CASE REPORT

Neonatal Graves' disease with unusual metabolic association from presentation to resolution

Manal Mustafa Khadora,¹ Mohammad Al Dubayee²

¹Department of Paediatrics, Latifa Hospital, Dubai Health Authority, Dubai, UAE
²Department of Paediatrics, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Correspondence to

Dr Manal Mustafa Khadora, mmkhadora@dha.gov.ae

Accepted 2 November 2014

SUMMARY

Neonatal Graves' disease is a rare disorder seen in 1 in 25 000 births and in 1% of the offspring of mothers with either established or cured Graves' disease. This is due to transplacental passage of thyroid-stimulating immunoglobulins (TSIs). A higher TSI titre in maternal serum makes hyperthyroidism more likely in the fetus or newborn; however, not all fetuses born by women with positive TSIs develop overt hyperthyroidism. In spite of its rarity, its serious nature (if not treated) and its association with multisystem abnormalities justifies careful clinical screening and management. We report a preterm 30 weeks neonate with neonatal thyrotoxicosis secondary to untreated maternal Graves' disease who, in addition to the typical hyperthyroidism symptoms, had unusual metabolic associations of neonatal cholestasis and hyperammonaemia. The patient was treated accordingly with a good response. This report supports previous reports on the association between neonatal hyperthyroidism and cholestatic liver disease. However, it is the second case report to describe the unusual association of hyperammonaemia and neonatal Graves' disease.

BACKGROUND

Fetal/neonatal hyperthyroidism is a serious condition that should not be overlooked. Our case report supports previous case reports of unusual association of neonatal Graves' disease with cholestatic jaundice. However, it is the second case report to describe unusual association of hyperammonaemia and neonatal Graves' disease. This will help to avoid unnecessary investigations and to prevent anxiety over the possible existence of separate underlying metabolic conditions.

It demonstrates the seriousness of this disorder and its implications with multiorgan dysfunction and metabolic derangements. Our report underscores the importance of screening pregnant mothers with active or cured Graves' disease by measuring their serum thyroid-stimulating immunoglobulins (TSIs) in order to prevent the potential manifestations of neonatal Graves' disease and to design timely and appropriate management plans.

CASE PRESENTATION

Our patient was a female neonate born prematurely at 30 weeks gestation by normal spontaneous vaginal delivery. The patient's mother, a 29-year-old gravida 7 para 3, had undergone three spontaneous abortions at early pregnancy due to unknown causes and has three healthy living children. She is from a rural area with no facilities for regular antenatal follow-up.

During labour, the mother was found to have exophthalmos, goitre and unexplained tachycardia

(heart rate >150 bpm) with no fever and a normal blood pressure. Her intrapartum cardiotocography monitoring revealed fetal tachycardia (fetal heart rate >160/min). She received dexamethasone and ceftriaxone during labour. The obstetrician requested a thyroid function test.

Additional maternal history, obtained after delivery, revealed antenatal symptoms of palpitation, irritability, heat intolerance, weight loss despite good appetite and anterior neck swelling. She had no antenatal follow-up. Her thyroid function test after delivery showed suppressed thyroid-stimulating hormone (TSH) <0.01 mIU/L (0.35–4.9), elevated free T4 (FT4; 49.2 pmol/L (9.0–19.0)) and FT3 (16.77 pmol/L (2.6–5.7)). She had a positive TSH receptor stimulating antibodies titre (>36.0 IU/L (<1.8)). There was no family history of thyroid or endocrine disorders.

The baby's clinical examination at birth revealed weight 1.45 kg, length 40 cm and head circumference 28 cm (all plotted on 50th centile). Shortly after birth, the neonate developed tachypnoea (respiratory rate 60 breaths/min), tachycardia (heart rate 219 bpm) and a blood pressure of 74/55 mm Hg with oxygen saturation of 92% on room air. The patient's chest radiography revealed signs of respiratory distress syndrome, for which she required mechanical ventilation and surfactant therapy. Intravenous antibiotics were started after samples were collected as part of a septic workup.

On the second day of life, the neonate became jaundiced with total serum bilirubin 79.8 µmol/L (3.4–20.5) and direct bilirubin 27.8 µmol/L (1.7–8.6). Double phototherapy was started. Phototherapy was stopped on the following day due to her total serum bilirubin having increased to reach a peak of 123.5 µmol/L with increasing direct fraction (peak 41.4 µmol/L). The baby's cord TSH was suppressed <0.01 mIU/L (0.35–30). Her liver enzymes showed normal alanine transaminase and aspartate aminotransferase with elevated GGT (γ-glutamyl transpeptidase; peak 831 U/L (9–36)). Subsequent evaluation revealed hyperammonaemia (confirmed on multiple samples, peak 129 µmol/L (11–35)). She also developed mild thrombocytopenia, platelet count (123×10⁹/L). She was ventilated for 4 days and received phototherapy for 1 day.

On the third day of life, tachycardia persisted and the neonate's thyroid function study revealed suppressed serum TSH <0.01 mIU/L (0.35–4.9), elevated FT4 (70.6 pmol/L (9.0–19.0)) and FT3 (13.58 pmol/L (2.6–5.7)). Her clinical examination showed staring eyes, exophthalmos (figure 1), irritability, a palpable thyroid gland and tachycardia, so the paediatric endocrinology team was consulted

CrossMark

To cite: Khadora MM, Al Dubayee M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206725

Figure 1 The neonate at the age of 3 days with staring eyes and exophthalmos.

and a diagnosis of neonatal Graves' disease secondary to untreated maternal Graves' disease was established. The baby was started on Lugol's solution (126 mg/mL) at one drop (8 mg) eight hourly and propranolol 2 mg/kg/day in three divided doses. Her heart rate normalised within 48 h.

On the fourth day of life, the baby was reviewed by paediatric cardiology, gastroenterology and metabolic teams. Her complete blood count, serum electrolytes, blood culture and chromosomal study were normal. Results of metabolic work-up for inborn errors of metabolism including measurement of plasma amino acids levels, lactic acid, tandem mass spectrometry (MS/MS), urine organic acid, galactose-1-phosphate uridylyltransferase (GAL-1-PUT) enzyme level were all within normal limits. Ultrasound of the abdomen revealed a normal-sized liver with normal intrahepatic biliary ducts, a hyperechoic partially defined area in the left liver lobe (measuring 1.2×1.3 cm), possibly intraparenchymal liver haematoma due to umbilical venous catheter (UVC), and normal gallbladder and spleen. Brain ultrasound showed a bilateral grade III intraventricular haemorrhage with ventricular dilation.

The baby's ECG showed regular sinus tachycardia and her echocardiography revealed mid-muscular ventricular septal defect (VSD) with left-to-right shunt and mild tricuspid regurgitation.

During the second week of life, the baby's heart rate remained normal, she gained weight on oral feeding and her repeat thyroid function revealed persistently suppressed TSH under 0.01 mIU/L, elevated FT4 >77 pmol/L and elevated FT3 45 pmol/L. The infant's TSH receptor stimulating antibodies were positive >36.0 IU/L (<1.8). Lugol's solution was stopped, methimazole was started with 0.5 mg/kg/day in three divided doses and the patient was continued on small doses

of propranolol. Her platelet count, conjugated hyperbilirubinaemia, elevated GGT and the hyperammonaemia gradually improved with improvement of thyroid function. Repeated follow-up abdomen ultrasound showed significant reduction in the size of the previously noted hypoechoic area in the left liver lobe (measuring 0.6×0.7 cm), which is consistent with resolving intraparenchymal haematoma from UVC. A repeated brain ultrasound showed similar to previous findings of grade III intraventricular haemorrhage.

In the third week of life, the infant's thyroid function studies continued to improve. Her TSH remained suppressed <0.01 mIU/L, but FT4 normalised to 15.3 pmol/L and FT3 to 4.65 pmol/L. Her direct serum bilirubin concentration declined gradually to 5.2 µmol/L (1.7–8.6) on day 29 of life. A brain CT scan performed at the age of 30 days revealed mild dilation of the ventricular system, resolving intraventricular haemorrhage and no craniostosis, with normal posterior fossa structures. Repeated echocardiography at the age of 38 days revealed small mid-muscular VSD with left-to-right shunt. The baby's heart rate remained normal, so propranolol was stopped at the age of 38 days.

She was discharged from the neonatal intensive care unit at the age of 38 days. A thyroid function test on discharge showed TSH <0.01 mIU/L, FT4 14.7 pmol/L, FT3 5.34 pmol/L and mildly elevated GGT 82 U/L (9–36). She was discharged on methimazole, with a follow-up appointment in paediatric endocrinology clinic.

In the first clinic visit, 1 week after discharge, the infant's TSH level had improved to 0.027 mIU/L but her FT4 levels had continued to decline to below the normal range to reach a nadir of 7.4 pmol/L, which is consistent with central hypothyroidism due to an altered hypothalamic–pituitary–thyroidal axis. Levothyroxine was started at 25 µg/day at the age of 46 days. At the age of 70 days, her TSH improved to 0.7 mIU/L with FT4 16.2 pmol/L, so thyroxine was stopped and methimazole was reduced to a once daily dose.

During the patient's follow-up visits to paediatric endocrinology clinic, she continued to gain weight on oral feeding and was clinically asymptomatic. Her thyroid function showed normal FT4 with TSH levels that rose slowly until normalised, and normal GGT, serum ammonia and direct bilirubin. The methimazole dose was tapered gradually until being stopped at the age of 5 months, when her repeated TSH receptor stimulating antibodies were negative.

INVESTIGATIONS

All investigations are mentioned in the case presentation above and summarised in [table 1](#).

TREATMENT

- ▶ Lugol's solution (126 mg/mL) one drop (8 mg) eight hourly.
- ▶ Propranolol 2 mg/kg/day in three divided doses.
- ▶ Methimazole 0.5 mg/kg/day in three divided doses.

OUTCOME AND FOLLOW-UP

The patient improved clinically and biochemically and became euthyroid after starting methimazole (antithyroid drug). She was gaining weight on oral feeds, her thyroid function test as well as cholestatic jaundice and hyperammonaemia normalised gradually during regular outpatient follow-up visits. Her TSH receptor stimulating antibodies became negative at the age of 5 months.

DISCUSSION

Overt thyrotoxicosis is uncommon in pregnancy, only affecting approximately 0.2% of pregnant women. This rate is low

Table 1 Summary of the patient's laboratory results

Age in days	TSH (mIU/L; 0.35–4.9)	FT4 (pmol/L; 9.0–19.0)	FT3 (pmol/L; 2.6–5.7)	Total bilirubin μmol/L (3.4–20.5)	Direct bilirubin μmol/L (1.7–8.6)	ALT U/L (5–55)	AST U/L (5–34)	GTP U/L (9–36)	Ammonia μmol/L (11–35)	Platelet count (10 ⁹ /L)
2				79.9	27.8			796		139
3	<0.01	70.6	13.58	123.5	41.4	10		646	129	128
5					56.9					123
7					27.5	16	30	831	82	193
14	<0.01	18		19.7	13.4	36		665		159
20	<0.01	15	4.65					280		171
31	<0.01	17.7	5.12					135	51	322
38	<0.01	14.7	5.34		5.2			87		543
46	0.027	7.4	3.24							
60	0.7	10.5	3.66					32		
70	0.265	16.2	5.09							
4 months	1.02	15.3	4.73							
5 months	0.7	16.7	4.7							

ALT, alanine transaminase; AST, aspartate aminotransferase; FT3, Free T3; GTP, γ-glutamyl transpeptidase; TSH, thyroid-stimulating hormone.

because fertility is reduced in thyrotoxicosis and because autoimmune responses tend to be suppressed during pregnancy. Graves' disease, an autoimmune disorder, is the most common cause of thyrotoxicosis in young women.¹ Thyrotoxicosis has a variety of negative influences on pregnancy: it is associated with increased pregnancy loss and serious medical complications for the mother as well as the infant. Furthermore, pregnancy complicates the diagnosis and treatment of hyperthyroidism in Graves' disease and influences its severity and clinical course.

Neonatal Graves' disease is uncommon due to the low incidence of thyrotoxicosis in pregnancy (1–2 cases per 1000 pregnancies)² and the neonatal disease occurs only in about 1 in 70 cases of thyrotoxic pregnancy. The development of fetal and neonatal thyrotoxicosis does not depend on prior treatment of the mother or the mother's thyroid status during pregnancy. It is usually due to transplacental passage of TSIs, which stimulate the fetal thyroid, from a mother with active or cured Graves' disease.^{3–4}

Fetal–neonatal hyperthyroidism may develop in pregnancies associated with autoimmune thyrotoxicosis and high titres of TSH receptor-stimulating autoantibodies. Pregnant women with Graves' disease who are at risk of higher TSIs titre include those with more severe hyperthyroidism and those with significant Graves' orbitopathy or infiltrative dermopathy.^{5–6}

Ideally, all women with Graves' disease should have their serum TSIs measured in early pregnancy. This applies to those currently treated for hyperthyroidism as well as to those who are now euthyroid, either spontaneously or on thyroxine replacement after ablative (radioactive iodine or surgery) therapy. A high TSI titre in maternal serum makes fetal and neonatal hyperthyroidism more likely. Unfortunately, this information is often not available at first evaluation and clinicians are confronted at first with the classical signs heralding fetal–neonatal hyperthyroidism such as tachycardia, goitre and intrauterine growth retardation. All pregnant patients with significant Graves' disease should be managed in close cooperation with endocrinologists and obstetricians who are experienced with modern techniques for monitoring the fetus for intrauterine thyroid dysfunction.

Graves' disease in the newborn is manifested by irritability, flushing, tachycardia, jaundice, hypertension, poor weight gain, thyroid enlargement and exophthalmos.⁷

The hyperbilirubinaemia of neonatal Graves' disease is classically indirect. However, some reports have shown isolated conjugated hyperbilirubinaemia, which was attributed solely to neonatal thyrotoxicosis.^{8–10} The differential diagnosis of neonatal cholestasis is extensive, including obstructive, infectious and metabolic causes. Hypothyroidism and hypopituitarism are two endocrinopathies associated with neonatal cholestasis.

There are several theories behind the direct hyperbilirubinaemia in neonatal Graves' disease. One theory suggests that it might be due to the congestive heart failure (CHF) that can accompany hyperthyroidism, usually seen in adults. The CHF then leads to liver dysfunction, cholestasis and direct hyperbilirubinaemia, but this is not the case in our patient. Another hypothesis is that the hyperthyroid state leads to increased metabolic rate and energy demand, meaning increased hepatic oxygen consumption without sufficient hepatic circulation. This in turn may precipitate liver dysfunction and rapid turnover of red blood cells with inability of the liver to remove the bilirubin leading to conjugated hyperbilirubinaemia.^{11–13} Lastly, some experimental studies on animals have demonstrated that thyroxine, perhaps by increasing oxygen consumption (VO₂), increases free radical generation, particularly in liver, thus inducing liver injury.¹⁴

Owing to an unclear mechanism, infants with neonatal Graves' disease may present with hepatosplenomegaly, thrombocytopaenia and hypoproteinaemia, a picture that may mimic congenital infections, sepsis or an inborn error of metabolism and that may lead to unnecessary investigations.^{8 15 16}

Hyperammonaemia with neonatal Graves' disease has not, to the best of our knowledge, been described previously except in one recent case report by Lewis *et al.*¹⁷ Our case report is the second to describe this unusual association. The exact mechanism of hyperammonaemia is unclear but may be related to significant hepatic dysfunction caused by hyperthyroidism. It resolves with normalisation of thyroid function, as observed in our patient.

The diagnosis of neonatal Graves' disease is confirmed by an undetectable serum TSH and by high levels of FT4 and FT3. In some neonates, the onset of symptoms and signs may be delayed as long as 8–9 days if they were born to a mother treated with antithyroid drugs.

Neonatal Graves' disease resolves spontaneously as maternal TSIs are cleared from the infant's circulation. The usual clinical course extends from 3 to 12 weeks. On the other hand, newborns with symptomatic hyperthyroidism should be admitted and their heart rate monitored.

Treatment of thyrotoxicosis is designed to impose restraint on thyroid hormone secretion through drugs that inhibit thyroid hormone synthesis or release. Treatments include β -blocking agents such as propranolol (1–2 mg/kg/day into four divided doses), which is used as an adjunct in management of some of the manifestations of thyrotoxicosis. Antithyroid drugs such as methimazole (0.5–1 mg/kg/day in divided doses at 8 h intervals) inhibit the oxidation and organic binding of thyroid iodide, thereby reducing the synthesis of thyroid hormone. Iodine (Lugol's solution or 10% potassium iodide) is often used initially as it rapidly inhibits thyroid hormone release. Glucocorticoids diminish peripheral conversion of T4 to T3 and may therefore be helpful. A therapeutic response should be observed within 24–36 h. If a satisfactory response is not observed, the dose of antithyroid drug and iodine can be increased.

During follow-up, while the patient remains on antithyroid drugs, thyroid function tests might reveal a picture of transient central hypothyroidism (suppressed TSH with low FT4) that may reflect an altered hypothalamic–pituitary–thyroidal axis caused by the prenatal exposure to intrauterine hyperthyroidism. Kempers *et al.*¹⁸ demonstrated pituitary dysfunction and central hypothyroidism in 17 of 18 neonates born to mothers with Graves' disease. Matsuura *et al.*¹⁹ hypothesised that transient hypothyroidism seen in neonates with Graves' disease results from the hyperthyroid intrauterine environment, impairing normal maturation of the fetal hypothalamic–pituitary–thyroid axis. Therefore, the hypothalamus and the pituitary are hyporesponsive to falling levels of FT4 as the TSIs and the accompanying hyperthyroidism resolve. This process was found to take up to a year. Kempers *et al.*¹⁸ also suggested a TRH (thyrotropin-releasing hormone) stimulation test to evaluate the maturity of the hypothalamic–pituitary–thyroid axis, where a normal TSH response could guide discontinuation of L-thyroxine supplementation. Higuchi *et al.*²⁰ presented three cases, 27–37 weeks of gestation, where all three neonates had central hypothyroidism confirmed by a TRH test.

Although the mechanism of hyperthyroidism-associated cholestasis in neonatal Graves' disease is unknown, improvement correlated with initiation of antithyroid therapy, as was observed in our patient.¹⁰ None of the previous reports in neonates or

adults listed potential causes for this observation. Further studies are required to delineate the exact mechanism.

Learning points

- ▶ Symptomatic neonatal Graves' disease is very rare. It can occur in the offspring of mothers with either established or cured Graves' disease. Pregnant mothers with active or cured Graves' disease should be screened by measuring their serum thyroid-stimulating immunoglobulins in early pregnancy.
- ▶ All pregnant patients with significant Graves' disease should be managed in close cooperation with endocrinologists and obstetricians who are experienced with modern techniques for monitoring the fetus for intrauterine thyroid dysfunction.
- ▶ Neonatal hyperthyroidism might be considered a potential aetiology of cholestasis and liver dysfunction in neonates.
- ▶ Further studies and long-term follow-up of these infants are required to delineate the exact mechanism and to establish the clinical significance of these unusual associated metabolic derangements to avoid unnecessary investigations and to prevent anxiety over the possible existence of separate underlying metabolic conditions.

Contributors MMK contributed to the planning, conduct, and reporting of the work described in the manuscript, and also performed the literature search, wrote the manuscript and is the guarantor. MAD had the idea for the manuscript. Both the authors identified and managed the case.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Aluvihare VR, Kallikourdis M, Betz AG. Tolerance, suppression and the fetal allograft. *J Mol Med* 2005;83:88–96.
- 2 Check JH, Rezvani I, Goodner D, *et al.* Prenatal treatment of thyrotoxicosis to prevent intrauterine growth retardation. *Obstet Gynecol* 1982;60:122–4.
- 3 Zimmerman D. Fetal and neonatal hyperthyroidism. *Thyroid* 1999;9:727–33.
- 4 Polak M, Legac I, Vuillard E, *et al.* Congenital hyperthyroidism: the fetus as a patient. *Horm Res* 2006;65:235–42.
- 5 Zakarija M, McKenzie JM. Pregnancy-associated changes in thyroid stimulating antibody of Graves' disease and the relationship to neonatal hyperthyroidism. *J Clin Endocrinol Metab* 1983;57:1036–40.
- 6 Mejias-Heredia A, Litchfield WR, Zurakowski D. Assessing the risk of neonatal Graves disease using TSI measurements (abstract P3). *77th Meeting of the Endocrine Society* 1995:460.
- 7 Polak M. Hyperthyroidism in early infancy: pathogenesis, clinical features and diagnosis with a focus on neonatal hyperthyroidism. *Thyroid* 1998;8:1171–7.
- 8 Beroukhi RS, Moon TD, Felner EI. Neonatal thyrotoxicosis and conjugated hyperbilirubinemia. *J Matern Fetal Neonatal Med* 2003;13:426–8.
- 9 Loomba-Albrecht LA, Bremer AA, Wong A, *et al.* Neonatal cholestasis due to hyperthyroidism: an unusual case and clinical implications. *J Pediatr Gastroenterol Nutr* 2012;54:433–4.
- 10 Hull K, Horenstein R, Naglieri R, *et al.* Two cases of thyroid storm-associated cholestatic jaundice. *Endocr Pract* 2007;13:476–80.
- 11 Farber S, Craig JM. Clinical pathological conference. *J Pediatr* 1959;54:829–38.
- 12 Potter EL, Craig JM. *Pathology of the Fetus and the Infant*. 3rd edn. Chicago: Year Book Medical Publishers, 1975:411.
- 13 Neal PR, Jansen RD, Lemons JA, *et al.* Unusual manifestations of neonatal hyperthyroidism. *Am J Perinatol*. 1985;2:231–5.

- 14 Lorijn RH, Nelson JC, Longo LD. Induced fetal hyperthyroidism: cardiac output and oxygen consumption. *Am J Physiol* 1980;239:H302–7.
- 15 Dryden C, Simpson JH, Hunter LE, *et al.* An unusual cause of neonatal coagulopathy and liver disease. *J Perinatol* 2007;27:320–2.
- 16 Adrouny A, Sandler RM, Carmel R. Variable presentation of thrombocytopenia in Graves' disease. *Arch Intern Med* 1982;142:1460–4.
- 17 Lewis KA, Engle W, Hainline BE, *et al.* Neonatal Graves' disease associated with severe metabolic abnormalities. *Pediatrics* 2011;128:e232–6.
- 18 Kempers MJ, van Tijn DA, van Trotsenburg AS, *et al.* Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *J Clin Endocrinol Metab* 2003;88:5851–7.
- 19 Matsuura N, Harada S, Ohyama Y, *et al.* The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. *Pediatr Res* 1997;42:214–18.
- 20 Higuchi R, Miyawaki M, Kumagai T, *et al.* Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks' gestation: 3 cases. *Pediatrics* 2005;115:623–5.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow