had a normal TSH level of 8 mU/L at screening was also found to have a high serum TSH level of more than 75 mU/L and a low FT4 level of 7.2 pmol/L. Thyroid ultrasound showed normal size and location of thyroid gland for the twins. According to the guidelines for diagnosis of congenital hypothyroidism, any infant with a low T4 concentration and increased serum TSH concentration is considered to have primary hypothyroidism in the confirmatory serum test.[1] The twin boys were diagnosed having congenital hypothyroidism. L-thyroxine (L-T4) replacement therapy was initiated and the initial dosage of L-T4 for the twins was 8 μg/d/kg. After one month of follow-up, thyroid function became normal, serum TSH level decreased to normal range and FT4 level increased (Table 1). The L-T4 dosage was reduced to 4 μg/d/kg at 3 months of follow-up. Thyroid function and development were all normal at the recent follow-up when the twins were 16 months of age.

Second Twin-pair

The monozygotic twin boys were born prematurely to healthy unrelated parents at 34 weeks of gestational age, with a low birth weight (twin A: 2100 g; twin B: 1900 g) after a cesarean section. The parents had no remarkable thyroid diseases. Mother's thyroid function and anti-thyroid autoantibodies were normal. The twin boys were referred to the neonatal ICU and intubated due to the twin to twin transfusion syndrome. Twin A had hyperbilirubinemia and received phototherapy. Twin B had severe anemia and was treated in NICU for 14 days. Neonatal screening was performed on postnatal day 4. Twin B was found to have a remarkable elevation of TSH at 31.6 mU/L at screening but twin A was normal (TSH level: 1.4 mU/L). Definitive analysis was performed for both boys on day 14 with a corrected gestational age of 36 weeks. The results showed that the two boys had a high serum TSH level (>75.0 mU/L) and low FT4 level (8.6 pmol/L and 5.3 pmol/L, respectively) (Table 1). Thyroid ultrasound results were normal in these two boys. The initial dosage of L-T4 for the boys was 8 μg/kg/d. Thyroid function was normalised after 1 month since the replacement therapy was initiated. Thyroid parameters and development were all normal at the last follow-up when the twins were 17 months of age.

Discussion

Twins are widely reported to have more morbidity than singletons, mainly because of a higher preterm birth rate. A more than 3-fold higher frequency of twins was found in the CH population than in the general population.[5] The prevalence of CH is 1/1800-1/2000 in the general population, in Zhejiang Province, China. Most of the twins are discordant for CH. According to Olivieri and his colleagues' report,[5] the concordance rate for permanent CH was only 4.3% in all the 80 couples of CH twins studied. Three couples (all boys with in situ gland and unknown zygosity) and one triplet (two girls and one boy with in situ gland) were concordant for CH at birth. Three couples had permanent CH and one triplet for transient CH. The monozygotic twin-pairs in the present study are very rare and both are concordant for CH. They will be followed and a trial-off therapy will be given at 3 year of age to assess if CH is permanent.

In about 10% of cases, congenital hypothyroidism is the consequence of defects in one of the steps of thyroid hormone synthesis, dyshormogenesis. Thyroid dysgenesis, accounts for about 85% of all cases with congenital hypothyroidism. These anomalies include thyroid (hemi) agenesis, ectopic thyroid tissue, cysts of the thyroglossal duct, and thyroid hypoplasia.[6] Thyroid dysgenesis is one of the common causes for monozygotic twins with CH.[7] For our cases, thyroid ultrasound results were normal. Dyshormonogenesis was one possible cause of CH in these twin boys. However, we cannot perform thyroid

Table 1. Thyroid function parameters of the two pairs of twins at screening, diagnosis and follow-up

Twins	Gender	Zygosity	TSH Screening (mU/L)	TSH Diagnosis (mU/L)	FT4 Diagnosis (pmol/L)	TSH Follow-up (mU/L)
1	Male	Monozygotic	13.5	> 75.0	6.6	1.51
	Male		8.0	> 75.0	7.2	0.80
2	Male	Monozygotic	31.6	> 75.0	8.6	0.59
	Male		1.4	> 75.0	5.3	1.33

radioisotope scan for them due to the facility limitation in our hospital. We also cannot know the fathers' real thyroid function without checking, although both of them denied thyroid function disorders. So the causes for these two twin-pairs are obscure. We should strengthen in checking the paternal thyroid function as well as the maternal thyroid function for the CH cases, and the maternal iodine intake should also be investigated in further practice.

In the present two twin pairs, one of each twin pair had normal TSH level at screening and delayed TSH level elevation was found at or after 14 days. In considering the high rate of prematurity and low birth weight in multi-pregnancies, twins with an initial blood spot TSH concentration greater than or equal to 9 mU/L will be recalled for definitive testing in our screening center. Both twins will be recalled even if only one of them was found to have positive screening results. The two boys with normal screening results in the present report (TSH=8.0 mU/L; TSH=1.4 mU/L) will be missed if they were not referred together with their affected twins. However, we still may miss the twins with fetal blood mixing, who may have normal screening results due to the free transfer of T4 from the euthyroid twin and maintain TSH in the normal range in the hypothyroid twin until a few days after delivery.[8] Therefore, a second screening in the same-sex twins at 14 days after birth is necessary.

Kugelman et al[9] suggested even if a re-screening policy is implemented, a high clinical index of suspicion should be kept for same-sex twins. Re-screening in all the same-sex twins is impossible now in our neonatal center due to the extra economic burden on the parents of the twins. False-negative results may occur at screening in the twins or multi-pregnancy. So, clinicians must be alert to symptoms or signs which are indicative of possible hypothyroidism and clinical symptoms and/or family history of thyroid disorders indicating the need for thyroid testing, regardless of newborn screening results.

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