Case Report

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Neonatal Cholestasis Caused by Graves' Disease: A Case Report and Literature Review

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What is already known on this topic?

Congenital endocrine disorders—such as hypopituitarism, adrenal cortex hyperplasia, and hypothyroidism—are well-established causes of neonatal cholestasis.

What this study adds?

neonatal Graves' disease must be included in the differential diagnosis of cholestasis, particularly in infants whose mothers have Graves' disease or a history of thyroid dysfunction.

Abstract

This is a case report of neonatal cholestasis caused by Graves' disease, accompanied by a literature review of previously published cases. Neonatal/Infantile cholestasis (NIC) is defined as an impairment in bile formation and/or flow presenting by the first year of age, typically within the first three months. Hyperthyroidism has been less frequently associated with this condition. Here, we report a case of neonatal cholestasis caused by Graves' disease and review relevant literature to summarize its clinical characteristics, and to enhance prompt and accurate recognition and diagnosis of this disease. A 28-day-old female infant was admitted to our center, presenting with jaundice, diarrhea, poor weight gain, and tachycardia. Laboratory examinations showed cholestasis, hyperthyroidism, and positive for thyrotropin receptor antibody (TRAb), confirming the diagnosis of neonatal Graves' disease. After treatment with propranolol and intravenous immunoglobulin (IVIG), the jaundice subsided, and thyroid function returned to normal. Neonatal Graves' disease must be included in the differential diagnosis of cholestasis, particularly in infants whose mothers have Graves' disease or a history of thyroid dysfunction. Early detection of hyperthyroidism in neonates with cholestasis is crucial.

Keywords: Neonatal cholestasis, neonatal Graves' disease, neonatal hyperthyroidism

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Introduction

Neonatal/Infantile cholestasis (NIC) is defined as an impairment in bile formation and/or flow presenting by the first year of age, typically within the first three months. This condition leads to the retention of bile and biliary substances in the liver, resulting in hepatobiliary damage (1). NIC results from diverse etiologies, including biliary atresia, infections, genetic-metabolic disorders, as well as hematologic and endocrine dysfunctions, etc. Congenital endocrine disorders—such as hypopituitarism, adrenal cortex hyperplasia, and hypothyroidism—are well-established causes of neonatal cholestasis. In contrast, hyperthyroidism has been less frequently associated with this condition. Here, we report a case of neonatal cholestasis caused by Graves' disease and review relevant literature to summarize its clinical characteristics, and to enhance prompt and accurate recognition and diagnosis of this disease.

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Children's Hospital of Fudan University waived the need for ethical approval for the case report. Informed consent was obtained from the patient's parents.

Case Report

The female neonate was delivered at 36 weeks and 5 days gestation to parents who were not consanguineous. The infant had a moderate birth weight of 2340 g. The primigravida experienced a pregnancy without complications, except for a history of Graves' disease, which was diagnosed approximately 3-4 years earlier and managed with the use of propylthiouracil (PTU). She showed stable euthyroidism, normal liver function during the whole pregnancy, and tested negative for thyrotropin receptor antibody (TRAb) at 12 weeks of gestation. Following the delivery, her thyroid function tests showed a suppressed level of thyroid-stimulating hormone (TSH, 0.05 mIU/L) and a normal level of free thyroxine (FT4).

Day of life (DOL) 1: The infant was admitted to a local neonatal ward due to the presence of jaundice, regurgitation, and meconium-stained amniotic fluid. Chest X-ray suggested pulmonary infection, and total serum bilirubin (TB) level was 130 μmol/L (normal range: 3.4–17.1 μmol/L). The thyroid function test was conducted in consideration of her mother's Graves' disease. The results showed a low TSH of 0.02 mIU/L (normal range: 0.25–7.31 mIU/L), but a normal FT4 of 15.61 pmol/L (normal range: 6.44–29.6 pmol/L). Therefore, the diagnosis of pneumonia and hyperbilirubinemia was established. Antibiotics and continuous phototherapy were given for one week. After that, the jaundice improved as the TB level dropped to 34.2 μmol/L.

DOL 8: Increased stool frequency (8-12 times per day) was overlooked because the patient had a healthy appetite and yellow-colored feces.

DOL 15-20: The patient's stool exhibited a gradual lightening in coloration (DOL 15), and jaundice reemerged (DOL 20). Consequently, she was referred to our liver center.

DOL 26: The infant was admitted to our liver center. Her weight was 2800 g. The sclera and skin were moderately yellowish. The heart rate and blood pressure were within the normal range. The abdomen was soft. the liver was 3 cm subcostal, with a firm consistency. The spleen was not palpable. Neurologic examination was unremarkable.

Diagnostic workup to exclude other causes: TORCH serology (Toxoplasma, Rubella, Cytomegalovirus, and Herpes simplex virus) and urine Cytomegalovirus PCR were negative. Newborn metabolic screening (blood spot and urine organic acids) was unremarkable. Serum total bile acids were elevated at 18.9 μmol/L (reference <10 μmol/L). Abdominal ultrasonography showed a normal gallbladder and no evidence of biliary atresia or choledochal cyst. Serum alpha-1 antitrypsin level was not measured, as the clinical presentation—combined with the maternal history of Graves' disease and the rapid improvement of cholestasis following antithyroid therapy—made alpha-1 antitrypsin deficiency highly unlikely. Family-based whole-exome sequencing was performed and revealed no pathogenic or likely pathogenic variants in genes associated with neonatal cholestasis.

Liver function and thyroid function: The liver function tests verified the presence of cholestasis characterized by a normal gamma-glutamyl transferase (GGT) level, and the coagulation function remained normal. The second thyroid function test still showed a low TSH and elevated FT4 and free triiodothyronine (FT3) levels (table 1).

DOL 27–33 (Clinical worsening): Despite treatment with ursodeoxycholic acid and fat-soluble vitamins, her cholestasis worsened, with a significant rise in bilirubin level within one week. Additionally, greasy stools and increased frequency of 6 to 12 bowel movements per day were noted. On DOL 33, the jaundiced baby developed tachypnea (respiratory rate 50–60 breaths/min) and tachycardia (heart rate 160–190 bpm) in the absence of identifiable predisposing factors. Electrocardiogram demonstrated sinus tachycardia. Echocardiography revealed mild to moderate mitral regurgitation, patent foramen ovale, and increased flow rate in the branch pulmonary arteries and descending aorta. These findings suggested hyperthyroidism as the underlying cause, as it explained all the infant's medical issues.

DOL 36 (Diagnosis and treatment): The infant's elevated TRAb level (7.89 IU/L, normal range: 0–1.75 IU/L) and persistent thyroid function abnormalities established the diagnosis of neonatal Graves' disease. Due to the risk of hepatotoxicity, PTU and methimazole (MMI) were not given to the infant with cholestasis. Propranolol and intravenous immunoglobulin (IVIG) (2 g/kg) were administered as an alternative. Following treatment, the infant demonstrated progressive clinical improvement. The heart and breathing rates returned to normal; the frequency of stools decreased; the bilirubin level dropped; and the body weight increased steadily.

Follow-up: At the 3-month follow-up evaluation, the patient demonstrated complete resolution of cholestasis with normalization of transaminases. Thyroid hormones and TRAb levels continued to improve. At 4.5 months of age, the infant exhibited normal growth and development, and all test results—including those for thyroid function, TRAb level, liver function, echocardiography, and liver ultrasound—were normal.

Discussion

Endocrine disorders may contribute to infantile cholestasis. Infantile cholestasis is linked to several endocrinopathies, including hypothyroidism, hypopituitarism, and adrenal cortex hyperplasia. Neonatal cholestasis is not commonly thought to be caused by hyperthyroidism. However, it has been reported in both pediatric and adult populations. To systematically identify reported cases of neonatal cholestasis secondary to Graves' disease, we conducted a comprehensive literature search in the PubMed and China National Knowledge Infrastructure (CNKI) databases. The search was performed from database inception up to June 2025. The following keywords and their combinations were used: (“neonatal” OR “infant”) AND (“Graves' disease” OR “hyperthyroidism”) AND (“cholestasis” OR “jaundice” OR “liver dysfunction”). The search was restricted to human studies published in English or Chinese. Reference lists of relevant articles were also manually screened to identify additional eligible cases. A total of 14 cases with detailed clinical data were identified and summarized in Table 2 (2-14). These cases, together with our case, support the consideration of hyperthyroidism as a potential cause of neonatal cholestasis and liver dysfunction.

Neonatal hyperthyroidism is less prevalent than congenital hypothyroidism. Most cases represent transient Graves' disease, secondary to transplacental passage of maternal TRAb. TRAb can cross the placenta freely. The types and titers of TRAb affect the thyroid status of the fetus and neonate, particularly in late pregnancy (15). The mother's thyroid function was normal, and she was negative for TRAb during pregnancy in our case. Therefore, neither the mother's earlier medical treatment nor her euthyroid status during pregnancy affects the development of newborn thyrotoxicosis. Among the 14 reviewed cases, 4 mothers were rendered hypothyroid and treated with levothyroxine, while 9 mothers had hyperthyroidism during pregnancy or postpartum and received treatments such as radioiodine, PTU, or subtotal thyroidectomy. Therefore, meticulous documentation of maternal thyroid disease history is essential when evaluating infants with cholestasis.

Among all 15 cases, 12 were male infants and 14 were preterm infants. Although no definitive conclusions can be drawn from this small case series, this finding suggests that male sex and prematurity may be associated with an increased risk of cholestasis in infants with neonatal hyperthyroidism—an observation that warrants further investigation in larger cohorts. The hepatobiliary manifestations include cholestasis (15/15, 100%), hepatosplenomegaly (11/15, 73.3%), coagulation dysfunction (3/15, 20%), hyperammonemia (3/15, 20%), liver failure (1/15, 6.7%). All newborns displayed jaundice during the neonatal period. and most of them reached their highest conjugated bilirubin levels by DOL 6, and 4 infants had pale stool. The medians of direct bilirubin (DB), ALT, AST were 110.7umol/L (range 41.1-633umol/L), 186U/L (range 10-504U/L), 600U/L (range 37-1197U/L) respectively. Beyond cholestasis, most infants exhibited classic symptoms of hyperthyroidism, including tachycardia, irritability, respiratory distress, goiter, exophthalmos, pulmonary and systemic hypertension. Notably, rashes and thrombocytopenia were also common. However, in our case, the severity of cholestasis did not correlate with the prominence of typical hyperthyroidism symptoms. Our patient manifested rapidly progressive cholestasis and atypical symptoms of hyperthyroidism, including diarrhea and poor weight gain. The initial improvement in TSH obscured the causal relationship between hyperthyroidism and cholestasis. It was not realized that the cholestasis may be secondary to hyperthyroidism until the emergence of tachycardia and tachypnea. Consequently, in any neonate with cholestasis delivered to a mother with Graves' disease, hyperthyroidism should be prioritized as the primary etiology. Comprehensive evaluation of thyroid function and TRAb must be included.

The etiology of neonatal hyperthyroidism-associated cholestasis and liver failure remains unknown, but several theories have been proposed. Hyperthyroidism increases the metabolic rate, and the liver requires more oxygen without a proportional increase in blood flow, which can cause relative hypoxia in hepatocytes and impair bile flow (16). This phenomenon has been well documented in clinical studies of adult patients with hyperthyroidism-induced cholestasis. A recent large cohort study reported that a cholestatic pattern was the most common type of liver injury, occurring in 46.5% of affected patients (17). Excess thyroid hormone frequently impairs liver function through oxidative stress, inflammation, and apoptosis. Excess thyroid hormones accelerate mitochondrial respiration and fatty acid oxidation. This leads to overgeneration of reactive oxygen and nitrogen species, which then damage liver cells (18). Severe hyperthyroidism may lead to high-output heart failure, resulting in blood backing up into the liver (congestive hepatopathy) and subsequent cholestasis (17, 19). In our case, the infant had no evidence of heart failure, making the first two mechanisms more likely; however, all of these mechanisms remain speculative, as most evidence comes from adult studies. Despite this uncertainty, cholestasis consistently improved when hyperthyroidism was treated, strongly suggesting that hyperthyroidism itself is the cause.

Neonatal Graves' disease is a self-limiting illness. Its duration depends on the persistence of TRAb, which is gradually cleared from the neonatal circulation over time (20). Most affected infants became euthyroid with undetectable antibody levels by 4 months of age. In our case and the cases reviewed, cholestasis tended to disappear after 2 to 4 months. Jaundice in one case resolved at the age of 9 months, and transaminases returned to normal within one year. However, among the documented cases, one infant died of respiratory failure within several hours after birth (2), and another infant developed liver failure (10). Our case showed rapidly progressive cholestasis. Therefore, attention still needs to be paid to monitoring liver function and follow-up. At present, the main treatment regimen is the use of antithyroid drugs, including propylthiouracil (PTU) and methimazole (MMI). PTU has certain hepatotoxicity, so MMI is preferred in neonates. However, the safe dose range of MMI and its long-term impact on neonates need further clinical research and evaluation (21). Severe cases have been reported to involve the use of immunoglobulins and plasma exchange (22, 23). Most evaluated infants with neonatal cholestasis with significant hyperthyroidism, received antithyroid medications, including MMI, PTU and iodine. However, two infants developed significant hepatotoxicity from MMI (5, 11), paralleling the risk in adults(24). Campos postulated that patients with underlying cholestasis–whether secondary to hyperthyroidism or other etiologies–may be more vulnerable to MMI-induced hepatotoxicity (25), highlighting that additional caution in these patients is warranted. In our case, antithyroid drugs were not used because of their potential hepatotoxicity. Instead, we administered propranolol at 2 mg/kg/day, consistent with recent reports on neonatal Graves' disease management (26). We also administered IVIG at 2 g/kg. Adegboye stated that IVIG is indicated for neonatal Graves' disease (27). They explained that pooled IgG from healthy donors interferes with maternal TRAb through Fc receptor blockade and FcRn saturation, reducing their ability to bind to neonatal tissues and accelerating their clearance. However, direct evidence for IVIG in neonatal Graves' disease is limited and mostly derived from other neonatal alloimmune disorders. In our patient, the rapid improvement of cholestasis and thyroid function after IVIG and propranolol was observed, but we cannot rule out spontaneous resolution due to natural clearance of maternal antibodies. Therefore, this treatment remains exploratory and requires larger studies to confirm its efficacy. We acknowledge the limitations of a single case report and small literature review, so our findings should be interpreted as hypothesis-generating rather than definitive.

Conclusion

We present a case of neonatal cholestasis secondary to Graves' disease and review 14 similar cases. Our case is unique in two aspects. Clinically, the infant did not develop tachycardia or tachypnea until late, showing that thyrotoxic symptoms can be subtle. Therapeutically, we used propranolol and IVIG instead of antithyroid drugs due to hepatotoxicity concerns, and the cholestasis resolved. Pathophysiologically, hepatic hypoxia and oxidative stress likely mediated the cholestasis in our case, as heart failure was absent. These observations support the key message: neonatal Graves' disease must be included in the differential diagnosis of cholestasis, particularly in infants of mothers with Graves' disease. Early detection is crucial, and targeted testing of thyroid function and TRAb is essential.

Ethics

Informed Consent: 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.

Footnotes

Authorship 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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Table 1: Infant laboratory studies

DOL	TB	DB	ALT	AST	GGT	TSH	FT4	FT3	TRAb
	3.4-17.1umol/L	**0-6umol/L**	**7-30U/L**	**14-44U/L**	**9-150U/L**	**0.25-7.31mIU/L**	**6.44-29.6pmol/L**	**2.73-8.6pmol/L**	**≤1.75IU/L**
1	130	/	7	38	89	/	/	/	
4	/	/	/	/		0.02	15.61	5.82	
23	/	/	/	/		0.23	87.58	40.72	
26	106	74.7	52	98	79	/	/	/	
28	152	108	58	97	82	/	/	/	
33	249	206	109	143	62	< 0.01	44.32	9.9	
36	207	154	189	198	65	/	/	/	7.89
42	120	94	234	232	48	/	/	/	
62	51	41	168	113	55	< 0.01	10.97	5.89	
91	7.1	4.7	55	51	18	0.02	9.64	8.2	< 0.8
138	6.8	2.8	40.1	33	20	0.44	10.73	6.14	

*Abbreviations: TB, total serum bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TRAb, thyrotropin receptor antibody. Reference ranges for laboratory values are shown under the row headings.

Table 2: A review of published cases of neonatal cholestasis caused by Graves' disease

Case	Sex	DOL	TB 3.4-17.1umol/L	DB 0-6umol/L	ALT 7-30U/L	AST 14-44U/L	GGT 9-150U/L	Hepatobiliary manifestations	Extrahepatic manifestations	Treatment	Outcome	Author and year of publication
1	M	1	196.65	119.7	/	/	/	hepatosplenomegaly	petechiae respiratory distress	no treatment	died 4 hours after admission	Patricia R[2] 1985
2	M	6	/	200.07	64	37	/	hepatomegaly jaundice	Irritability tremulousness tachypnea tachycardia hypertension pulmonary hypertension thrombocytopenia	PTU propranolol iodine	DOL 33, normal bilirubin. DOL120, euthyroid	Beroukhim[3] 2003
3	F	1	300	201	186	1111	46	hepatosplenomegaly icterus coagulopathy	tachycardia tachypnea irritability	carbimazole propranolol iodine	DOL 49, normal FT4	C Dryden[4] 2007
4	M	6	372.78	249.66	79	200	/	jaundice DIC	respiratory distress tachycardia thrombocytopenia hypoglycemia hypertension pulmonary hypertension	propranolol PTU MMI	DOL 67, normal bilirubin. DOL127, normal transaminase	Lindsey A[5] 2012
5	M	1	564	352	282	1197	/	jaundice hyperammonemia hepatosplenomegaly	tachypnea tachycardia thrombocytopenia leukocytosis	propranolol PTU thyroid	8 wks, normal ammonia. 9 mos, normal liver enzyme	Katherine A[6] 2011
6	M	6	923	633	/	600	/	hepatosplenomegaly jaundice hyperammonemia	petechiae tachycardia thrombocytopenia leukocytosis	propranolol levothyroxine	4 wks, TB dropped to 159. then, lost to follow-up	
7	M	15	/	51.3	170	289	234	jaundice pigmented stools	respiratory distress proptosis irritability vigorousness	no treatment	2.5 mos, resolved cholestasis. 1 y, normal transaminases	Raghu U[7] 2015
8	F	3	123.5	41.4	10	/	646	jaundice hyperammonemia	ARDS thrombocytopenia exophthalmos irritability tachycardia	iodine propranolol MMI levothyroxine	DOL 20, euthyroid. DOL 29, normal DB. 5 mos, negative TRAb	Manal [8] 2014
9	M	5	/	229.14	elevated	elevated	/	jaundice hepatomegaly pale stools	emaciation purpuric rash tachycardia mild proptosis	iodide propranolol MMI	D79, normal	Gangaram [9] 2017
10	M	1	298.2	101	504	633	497	hepatosplenomegaly icteric conjunctiva hepatic failure	low birth weight tachycardia irritability pulmonary hypertension thrombocytopenia	carbimazole	8 wks, normal	Mohammd[10] 2017
11	M	1	219	83	24	82	600	hepatosplenomegaly	erythematous macules tachycardia cardiomegaly hypertension thrombocytopenia leukocytosis	MMI propranolol iodine	improved	Nurin [11] 2019
12	M	30	142.7	114.8	226	380	/	white clay-like stool jaundice hepatomegaly	irritability diarrhea poor weight gain tachycardia	PTU	3.5 mos, euthyroid 3 mos, disappeared jaundice. 4 mos, normal liver enzymes	Ya Ping[12] 2025
13	M	27	401.8	253.6	213	617	/	jaundice hepatomegaly	tachycardia poor weight gain	PTU	4 mos, normal liver enzyme and euthyroid	Xiu Jing[13] 2006

								mild proptosis				
14	M	25	398	247.5	221	608	/	jaundice	irritability tachypnea tachycardia poor weight gain mild proptosis	Propranolol Hydrocortisone PTU	4 mos, normal liver enzyme and euthyroid	Gang[14] 2011
15	F	33	249	74.7	52	98	79	jaundice Clay-colored stools hepatomegaly	tachypnoea tachycardia poor weight gain	Propranolol IVIG	3 mos, normal liver enzyme. 4 mos, euthyroid	our case

*Abbreviations: TB, total serum bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase. Reference ranges for laboratory values are shown under the row headings.