Screening Babies at risk of congenital hyperthyroidism

GL354

Approval and Authorisation

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MANAGEMENT OF BABIES OF MOTHERS WITH THYROID DISEASE.

Neonatal thyrotoxicosis is a rare disorder and is defined as a hyper metabolic state resulting from excessive thyroid hormone activity in the newborn (1). There is much confusion about the incidence, with figures varying between 1 in 6,000 to 1 in 40,000 live births, with an overall mortality rate between 16 and 28%. However, most of these figures are from early studies carried out in the 1970’s. Nevertheless it seems likely modern neonatal intensive care has lowered this figure, but there is no up to date mortality data to confirm this. The early recognition and treatment of severely affected infants will ensure the best outcome.

Pathophysiology

Neonatal thyrotoxicosis is caused by the transplacental passage of IgG thyroid stimulating immunoglobulin (TSI) present in the serum of mothers with Graves’ disease (>90% of cases) (2). Only 1 to 2% of mothers with Graves’ disease give birth to thyrotoxic infants. The antibodies have a half-life of approximately 12 days; therefore, the condition is transient with duration of between 3 and 12 weeks. Onset of symptoms is usually within 24 – 48 hours of birth, but may be delayed up to 5 to 10 days in those infants of mothers treated antenatally with antithyroid drugs (3). Rarely infants acquire multiple antibodies, some of which have TSH – receptor activity and the onset may be as late as 6 weeks (2).

Some mothers, with inactive Graves’ disease, who are on antithyroid drugs and who have had a previous thyroidectomy, or have been treated with radioiodine, may continue to produce significant amounts of TSI. The maternal clinical state, therefore, can not reliably predict neonatal disease.

Antenatally, the acquisition of transplacental IgG increases dramatically between 22 and 28 weeks gestation, at around the time when the fetal thyroid becomes fully responsive to stimulation (3). During this time there is an increased rate of
miscarriage, stillbirth, intrauterine growth retardation, premature birth, advanced bone age and craniosynostosis in those babies significantly affected in utero. If there is fetal compromise then treatment should be given to prevent further complications. The mother should be given low doses of antithyroid drugs which cross the placenta to depress the fetal thyroid.

Unfortunately at the present time, studies looking at the usefulness of measuring TSH as a predictor for neonatal disease (2) in pregnant mothers have not found to be of value.

Clinical features of affected infants.

The signs and symptoms of neonatal thyrotoxicosis are shown on page 13. Many are non-specific and can mimic narcotic withdrawal in infants of addicted mothers.

Diagnosis.

Raised free T4 and/or free T3 levels in a symptomatic neonate with undetectable TSH confirm the diagnosis. Neonatal free T4 and free T3 values must be interpreted with the knowledge of normal values in this age group, due to the normal postnatal surge in thyroid hormone level. The most severely affected infants are those in the high output cardiac failure group with atrial tachyarrhythmias, which can be very difficult to treat.

Remember thyroid function test normal ranges change rapidly in first 7 days (see Appendix 1). For preterms see ref 4 page 191 on Buscot

Management.

The majority of infants are asymptomatic at birth and contain to remain so. Those who develop symptoms usually do so within 48 hours. The infants who fall into the high-risk groups should have cord blood taken for freeT4, TSH, and a clinical examination. They should be admitted to the post-natal ward with their mothers, unless there are other reasons for their admission to the Neonatal Unit. They should be reassessed at 48 hours, and clinically examine, if asymptomatic, they may be allowed home with the parents and repeated freeT4 and TSH taken at 7 days of age.
The parents should be taught to recognise the important clinical symptoms (see letter p16) and told to seek advice and help if any are present.

In any symptomatic infant when the diagnosis is strongly suspected treatment should be commenced without waiting for the results of the TFT’s, as delay may cause further deterioration. They must be admitted to the Neonatal Unit for treatment, cardiac monitoring and other supportive measures; fluid replacement, high calorie intake, temperature control and the minimum of external stimuli. Rarely, intubation and ventilation are required usually in the most severely affected infants with cardiac failure. (3)

In all cases discuss with Dr Nick Mann or, if on holiday, Dr Fiona Ryan, Consultant Paediatric Endocrinologist at Oxford.
Babies at risk of congenital hyperthyroidism

1. Evidence of fetal involvement i.e. any mother with thyroid disease who has a fetus with an unexplained tachycardia/hydrops.

2. The mother has had, or is currently being treated for Graves’ disease or has ever been treated with carbimazole/radio-iodine or had total thyroidectomy for Graves’.

3. Previously affected infant.

4. Infants whose mothers are taking thyroxine should not be routinely tested, unless they fall into the above three groups, or show clinical symptoms.

Clinical examination at birth (if symptoms check TSH & Free T4)

If normal examination, does not require blood tests

Infant 2 days old

Clinical examination

NORMAL

No treatment

Observe and check Free T4,TSH at a week of age.

Information sheet to parents

Inform G.P.

Samples required for Thyroid Function Tests:

- 2 yellow micro-containers,
- Free T4 must be requested on form, the Lab will not routinely test otherwise,

HYPERTHYROID

Repeat Free T4,TSH

Start treatment (see below)

Inform Dr Nick Mann

(If NM on leave D/W Dr Fiona Ryan, Oxford)
Results should be obtained within 24 hours.

**Drug Therapy for treatment of symptoms.**

This is outlined on page 12.

Anti-thyroid drugs are the mainstays of treatment, with beta-blockers alleviating many of the features of sympathetic over-activity. The latter must be used with caution or avoided if cardiac failure is present. Carbimazole is normally used as the anti-thyroid drug of choice. However, propylthiouracil has a faster onset of action than carbimazole and inhibits peripheral conversion of free thyroxine (Free T4) to the more biologically active Free T3. Lugol’s iodine has the most rapid onset of action of all drugs and is used in severe cases - see below.

Therefore, in the mild to moderately affected group, carbimazole should alleviate symptoms with propranolol being considered if the infant shows signs of and is distressed by sympathetic over-activity. Alternatively sedatives can be of benefit if the infant is very irritable.

In severely affected infants, Lugol’s iodine, propylthiouracil, carbimizole and propranolol are the drugs of choice. Occasionally cortico-steroids are needed. These benefit by inhibiting the peripheral conversion of Free T4 to Free T3. Digoxin may be required for tachy-arrhythmias and if heart failure is present diuretics. Exchange transfusion has been used but is potentially hazardous in infants with established cardiac failure. Sedatives can also help with irritability.
Clinical response.

This should be achieved in 24 - 36 hours, the dose of anti-thyroid drugs and iodine may be increased by 50 % if necessary.

Infants should be rendered euthyroid/minimally hyperthyroid clinically by 72 hours of treatment. Serum free T3 levels should have fallen into the upper normal range, although free T4 levels may take longer to plateau. Once control is established, iodine can be stopped after 7 – 10 days with a reduction in the dose of propranolol. Antithyroid drugs and propranolol can be weaned down over the next 4 – 8 weeks, monitoring clinical state and TFT’s. Antithyroid drugs can be stopped when the free T4 falls below the normal range or the TSH starts to rise. Close monitoring is required as the infant may become clinically hypothyroid during treatment. The infant is normally treated for 4 – 8 weeks and rarely longer than 3 months. Infants are followed up for at least 6 months and maybe up to 1 year of age. Late onset hypothyroidism may occur due to the persistence of blocking antibodies, or delay in pituitary thyroid axis responsiveness.
Maternal Hypothyroidism in pregnancy.

Hypothyroidism in pregnant women is usually secondary to autoimmune disorders or Hashimoto’s thyroiditis. They may be producing thyroid inhibiting or rarely thyroid stimulating antibodies so the risks of producing a thyrotoxic infant are extremely low. The infant may, therefore, develop transient hypothyroidism or very rarely hyperthyroidism. Transient hypothyroidism is quite rare, the most severe cases being picked up on the Guthrie test at a week of age.

In current obstetric practice mothers are occasionally being prescribed thyroxine, on the basis of previous miscarriages or infertility, without fitting into the above disorders.
Summary.

Neonatal thyrotoxicosis is a rare, transient but potentially fatal disorder. In addition the maternal clinical state does not predict reliably, the severity of neonatal disease. Treatment is effective in those infants who show clinical symptoms, are treated early and should be clinically euthyroid by 72 hours of age. Drugs can be reduced and withdrawn over a period of 4 – 8 weeks with close monitoring of clinical state, TFTs and follow up in clinic.

As this is a rare disorder, and confusion about its incidence, with estimates varying between 1 in 6,000 and 1 in 40,000 live births, we would expect in Reading to have an affected baby every one to seven years. It seems logical, therefore, to screen only those infants who fall into the high risks group i.e.

1) Where the mother has or has had Graves’ disease at any time, and has ever been treated with carbimazole (although this usually causes a transient hypothyroidism in the baby), therefore, check TFTs on d3-4. Particular care being given to mothers who develop thyrotoxicosis during the pregnancy:

2) where there has been evidence of fetal involvement. This would be any mother with thyroid disease who has a fetus with an unexplained tachycardia or hydrops.

3) Previously affected infant,

Infants whose mothers are taking thyroxine, should not routinely be tested, unless they fall into the above three groups, or show clinical symptoms.
Clinical Features of thyrotoxicosis

Mild to moderately affected

- Tachycardia > 160/minute
- Irritability/tremor
- Flushing/sweating
- Goitre
- Poor weight gain despite high calorie requirements
- Eye signs: - lid retraction
  - periorbital oedema/purpura (due to thrombocytopenia)
- Exophthalmos
- Hypertension
- Diarrhoea
- Jaundice
- Hepatosplenomegaly

Severely affected

- Tachycardia > 200/min.
- Arrhythmias – atrial flutter
  - Supraventricular tachycardia
  - Atrial fibrillation with rapid ventricular rate
- Cardiac failure
Drug therapy

Antithyroid Drugs:

Carbimazole 250 microgram/kg 8 hourly or

Propylthiouracil 5mg/kg 12 hourly

Lugol’s Iodine (5% iodine and 10% potassium iodine solution = 126 mg iodine/ml) 1 drop every 8 hours. Dilute with milk or water.

Beta Blockers

Propranolol 250 – 750 microgram/kg 8 hourly (beware hypoglycaemia)

All of the above can be given either orally or via a nasogastric tube.

Corticosteroids

Hydrocortisone 2 mg/kg/dose IV 6 – 8 hourly for 1 – 2 days

Prednisolone 2mg/kg/day orally

Treatment

Mild to moderately affected:

- Carbimazole
- Consider propranolol
Administer until euthyroid and then gradually reduce the dose. Monitor thyroid function.

**Severely affected (for definition see table on page 13):**

1. Lugol’s iodine
2. Propranolol (unless overt signs of heart failure)
3. Carbimazole or propylthiouracil
4. Occasionally corticosteroids are required.
5. Digoxin may be necessary for tachyarrhythmia

A significant clinical response should be achieved in 24 - 36 hours. If not, the dose of antithyroid drugs and iodine may be increased by 50%. Infants should be rendered euthyroid / minimally hypothyroid clinically by 72hr of treatment.

**Sedatives**

Chloral Hydrate 25mg/kg/dose 6 hourly

**Others**

- Diuretics
- Exchange transfusion
See full Protocol for information on clinical response, how to reduce medication and achieve control of symptoms.

Treatment is usually required for 4 – 8 weeks, and rarely exceeds 3 months.

Follow up is by the Dr Nick Mann in Endocrine Clinic.

NOTE: In symptomatic infants when the diagnosis is strongly suspected, especially if there is an antenatal history of Graves’ disease, treatment should be commenced immediately without the results of the thyroid function tests being known, as delay may result in progressive deterioration.

**Breast Feeding**

Is not contra-indicated and should be encouraged. Both propylthiouracil and carbimazole are detected in breast milk but appear not to affect neonatal thyroid function if the maternal dose of carbimazole is <15mg/day and propylthiouracil dose is <150mg/day.

**Mothers on Propranolol:**

In addition to the above screening, the infant will need blood glucose checking pre-feeds for at least 36 hours because of the risk of hypoglycaemia. The blood pressure and heart rate will need to be checked 12 hourly (for 48 hours) on Buscot, as there is a theoretical risk of hypotension and bradycardia. Any abnormal findings must be reported to the Registrar immediately.
Information to mothers who have been having thyroid problems during pregnancy

Thyroid problems due to an over-active thyroid gland can sometimes affect your baby, although this is rare. We would, therefore, like you to check your baby for 4 weeks, and contact your GP or midwife if the following symptoms occur:

- always seems irritable and shaky
- never sleeps
- does not put on weight after 10 days of age despite feeding all the time
- has persistent diarrhoea
- always looks flushed (red)
- the eyes look very swollen
- has jaundice (yellow skin)

If you are at all concerned please inform your GP or midwife, so that your baby can be seen and examined.
References:

1) Thyroid Foundation of Canada. June 2000
2) Mustafa M.S. Betts P.R. Neonatal Thyrotoxicosis
   Current Paediatrics 1997; 7; 88 – 91
3) Matsuda T et al. Transient Neonatal Hyperthyroidism and Maternal TSI
   Univ Press 2006 .

Appendix 1

Normal reference ranges for TSH and free T4 for term babies

Day 1 TSH 3-120 mU/l; T4 16.7-48 pmol/l
Day 2 TSH 3-30 mU/l; T4 16.7-48 pmol/l
Day 3 Similar to above
Day 7 TSH 3-8 mU/l; T4 13.7-28 pmol/l

Reviewed July 2011 (NPM).