HK J Paediatr (new series) 2020;**25**:236-239

Case Report

Two Cases of Neonatal Graves' Disease Illustrating the Role of Thyrotropin-receptor Antibody (TRAb) as a Diagnostic and Surveillance Marker

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Abstract Neonatal Graves' disease is an important but rare neonatal condition. We report two cases of neonatal Graves' disease with drastically different clinical manifestations. These cases highlight the importance of accurate history taking in pregnant patients and demonstrates the clinical utility of thyrotropin-receptor antibody (TRAb) as a predictor of neonatal hyperthyroidism.

Key words Anti-TSHR; Graves' disease; Hyperthyroidism; Neonatal thyrotoxicosis; TRAb

Introduction

Neonatal Graves' disease results from the maternal transfer of thyrotropin-receptor antibodies (TRAbs) to the foetus during the second half of pregnancy. TRAbs are heterogeneous in terms of their molecular and functional properties. They can be classified into different subclasses: stimulating (TSAbs), blocking (TBAbs), or neutral (N-TRAbs).[1] The relative proportion of stimulating and blocking activities in the maternal circulation and their clearance rate from the neonatal circulation determine the severity of symptoms and the timing of disease onset.

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Received September 28, 2019

Case Report

Case 1: Our first patient was a premature female infant born in June 2016. The baby's mother was a 26-year-old primigravida who did not receive antenatal medical care. She was admitted for rupture of membranes at 30 weeks' gestation when she was diagnosed with Graves' thyrotoxicosis. Her serum TRAb level was >40 IU/L (Reference range: <1 IU/L). She was started on propylthiouracil (PTU) and propranolol. She delivered her baby two days after admission. Her baby weighed 1330 grams and required respiratory support at birth. She had triangular facies and bilateral exophthalmos, without the presence of goitre. Developmental maturity was estimated to be 36-38 weeks by the New Ballard score. Knee radiographs showed ossification of both distal femoral epiphysis and proximal tibial epiphysis, indicating the baby reached full term maturity, which likely resulted from thyrotoxicosis due to uncontrolled maternal Graves' disease.

During the first few days of life, the baby remained euthyroid. Serum TSH level was suppressed at <0.01 mIU/L (Reference range: 0.70-15.2 mIU/L) and fT4 level was normal. The baby remained stable on the subsequent few days. On day 9, the baby developed tachycardia, tachypnoea and excessive irritability. Serum fT4 was >100 pmol/L (Reference range: 11.5-28.3 pmol/L). Thyrotoxicosis was diagnosed and antithyroid treatment was started right away. PTU was commenced at a dose of

5 mg/kg/day. Propranolol and Lugol's solution were also given. The baby's symptoms resolved with treatment. Her thyroid function returned to normal upon stepwise adjustment of PTU. All medications were discontinued on day 65. The serum thyrotropin-receptor antibody (TRAb) level also decreased gradually with time (Figure 1). The baby had satisfactory weight gain after treatment and was discharged from the hospital at one and a half months old.

Case 2: Our second patient was a full-term female infant born in January 2017. The baby's mother was a 31-year-old primigravida with a history of autoimmune thyrotoxicosis. She received two courses of radioactive iodine (RAI) treatment in 2014 and 2015 respectively and was on regular thyroxine replacement. Maternal thyroid function and foetal ultrasound surveillance were normal throughout pregnancy. TRAb test was not done during the antenatal period. She delivered her baby girl at 38 weeks' gestation. The baby weighed 2680 grams and was born in good condition. She had no goitre and was euthyroid. Cord blood showed mildly elevated fT4 at 38.47 pmol/L (Reference range: 11.5-28.3 pmol/L) and suppressed thyroid stimulating hormone (TSH) at <0.01 mIU/L (Reference range: 0.72-11.0 mIU/L). These blood tests results were not available initially because of a long turnaround time.

During the first 5 days of life, the infant remained asymptomatic. However, thyroid function test on day 6 showed biochemical evidence of thyrotoxicosis. Serum fT4 level was >100 pmol/L (Reference range: 11.0-32.0 pmol/L). Antithyroid treatment was started on day 7. PTU

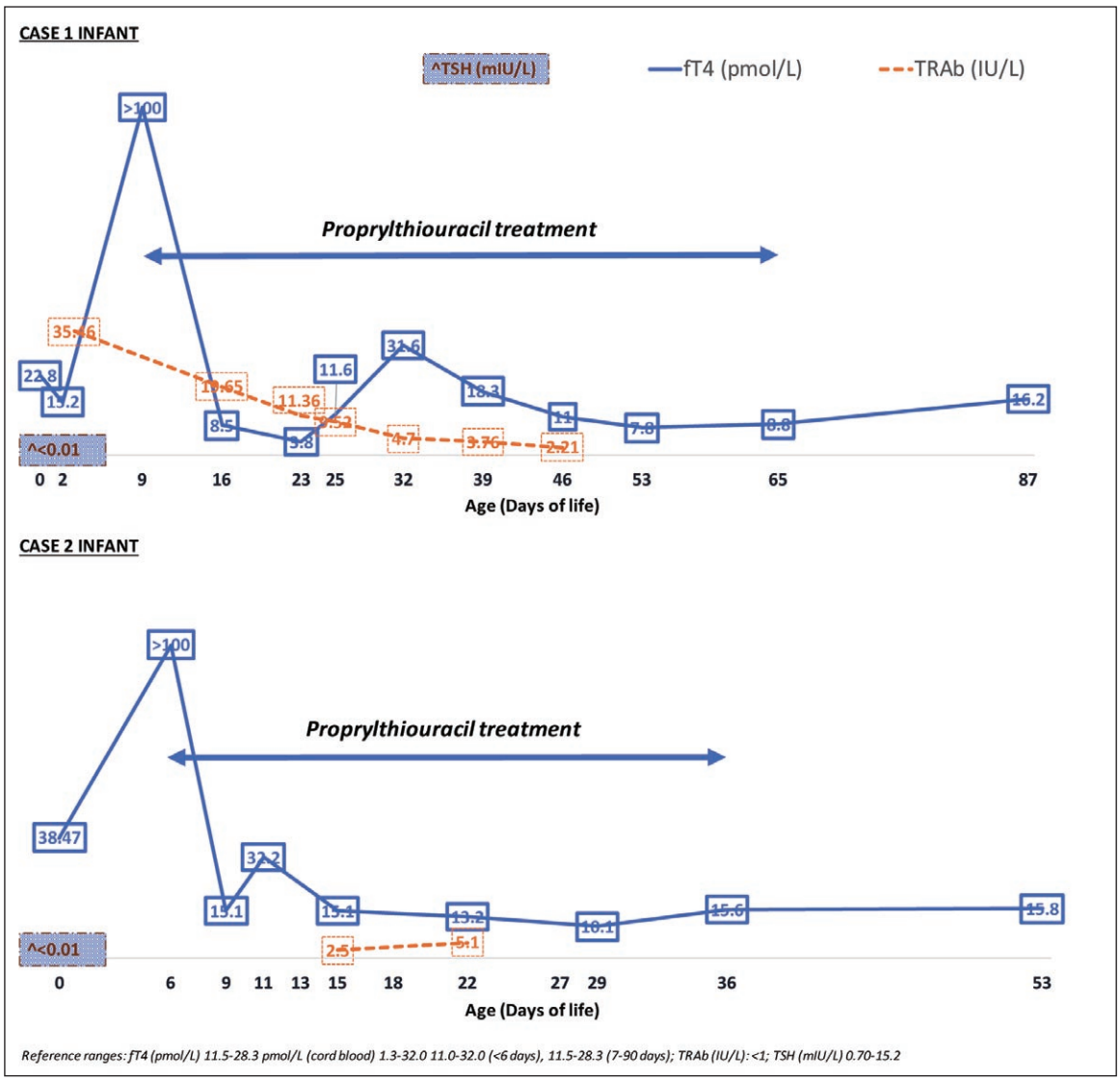

Figure 1 Serum fT4 and TRAb levels in case 1 and case 2 infant.

was given at a dose of 5 mg/kg/day, together with propranolol and Lugol's solution. Serum fT4 level returned to normal on day 9 and TSH level normalised on day 15. The baby was discharged from special care baby unit on day 26. The dosage of PTU was tapered and discontinued on day 36. All along the baby did not exhibit any clinical sign of thyrotoxicosis. The corresponding maternal TRAb level on day 21 was 4.6 IU/L. (Reference range: <1 IU/L).

Discussion

Severity of Disease

Previous studies have shown a strong correlation between maternal and neonatal TRAb levels.[2,3] This could be reflected on the postnatal course of our infants. Both infants developed thyrotoxicosis with high fT4 yet they presented with different clinical pictures. This can be attributed to different end organ responses to thyroxine in different individuals. Figure 1 shows that both infants' fT4 levels fluctuated after the start of PTU treatment. The first infant's fT4 dropped to 3.8 pmol/L (Reference range: 11.5-28.3 pmol/L) on day 23 as a result of overtreatment. Overdosing of antithyroid drugs occurs not uncommonly in neonates where dose titration is especially difficult.

Timing of Disease Onset

Infants born to mothers with Graves' disease can present at different times after birth. This depends on the metabolism of maternal antithyroid drugs (ATD) and the relative clearance of TRAb functional subclasses from the infant's body. The first infant was asymptomatic on the first few days of life because of the effects of maternal antithyroid ATD. Since ATD were metabolised faster than TRAbs,[4] the infant ultimately became hyperthyroid. On the other hand, the second case demonstrates that even without the effects of ATD, the onset of neonatal Graves' disease could be delayed, owing to the more rapid clearance of TBAbs than TSAbs in the infant's circulation. Delayed presentation of up to 45 days has been reported in the literature.[5]

Antenatal Screening

Conventionally tested thyroglobulin antibodies and anti-thyroid peroxidase antibodies during pregnancy are not related to the pathophysiology of neonatal Graves' disease. Instead, it is the transplacental transfer of TRAbs that causes neonatal hyperthyroidism or hypothyroidism. TRAb, therefore, is both a pathogenic and diagnostic hallmark for neonatal Graves' disease. Testing of TRAb is particularly useful to identify pregnant women who have treated autoimmune thyroid disease and who remain euthyroid during pregnancy. TRAb levels can remain elevated after definitive antithyroid treatment in spite of normal thyroid status.[6,7] As illustrated in our second case, the mother continued to harbour a significant level of serum TRAb even though she had received RAI treatment before. This could be explained by the escape of the autoreactive T cells and the shed A-subunit of TSH receptor in the circulation. Laurberg et al reported that TRAb levels continued to be elevated in 40% of patients five years after RAI treatment.[7]

Testing of maternal TRAb level can predict the development of neonatal Graves' disease. A maternal TRAb value >5 IU/L or 3 times the ULN of the second-generation assay has been proposed as a cut-off value to identify high-risk cases.[3,8] The American Thyroid Association recommends maternal TRAb testing in selected patients as shown in Table 1.[4] No further testing is required if the initial TRAb level is below the reference range, as a negative TRAb has a high negative predictive value of neonatal Graves' disease.[3,4,8]

Postnatal Surveillance

Determining TRAb level of the infant from the cord blood or immediately after birth could help identify infants at risk of neonatal Graves' disease. As neonatal thyrotoxicosis can develop acutely, parents of high-risk infants should be educated about the symptoms of thyrotoxicosis. In our first infant, there was a sudden onset of symptoms on day 9. In our second infant who only had biochemical thyrotoxicosis, there was also a very rapid rise of serum fT4 level from 32.3 pmol/L to >100 pmol/L (Reference range: 11.5-28.3 pmol/L) within a day. In fact, the suppressed cord blood TSH in both infants predicted the subsequent development of thyrotoxicosis. Therefore it would be ideal to have readily available in-house measurements of TSH to help pick up these suspected cases quickly.

Table 1 Indications for ordering a TRAb test in pregnant women

(a) History of thyroidectomy for the treatment of hyperthyroidism in pregnancy
(b) Untreated or antithyroid drug-treated hyperthyroidism in pregnancy
(c) History of Graves' disease with past treatment with radioactive iodine or surgery
(d) History of delivering an infant with hyperthyroidism

Currently, there is no consensus on the optimal follow-up interval of high-risk infants. However, close surveillance of the biochemical and clinical thyroid status is important even if the infants are asymptomatic at birth. A literature-based review by van der Kaay et al recommends testing TRAb in high-risk infants' cord blood, with monitoring of thyroid function on day 3-5 and day 10-14 respectively, followed by outpatient follow-up till 2 to 3 months old.[2] On the other hand, infants with a negative test could be discharged from follow-up.[2] A French recommendation also advocates testing of TRAb in high-risk neonates as part of the postnatal management.[9] Presently, TRAb testing is not widely available in Hong Kong because of resources limitation. This has become a major obstacle for local clinicians to adopt the recommendations from international guidelines.

Conclusion

There are a few clinical pearls presented in our cases. Firstly, the severity and time of onset of neonatal Graves' disease are highly variable. Parents should be counselled on the possibility of a delayed but acute onset of the disease. Secondly, past medical history of thyroid problems in all pregnant women should be accurately ascertained. Finally, TRAb testing should be advocated in selected pregnant women and infants as it has an important implication on Graves' disease identification and management.

Declaration of Interest

There is no conflict of interest to declare.

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