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Case Report

Congenital central hypothyroidism in a neonate born to thyrotoxic mother

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ABSTRACT

Maternal thyrotoxicosis is associated with significant risk of low birth weight premature & small for gestational age neonates; as well as intrauterine death. The abnormal thyroid functions seen in babies of thyrotoxic mothers include neonatal hyperthyroidism, transient neonatal primary hypothyroidism and transient central hypothyroidism. Transient central hypothyroidism is a unique entity which is not widely recognized. It is usually seen in neonates born from mothers with uncontrolled thyrotoxicosis. We report a case of congenital central hypothyroidism in a neonate, who born to thyrotoxic Rh negative mother. Neonate presented with anemia and prolonged cholestatic jaundice. It is important to recognize this condition timely as its delayed diagnosis & treatment results in permanent mental retardation. To avoid missing of this condition, FT4 should be monitored serially in all infants born to thyrotoxic mothers. With thyroid hormone replacement therapy there was tremendous improvement both clinically as well as biochemically in our case.

Keywords: Maternal thyrotoxicosis, Congenital central hypothyroidism, Cholestatic jaundice

INTRODUCTION

Central hypothyroidism is characterized by impaired secretion of thyroid hormone due to defect in the hypothalamic-pituitary-thyroid (HPT) regulatory system. Congenital central hypothyroidism due to maternal hyperthyroidism is not an uncommon entity, but often remains unrecognized unless specific attention is given. Exposure of fetal HPT system to a higher thyroid hormone concentration might impair its physiological maturation leading to central hypothyroidism in neonates born to thyrotoxic mothers. We report a case of neonate with congenital central hypothyroidism born to a mother with uncontrolled thyrotoxicosis who presented with prolonged cholestatic jaundice.

CASE REPORT

A male neonate with 37 weeks of gestation was born normal vaginally with birth weight of 2.2 kg to a unbooked multipara mother (gravida 5, para 5, abortion 0, number of living child 5) at hospital. She was known case of hyperthyroidism diagnosed 3 years back and was on irregular treatment. She was also Rh negative and did not receive anti-D during her previous pregnancies.

Immediate post-natal period was uneventful and was discharged on day 2nd of life. Parents noticed yellowish discoloration of skin on 5th day of life, which was gradually increased and was associated with excessive cry. For the same complaint baby was taken to pediatrician on 16th day of life. Investigations revealed baby's blood group B positive, hemoglobin-7.3 gm%, total serum billirubin- total-10.3 mg%, direct-6 mg%, indirect-4.3 mg%. As yellowish discoloration was increasing, parents consulted another pediatrician and infant was reinvestigated. On day 23rd of life hemoglobin was 6.5 gm%, septic screen was negative, serum billirubin- total -18mg%, direct-10.2mg%, indirect-7.8mg%. Baby was referred to our hospital for further management.

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Weight on admission was 2.1 kg. Infant was pale looking and icteric till thighs. On per abdominal examination there was no organomegaly and other findings were inconclusive. On arrival hemoglobin was 6gm%, septic screen was negative, serum billirubin- total 13.8mg%, direct-10.1mg%, indirect-3.7mg%, SGPT -109 IU/l, SGOT- 124 IU/l, alkaline phosphatase- 78 u/l, GGT- 140 u/l. Coagulation profile, renal function test and electrolytes were normal. DCT was negative. Blood culture and urine culture were negative. Urine routine examination was normal and urine for reducing substance was negative. Ultrasonography of liver and biliary system was normal (which ruled out inspisatted bile syndrome which was also likely possibility in our case-as there was Rh incompatibility with severe hemolytic anemia). Infant's TORCH titres, HIV, HBsAg and VDRL were negative. Fundus examination was normal.

Infant thyroid function test showed TSH-0.08 mU/ml, T_4 -6.2 µg/dl, free T_4 - 0.56ng/dl. Ultrasonography of thyroid gland was normal. As TSH was low and free T_4 was on lower side, diagnosis of central hypothyroidism was made. On suspicion of permanent congenital central hypothyroidism further work-up was done. MRI of sellar region (to rule out septo-optic dysplaia or pituitary hypoplasia) was normal. Pituitary gland related hormones - GH, IGF-1, cortisol, FSH, LH, testosterone all were in normal range. As other pituitary hormones were normal we suspected child having central hypothyroidism due to isolated TSH deficiency (TSH β subunit gene mutation) or thyrotropin releasing hormone resistance (TRH receptor gene mutation) or isolated TRH deficiency. As mother was not precise about her thyroid related problem (hypothyroidism or hyperthyroidism) and as she was not having any documents, her thyroid function test was done which showed TSH <0.01mU/ml, free T_4- 7.62 ng/dl suggestive of maternal hyperthyroidism.

Patient's definitive treatment was started in form of Thyroxin (25µg/day) along with Supportive and symptomatic care.

On subsequent follow up after 4 month of therapy infant became euthyroid with normal billirubin and liver enzymes.

DISSCUSION

Only a minority of newborns from mothers with grave's disease develop congenital central hypothyroidism. Its occurrence was first described by Matsuura *et al.* in 1988.[1] There are published reports suggesting this condition a rare occurrence, but from analysis of its clinical course it is speculated that its risk of occurrence is probable underestimated. It often remains unrecognized unless specific attention is given to this condition.[2] Occurrence of this type of congenital central hypothyroidism is estimated to be 1 in 35,000 neonates.[3]

It is usually seen with uncontrolled maternal thyrotoxicosis, though rarely associated with well controlled disease also. Exact mechanism for development of this condition is not fully understood.[3] The free T4 levels at birth in such infants were found to be higher than those at 5 days of life.[4] Higuchi et al. (2005) also reported a phase of transient hyperthyroxinemia before setting down to a hypothyroid phase in infants born to mothers with Grave's disease. These reports suggest that fetal T4 level in this situation may would have remained higher due to passive transfer of maternal thyroxine during last trimester leading to suppression of fetal pituitary-thyroid axis. Exposure to higher thyroxine concentrations might have impaired physiological maturation of fetal hypothalamic-pituitary-thyroid system during intrauterine life. Recent case reports of central hypothyroidism in preterm infants born before 32 weeks of gestation from mothers with thyrotoxicosis suggests gestational period earlier than 32 weeks may be the critical time for development of central hypothyroidism. Undetectable TSH in fetal cord serum in presence of markedly elevated free T4 suggests pituitary negative feedback at as early as 20 weeks'

gestation.[5] The minimum duration of passive hyperthyroidism during fetal life that can lead to central hypothyroidism is unknown.

The prevalence of thyrotoxicosis during pregnancy is about 0.1- 0.2%. Grave's disease is by far the most common cause of thyrotoxicosis in women of reproductive age. Maternal grave's disease is associated with significant risk of low birth weight, prematurity, small for gestational age, and intrauterine death. Adverse maternal and fetal outcome are related to duration of hyperthyroidism and degree of control of hyperthyroidism during pregnancy.[6]

The abnormal thyroid functions seen in babies of thyrotoxic mothers include neonatal hyperthyroidism, transient neonatal primary hypothyroidism and transient central hypothyroidism.[6]

Neonatal grave's disease occurs rarely in about 1 neonate born out of 70 pregnant women with grave's disease. Neonatal grave's disease is usually transient and resolve when maternal antibody level drops over four to six months.[6]

Transient primary hypothyroidism commonly occurs due to transfer of antithyroid drugs across the placenta and is related to the last few weeks of the gestation. It is important to keep the maternal drug dose to the minimum so as to minimize the amount of antithyroid drugs transferred to the fetus in utero.[6,7]

Transient central hypothyroidism is a unique entity which is not widely recognized. It is usually seen in neonates born from mothers with uncontrolled thyrotoxicosis.[6]

The thyroid function of these infants will subsequently normalize over a variable period of time. TSH function will recover within months to years in most of these infants.[6] Monitoring of these infants include regular checking of thyroid hormone levels to keep the infants in euthyroid state. Checking of TSH is not going to guide as it will remain low. If TRH stimulation test is available, it should be done at 3 monthly intervals to guide the continuation of therapy. Normal response to TRH stimulation test (increase in TSH level by >10 micro IU/ml from baseline after 30 minutes of I.V TRH given at a dose of 10 ug/kg) indicate recovery of pituitary function and one can stop thyroxine safely then.[7] If TRH stimulation test is not available, it would be prudent to continue L-thyroxine replacement therapy until 2 to 3 years of age to optimize neurological development.[8] Discontinuation of L-thyroxine supplementation can be tried then. Normal thyroid function test without thyroxine supplementation indicates recovery of pituitary function. Long-term follow up of thyroid function, as well as physical and mental development, are necessary to clarify the clinical course and prognosis of this unusual clinical condition.

TSH based neonatal screening cannot detect congenital central hypothyroidism. T4 based screening has been reported to be useful for detecting central hypothyroidism.[5] It is recommended that all infants born to mothers with Grave's disease should not only have FT_4 and TSH measured in the cord blood, but also be monitored serially (such as at days 4 and 7), even if either of the cord measurements appear normal. It is suggested to monitor once a week till TSH normalizes to watch for delayed development of central hypothyroidism.[3]

The preferential strategy to prevent maternal grave's disease associated congenital hypothyroidism is control of thyroid function throughout pregnancy.[5] Routine screening of thyroid function during pregnancy is important as some of the women with grave's disease may escape from clinical recognition. In diagnostic work-up of patients with central congenital hypothyroidism, evaluation of maternal thyroid function should be incorporated.[2]

CONCLUSION

In diagnostic work-up of patients with central congenital hypothyroidism, evaluation of maternal

thyroid function should be incorporated.

Preferential strategy to prevent maternal Grave's disease associated hypothyroidism is good control of thyroid function throughout pregnancy.

T_4 based screening programs are useful for detecting central hypothyroidism.

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