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The Subtle Signs Of Neonatal Grave's Disease- A Case Report And Review

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Abstract
A newborn male is born via caesarean section at 37 weeks of gestation to a 25-year-old primigravida mother. Mother was a known case of Grave's disease (TSH receptor antibody positive) on Carbimazole with gestational diabetes mellitus on Insulin, her antenatal course was otherwise uneventful, with normal fetal heart rate monitoring and appropriate fetal growth. She was admitted with complaints of pain abdomen and decreased fetal movement. She was planned for emergency section and a live, healthy male baby was born with a birth weight of 2.962 kg, appropriate for gestation age with APGAR 8/9. Postnatal examination was negative for congenital anomalies and no systemic involvement was noticed. The baby was discharged on close follow-up. On day 7th of life, the baby was re-admitted for phototherapy. In this admission, the baby was noticed to have a resting tachycardia heart rate of 170-180/min, no murmur or abnormal heart sound was noticed on examination. The baby had no significant weight loss or history of feeding difficulties. In consideration of maternal grave disease, a further workup for the baby was planned, which revealed a Cord TSH (0.007microIU/ml) range (2.30-13.20) and free T4 1.52 ng/dl (Range 1.10-2.00). Further, the workup revealed TSH receptor antibody positive 23.76 IU/L range (less than 1.22), free T4 7.77 ng/dl (1.120-2.00), TSH less than 0.005 microIU/ml. However, As per the paediatric Endocrinologist's opinion, the baby was started on propranolol and propylthiouracil. The resting tachycardia resolved upon starting the drug. On subsequent follow-up, the baby had an improving thyroid profile.

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I. Introduction

Neonatal hyperthyroidism (NH) is a rare condition that is seen in 1-5 per cent of newborns born to mothers who have active or past Graves' disease.1

It is due to the placental transfer of TSH receptor antibodies from mother to fetus, although uncommon but it could have life-threatening morbidities. One dreadful complication of neonatal hyperthyroidism is neonatal thyrotoxicosis, which can lead to, cardiac failure and death if prompt treatment with antithyroid medication is not started.

Due to the lack of specific symptoms and diverse clinical manifestations, it is easy to overlook and misdiagnose cases of neonatal thyrotoxicosis.

We report a case of neonatal hyperthyroidism in a baby born to a mother with Grave's disease, who presented with subtle signs of hyperthyroidism

	CORD	7TH DOL	2months	5month	7month	9month
TSH *microIU/ml*	0.007 ⬇	≤0.005 ⬇	0.90	0.417 ⬇	0.660 ⬇	0.92
FT3 pg/ml				1.01	1.32	3.9
FT4 *ng/dl*	1.52	7.77	0.85	1.07	4.73	1.24

The medications were stopped after 1 month of age as thyroid status improved.. However, TSH continues to be lower range till 7 months of age. Baby is continuously followed up with a Paediatric endocrinologist for thyroid status monitoring.

II. Discussion-

Fetal Thyroid Physiology

Thyroid function in fetuses of mothers with Graves' disease is affected by the transplacental passage of thyroid-blocking or stimulating antibodies (both may coexist) and by ATDs.

The fetal thyroid by 12 weeks gestation, is capable of concentrating iodide, producing thyroglobulin and accumulating colloid.

By the end of 25 weeks of gestation, the capability of the TSH receptor in responding to TSH (and TRAb increases, but the fetal concentration of TRAb is low. However, by the end of the second trimester when placental permeability to immunoglobulins increases, the antibody level increases in fetus. Hence, fetal hyperthyroidism in mothers with Graves' disease will only occur in the second half of pregnancy.2

Neonatal Grave's Disease

Neonatal hyperthyroidism is of two types Autoimmune hyperthyroidism (neonatal GD) and Nonautoimmune hyperthyroidism

Autoimmune hyperthyroidism is due to the Transplacental passage of TRAb from mother to fetus, it is a Transient condition and (generally resolves in 4–5 months after TRAb clearance).

Non-autoimmune hyperthyroidism is inherited in an autosomal dominant manner and is caused by an activating mutation in the GNAS gene (McCune-Albright syndrome). This condition is permanent and continues beyond the neonatal period. Thyroid receptor antibodies are class G immunoglobulin, which freely crosses the placenta. TRAB can be, either (TSH receptor stimulating antibodies, TSI) which binds to the thyroid and stimulate its production or (TSH receptor blocking antibodies TBI), which block its production.

Graves' disease in neonates is caused by transplacental passage of maternal stimulating TSHR antibodies (TRAb), which causes unregulated activation of the Thyroid hormone.

The risk of neonatal thyrotoxicosis rises directly with the levels of TRAb antibodies in the third trimester and in cord blood, particularly when TRAb exceeds 3 to 5 times the upper normal limit.

Manifestations of Hyperthyroidism in the Fetus

Features of hyperthyroidism in the fetus, which are highly predictive of neonatal hyperthyroidism include fetal tachycardia (heart rate >160 beats/min), thyroid enlargement (goitre; fetal neck circumference >95%), intrauterine growth retardation, polyhydramnios or oligohydramnios, advanced bone age, craniosynostosis with microcephaly, and hydrops.4

Manifestations of Hyperthyroidism in Neonates

Neonates may present with excessive irritability, tachycardia, tremors, poor feeding, sweating, and difficulty sleeping secondary to thyrotoxicosis. Newborns may have emaciated appearance, proptosis with a stare, and goitre, craniosynostosis with and microcephaly. Other rare signs of neonatal hyperthyroidism that may be confused with infection/sepsis include thrombocytopenia.

Screening for Neonatal Hyperthyroidism

According to the American Thyroid Association (ATA)5 2016 guidelines, patients with Graves' disease should be screened for TRAb during the first trimester of pregnancy. If TRAb levels are elevated, re-testing should take place at 18–22 weeks and again at 30–34 weeks. A TRAb level of ≥5 IU/L or more than three times the upper limit of the reference value indicates a high risk of fetal or neonatal hyperthyroidism. Pregnant women with positive TRAb results should have a fetal thyroid ultrasound to further assess fetal thyroid function. Therefore, for high-risk pregnant women with a history of thyroid disease, it is vital to evaluate thyroid function and serum TRAb levels as early as possible. Close monitoring of early hyperthyroidism symptoms is essential for prompt diagnosis.

Risk factors for neonates to develop thyrotoxicosis are
(1) infants born to mothers with GD, especially if the maternal TRAb level is greater than 2 to 3 times the upper limit of normal;
(2) infants in whom intrauterine surveillance revealed fetal signs of hyperthyroidism; and
(3) infants with a known family history of genetic causes of congenital hyperthyroidism, including activating mutations in the TSHR.

In cases of neonatal Graves' disease, maternal TRAb usually clears from the infant's circulation by 4 to 6 months of age, leading to the resolution of hyperthyroidism.6

In cases where neonatal hyperthyroidism is suspected, particularly with biochemical evidence of the condition, treatment with methimazole (MMI) should begin at a dosage of 0.2 to 0.5 mg/kg per day. For infants displaying signs of sympathetic hyperactivity, such as elevated heart rate and high blood pressure, propranolol can be administered at a dosage of 2 mg/kg per day. The use of propylthiouracil (PTU) is not advised for neonates or children due to a higher risk of liver toxicity.7 In instances of severe hemodynamic instability, treatments like Lugol's solution or potassium iodide may be administered. Short-term use of glucocorticoids can also be advantageous. Since neonatal hyperthyroidism is typically temporary and resolves as maternal thyroid-stimulating antibodies clear from the infant's system, it is crucial to monitor thyroid function tests every 1 to 2 weeks after starting treatment to adjust the MMI dosage appropriately.

For cases of non-autoimmune neonatal hyperthyroidism, such as those caused by activating mutations of the thyroid-stimulating hormone receptor or McCune-Albright syndrome, MMI should be used similarly to the approach for neonatal Graves' disease. Although definitive treatments like thyroidectomy or radioactive iodine (RAI) may eventually be necessary, they can be postponed for several months or years if the infant responds well to medical management.8 Current guidelines suggest that breastfeeding is safe for mothers taking antithyroid medications at moderate doses of MMI (20–30 mg per day) and PTU (less than 300 mg).9

Additionally, infants born to mothers with Graves' disease who are breastfeeding should undergo regular thyroid function screenings to check for potential hypothyroidism. A study of 42 breastfeeding mothers who were treated with moderate doses of MMI found no significant differences in the growth or cognitive development of their children when evaluated between the ages of 48 and 84 months.10

III. Conclusion

The neonatal graves' disease can present with a masquerade of symptoms and can be easily misdiagnosed as sepsis or PPHN if a high index of suspicion is not kept for mothers with hyperthyroidism. Antenatal TRAB level monitoring should be done for all women with the grave disease as it predicts the chances of the baby being born with grave disease and risk of neonatal thyrotoxicosis. Quality improvement initiatives should be designed to ensure proper implementation of screening guidelines for pregnant women with hyperthyroidism as well as appropriate screening and management for fetal/neonatal hyperthyroidism. Early diagnosis and initiation of treatment are essential to prevent both short-term and potential long-term complications of neonatal thyrotoxicosis.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants by the local legislation and institutional requirements.

Author contributions

PK prepared the manuscript and performed the literature search. VG, I.P.S SB and PK and SB managed the case. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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