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CASE REPORT

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Neonatal graves' disease complicated with cholestatic jaundice: a case report

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Abstract

Background Neonatal cholestatic jaundice and elevated liver enzymes can result from various etiologies, including anatomical, infectious, endocrine, and metabolic abnormalities. Unlike hypothyroidism, hyperthyroidism is rarely associated with neonatal cholestasis. This study presents a unique case of neonatal Graves' disease complicated by cholestatic jaundice and discusses the challenges in diagnosis, treatment, and management.

Case presentation We report a 30-day-old male infant, born by vaginal delivery at 36.4 weeks gestational age, born weight was 2550 g, to a mother with a history of hypothyroidism during pregnancy, undiagnosed thyroid disease before. The infant developed manifestations of hyperthyroidism, poor weight gain, and cholestatic jaundice shortly after his inception. A variety of tests were used to confirm the diagnosis of neonatal Graves' disease. After 6 weeks of propylthiouracil and hepatoprotective choleretic therapy, thyroid-thyrotropic hormonal metabolism returned to normal, cholestatic jaundice disappeared after 2 months, and liver enzymes returned to normal after 3 months. In addition, the child's weight and length growth returned to the normal range during the follow-up period.

Conclusions Neonatal Graves' disease can be associated with cholestatic jaundice and may have long-term health consequences for the newborn. Early diagnosis and appropriate treatment are crucial for improving the prognosis. This case emphasizes the importance of monitoring pregnant women for thyroid dysfunction and its potential impact on the newborn.

Keywords Graves' disease, Jaundice, Cholestasis, Infant, Diagnosis

Introduction

Graves' disease is an autoimmune disease characterized by hyperthyroidism. It is common in adults but is rare in neonates, particularly as a metastatic disease associated with pregnancy. Neonatal Graves' disease is usually caused by the transmission of mother-produced stimulatory thyroid receptor antibodies (TRAb) across the placenta to the fetus, causing hyperthyroidism in the fetus and neonates [1]. Cholestatic jaundice is a common condition in the neonatal period and involves obstruction of bile excretion or circulation. Causes may include structural abnormalities of the biliary tract, inherited metabolic disorders, or infections, and are less often associated with cholestasis than hypothyroidism. Although cholestatic jaundice is relatively common in neonates, its association with neonatal Graves' disease is very rare, complicating diagnosis and treatment [2].

Past studies have focused on the diagnosis and treatment of adult Graves' disease, and relatively few cases of neonatal Graves' disease have been reported, especially those with complex cases such as cholestatic jaundice [3]. These studies suggest that diagnosing neonatal Graves'

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disease is challenging, even in the presence of a high level of alertness, and requires a combination of clinical presentation and laboratory indicators. This study provided a detailed case report on neonatal Graves' disease complicated with cholestatic jaundice, and through the in-depth analysis of this particular case, the medical community can deepen the understanding of this rare disease combination and promote the development of more effective diagnostic and treatment strategies.

Case presentation

We report a rare case of fetal/neonatal Graves' disease with cholestatic jaundice. The child was a 30-day-old male, with a gestational age of 36.4 weeks and a birth weight of 2550 g (P40), who had been hospitalized for neonatal wet lung and neonatal ABO blood group incompatible hemolytic disease for 7 days after birth, and there was no special abnormality in cardiac ultrasound during the period. Postnatal the infant was breastfed with preterm formula milk, reached exclusive breastfeeding on the 3rd day after birth, and regained birth weight on the 8th day after birth, and did not routinely measure thyroid-thyrotropic hormonal metabolism. On the 21st day after birth, the infant showed irritability, which was not easy to comfort, the amount of milk increased, and the frequency of stool increased, 8–10 times per day, from yellow paste stool to white clay-like loose stool, and the weight was 2740 g on 30th day after birth, which was lower than the 3rd percentile weight of infants of the same age and sex.

The patient's mother was 30 years old, denied family hereditary diseases, had 2 pregnancies, 1 spontaneous abortion, and was diagnosed with hypothyroidism during this pregnancy, and treated with levothyroxine at the 14th week of pregnancy, and adjusted the medication according to the monitoring of TSH fluctuations (shown in Fig. 1) (normal level during pregnancy is 0.1–2.5 mIU/L). Fetal ultrasound in the 19.6th week of pregnancy showed rapid heart rate, in the 23.6th week showed fetal heart enlargement, in the 25.4th week fetal heart rate enlargement, fetal heart rate baseline 160–170 beats/min, and then monitoring returned to normal. 5 weeks after delivery, the TRAb was 40.00 IU/L, T3 was significantly increased, TSH was significantly decreased, and Hashimoto's thyroiditis was diagnosed later.

Physical examination of the patient admitted to the hospital showed that the whole body was emaciated, the subcutaneous fat was thin, the skin of the face and trunk was moderately yellowish, and the complexion was dark yellow. The cardiopulmonary auscultation was negative, the heart rate was 170 beats/min, the abdomen was soft, the liver was 3 cm subcostal, the middle was medium, and the spleen was not palpated. A right-sided inguinal hernia was present, with the contents of the hernia sac extending into the abdominal cavity. Primitive reflexes were elicited normally, and the extremities displayed normal muscle tone. Laboratory studies: normal arterial blood gas analysis. Routine tests of blood, urine, and stool were normal, CRP 0.81 mg/L and blood culture was negative. Blood biochemistry indexes: alanine aminotransferase (ALT) 226 U/L, aspartate aminotransferase (AST) 380 U/L, total bilirubin 142.7 μmol/L, direct bilirubin 114.8 μmol/L, total bile acids 323.3 μmol/L. The trend of ancillary examinations with the age of the children is shown in Fig. 1A-D. Thyroid-thyrotropic hormonal metabolism: FT4 > 100.0pmol/L, FT3 49.8pmol/L, T3 > 10.0nmol/L, T4 > 320.0nmol/L, TSH 0.006uIU/ml. The TRAb level was 40.00 IU/L, thyroglobulin antibody was 10.0 IU/ml, and thyroid peroxidase antibody was 13.0 IU/ml. Parathyroid hormone levels were within the normal range. The thyroid ultrasound indicated thyroid enlargement (isthmus thickness: 0.4 cm, left lobe thickness: 0.9 cm, right lobe thickness: 1.2 cm), with increased blood flow velocity in both bilateral superior thyroid arteries, showing a left peak systolic velocity (PSV) of 42.2 cm/s and a right PSV of 40.9 cm/s. PCR testing for EBV, CMV, EV71, B19 virus, coxsackievirus, hepatitis B virus, and other viruses returned negative results. The ECG showed sinus tachycardia, and the chest X-ray revealed no significant abnormalities. The fundus examination was unremarkable. Screening for hematuria, as well as inherited and metabolic diseases, was normal.

Diagnosis and follow-up: After admission, the child was initially evaluated, with a milk volume of 230 ml/kg.d and a calorie of about 150 kcal/kg.d. There was no vomiting, abdominal distention, blood in the stool or obvious diarrhea, except for feeding intolerance. Due to the simultaneous presence of abnormal liver function, cholestasis, and slow growth, we considered the etiology was complex, actively improved the examination, and treated with reduced glutathione, vitamin C for hepatotherapy, ursodeoxycholic acid capsule for choleretic therapy, changed breast milk to medium-chain fatty acid formula feeding to reduce the burden on the patient's liver. Supplementation with fat-soluble vitamins and other treatments. On the second day of admission, the thyroid-thyrotropic hormonal metabolism report showed hyperthyroidism, and propylthiouracil 5 mg/kg.d was added for oral treatment 3 times. After 6 weeks of treatment, thyroid-thyrotropic hormonal metabolism was completely recovered, thyroid-stimulating hormone antibody receptor disappeared, cholestatic jaundice disappeared after 2 months, liver enzymes decreased to normal after 3 months, weight and length growth within 1 year of age were in the 10th percentile, head circumference growth was in the 50th percentile, and no special abnormalities were found in subsequent monitoring of growth and development.

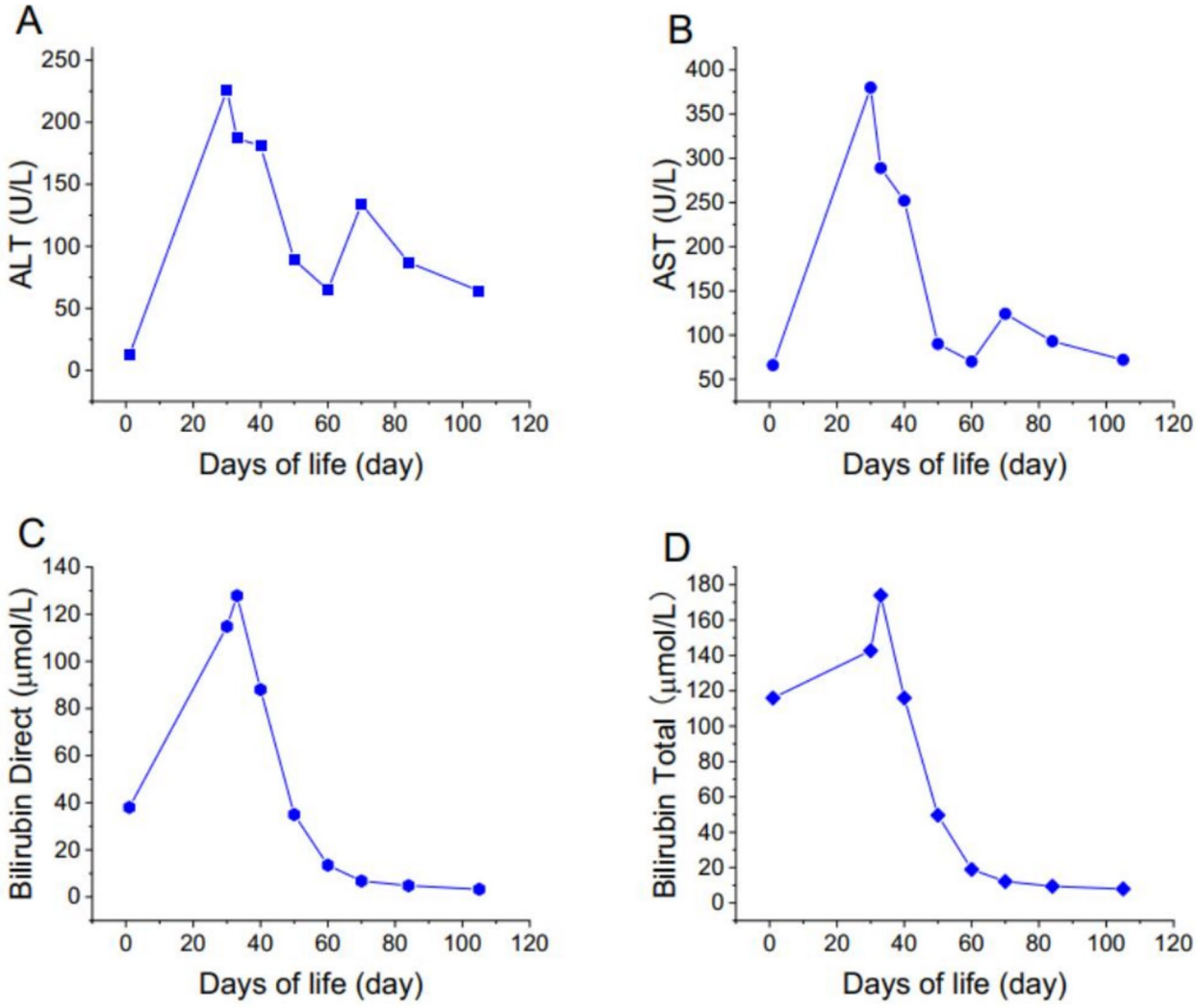

Fig. 1 Some laboratory indexes showed a trend with the age of infants. **(A)** alanine aminotransferase; **(B)** aspartate aminotransferase; **(C)** total bilirubin; **(D)** Direct bilirubin

Discussion

In this study, we report a rare case of fetal/neonatal Graves' disease, manifested by fetal heart rate increase, heart enlargement, neonatal goiter, hyperthyroidism, cholestatic jaundice, elevated liver enzymes, poor weight gain, and no abnormalities in neonatal disease screening, his mother had no diagnosis of thyroid disease before pregnancy and was treated with oral levothyroxine in the second trimester of pregnancy. After 6 weeks of treatment with propylthiouracil and hepatoprotective choleretic, the thyroid-thyrotropic hormonal metabolism was completely restored, the thyroid-stimulating hormone antibody receptor disappeared, the cholestatic jaundice disappeared after 2 months, the liver enzymes decreased to normal after 3 months, and the weight gain was satisfactory.

Fetal/neonatal Graves' disease is a relatively rare disorder. A small number of babies born to women with autoimmune thyroid disease, whether pre-existing or occurring during pregnancy, will exhibit hyperthyroidism. Neonatal Graves' disease may represent the persistence of fetal hyperthyroidism, mainly due to probable transplacental transfer of TRAb from the mother to the fetus [4]. Rare cases of neonatal hyperthyroidism may be secondary to activating mutations in the TSH receptor gene or mutations in the GNAS gene, which encodes the α subunit of the stimulatory G protein (observed in McCune-Albright syndrome), which usually results in persistent hyperthyroidism. However, the vast majority of affected newborns are born to mothers with definite Graves' disease or who have previously undergone a thyroidectomy or radioactive iodine therapy [5]. TRAb, which belongs to IgG or radioactive iodine therapy. TRAbs belong to the IgG class and can freely cross the placenta and mainly include three types: thyroid-stimulating antibody (TSAb), thyroid-suppressing antibody

(TSBAb), and thyroid growth immunoglobulin (TGI). Among them, TSAb can competitively bind to TSH receptors, and when TSAb binds to TSH receptors beyond a certain amount, it activates adenylyl cyclase (cAMP system), thereby increasing the synthesis and secretion of thyroid hormones while inhibiting TSH secretion. Fetal tachycardia is an important indicator of fetal hyperthyroidism. In this case, the patient's mother took levothyroxine for hypothyroidism in the second trimester, leading to a significant decrease in TSH during pregnancy. Despite signs of fetal hyperthyroidism, including an enlarged heart and increased heart rate, the obstetrician adjusted the thyroxine dose without further investigation. After the newborn's diagnosis, additional tests revealed elevated thyroid peroxidase and thyroglobulin antibodies, with TRAbs > 40 IU/L, confirming maternal Hashimoto's thyroiditis. To our knowledge, this is the first reported case in China of neonatal hyperthyroidism linked to maternal Hashimoto's thyroiditis. The absence of maternal hyperthyroidism may result from autoimmune-induced thyroid damage that impairs thyroid function while maintaining sufficient hormone production for a euthyroid state, though this may only play a partial role. More importantly, studies indicate that the autonomic nervous system has a direct and substantial impact on thyroid function, whereas the immune system, mediated by antibodies, plays a secondary role in thyroid pathology [6–8]. This secondary effect works synergistically with the autonomic nervous system and interstitial channels, contributing to overall thyroid dysfunction. Further exploration of these mechanisms could provide critical insights into the underlying causes of thyroid disorders in both mothers and neonates, potentially leading to improved clinical approaches.

Liver involvement in patients with Graves' disease has been reported in both adults and neonates. Although hepatic manifestations of neonatal Graves' disease are exceptionally rare, cases of neonatal hyperthyroidism with hepatic involvement have been described in the literature [9]. Notably, these manifestations are likely to result from complex mechanisms rather than a direct causal relationship. For instance, immune-mediated injury, metabolic dysregulation, or other secondary processes may contribute to hepatic involvement in neonatal Graves' disease. Most hepatosplenomegaly and cholestatic jaundice appear at birth or within 1 week after birth, and there is no relevant data on the recovery time after treatment. Our patient had cholestatic jaundice resolution after 2 months of treatment and liver enzymes decreased to normal after 3 months. The incidence of neonatal direct bilirubinemia is 1/2500, which can cause progressive and long-term jaundice in neonates, and its differential diagnosis is widespread, but neonatal Graves' disease is not included in the differential diagnosis of cholestatic jaundice guidelines. Although neonatal Graves' disease is considered to be temporary, it can be combined with comorbidities such as heart failure and liver failure in the acute stage, and sequelae such as microcephaly and mental retardation in the long term, so early and reasonable treatment is advocated. At present, the main treatment regimen is the use of antithyroid drugs, including propylthiouracil (PTU) and methimazole (MMI), among which PTU has certain hepatotoxicity and MMI is preferred in neonates, but the safe dose range of MMI and the long-term impact on neonates need further clinical research and evaluation [10]. In view of our lack of understanding of antithyroid drugs, the child was treated with PTU, but fortunately, the preexisting liver function abnormalities and other adverse effects were not aggravated during treatment.

Regarding neonatal Graves' disease and breastfeeding, literature statistics show that the average content of thyroxine in breast milk is about 0.83 μg/L, and the infant receives less than 1% of thyroxine from the mother, so the amount of thyroxine in the breast milk of the mother taking thyroxine due to thyroid disease is not enough to cause the infant to have hyperthyroidism or inhibition of TSH secretion [11]. The delay in the onset of symptoms of hyperthyroidism in these children should be independent of the oral thyroxine tablets of their mothers while breastfeeding. For mothers with oral antithyroid drugs for hyperthyroidism, there is no contraindication to breastfeeding when treated with moderate amounts (MMI 20 ~ 30 mg/d, PTU less than 300 mg/d), but the infant's thyroid-thyrotropic hormonal metabolism needs to be monitored regularly.

Conclusion

In conclusion, this case report highlights the rarity and diagnostic challenges of concurrent cholestasis and hyperthyroidism in neonates. Through a thorough analysis of this case, we suggest that clinicians should consider multiple potential causes when encountering similar conditions, conduct detailed clinical assessments, and adopt a multidisciplinary approach to ensure precise and effective treatment. It is hypothesized that the occurrence of Graves' disease may be related to antibody transfer, particularly involving a nervous mechanism that could interact with other underlying processes. Future research should focus on optimizing diagnostic and therapeutic strategies for neonatal thyroid and liver diseases, as well as exploring the mechanisms behind such complex interactions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01938-9.

Supplementary Material 1

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Author contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Data availability
Data will be made available on request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and informed consent is waived with the approval of the Ethics Committee of Peking University International Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Written informed consent for the release of identifying images or other personal or clinical details has been obtained from the participant's parent or legal guardian.

Competing interests
The authors declare no competing interests.

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References

1. Vaidyanathan P. Update on pediatric hyperthyroidism. Adv Pediatr. 2022;69(1):219–29. https://doi.org/10.1016/j.yapd.2022.04.004.
2. Abebe A, Eck LM, Holyoak M. Severe cholestatic jaundice associated with graves' disease. Clin Case Rep. 2018;6(11):2240–5. https://doi.org/10.1002/ccr3.1859.
3. Khan AA, Ata F, Aziz A, et al. Clinical characteristics and outcomes of patients with antithyroid Drug-Related liver injury. J Endocr Soc. 2023;8(1):bvad133. https://doi.org/10.1210/jendso/bvad133.
4. Castellnou S, Bretones P, Abeillon J, et al. Congenital hypothyroidism due to a low level of maternal Thyrotropin Receptor-Blocking antibodies. Eur Thyroid J. 2021;10(2):174–8. https://doi.org/10.1159/000509015.
5. van Trotsenburg ASP. Management of neonates born to mothers with thyroid dysfunction, and points for attention during pregnancy. Best Pract Res Clin Endocrinol Metab. 2020;34(4):101437. https://doi.org/10.1016/j.beem.2020.101437.
6. Sawicka-Gutaj N, Zawalna N, Gut P, Ruchała M. Relationship between thyroid hormones and central nervous system metabolism in physiological and pathological conditions. Pharmacol Rep. 2022;74(5):847–58. https://doi.org/10.1007/s43440-022-00377-w.
7. Ushakov AV. Case of graves' disease recovery. J Clin Translational Endocrinology: Case Rep. 2023;57:100139. https://doi.org/10.1016/j.jecr.2023.100139.
8. Ushakov AV. Minor hyperthyroidism with normal levels of thyroid-stimulating hormone receptor antibodies: a case report. J Med Life. 2024;17(2):236–8. https://doi.org/10.25122/jml-2023-0458.
9. Sabra MK, Joudeh A, Al Niserat M, Hammamy R. A young patient with graves' disease presenting with a triad of heart failure, pancytopenia, and jaundice: A case report. Clin Case Rep. 2024;12(5):e8698. https://doi.org/10.1002/ccr3.8698.
10. Yoshimura Noh J, Inoue K, Suzuki N, et al. Dose-dependent incidence of agranulocytosis in patients treated with methimazole and propylthiouracil. Endocr J Published Online May. 2024;3. https://doi.org/10.1507/endocrj.EJ24-0135.
11. Watanabe N, Yoshimura Noh J, Akamizu T, Yamada M, study group members of the Japan Thyroid Association. Survey of the actual administration of thiamazole for hyperthyroidism in Japan by the Japan thyroid association. Endocr J. 2022;69(1):35–43. https://doi.org/10.1507/endocrj.EJ21-0238.

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