Severe hypothyroidism following a single topical exposure to iodine in a premature neonate

Catherine Mary Breen , Monica Fahim Salama, Michael A Boyle

Department of Neonatology, Rotunda Hospital, Dublin, Ireland

Correspondence to
Dr Catherine Mary Breen; catherinebreen1411@gmail.com

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SUMMARY

A neonate, born at 24 weeks, underwent a patent ductus arteriosus ligation, with previous normal thyroid stimulating hormone (TSH) levels, developed severe hypothyroidism from topical exposure to iodine following a single surgical procedure at 28 days of life. A low free T4 level of 0.05 ng/dL and a high TSH level of 228 mIU/L was detected with an increased urinary iodine excretion level of 178 mg/L (reference range 0.30–1.97 mg/L). The thyroid ultrasound was normal. Levothyroxine was started immediately but thyroid function did not recover fully during admission and levothyroxine was required beyond term corrected. This case highlighted how susceptible extremely preterm infants are to iodine induced hypothyroidism, even short-term topical exposure. Delayed treatment of hypothyroidism can lead to profound neurodevelopmental delay. As surgical advances allow for interventions at earlier gestations, the importance of early thyroid function testing postexposure to iodine is highlighted and ultimately topical iodine should be avoided in these susceptible infants.

BACKGROUND

Delayed treatment in hypothyroidism leads to profound neurodevelopmental delay and therefore early detection and treatment is crucial. Even though, the onset of fetal thyroid synthesis is approximately at 11 weeks' gestation, maturation of thyroid axis does not occur until the third trimester. Thus, premature infants are extremely susceptible to iodine-induced hypothyroidism. The literature cites neonates with congenital heart disease as having an increased risk of transient hypothyroidism secondary to exposure to excess iodine from the administration of iodinated contrast during cardiac catheterisation, as well as topical application of iodine containing antiseptics and iodinated dressings in the operative setting. However, this case illustrates the severity of hypothyroidism that can result from topical exposure alone. Patent ductus arteriosus (PDA) is the most common congenital heart disease in term infants with a reported incidence of 1 in 2000.[1] The incidence of PDA in preterm neonates is far greater, with reports ranging from 20% to 60% (depending on population and diagnostic criteria).[1] As an increasing number of extremely preterm infants are surviving from earlier gestational ages, there will be a proportional increase in surgical procedures in the cohort of the most immature and smallest infants. Therefore, it is important to be aware and screen for this preventable cause of hypothyroidism and prevent further neurodisability is this already vulnerable group.

CASE PRESENTATION

A 24-week dichorionic-diamniotic twins were born by emergency caesarean section for a non-reassuring cardiotocography (CTG) and premature rupture of membranes. Twin 2 had an antenatal diagnosis of anencephaly and received comfort care as part of a planned palliative approach and died shortly after birth. Twin 1 was intubated and ventilated at 6 min of life and received surfactant. Her Apgar scores were 5 at 1 min and 7 at 10 min. Twin 1 was admitted to neonatal intensive care unit due to her prematurity, low birth weight of 630 g and respiratory distress. She had a partial septic workup and received intravenous antibiotics. She had hyperglycaemia and received insulin infusion for 24 hours. She is the first child of a non-consanguineous couple, conceived by in vitro fertilisation (IVF). There was no family history of thyroid disease, congenital heart disease or metabolic disease. Maternal viral serology was negative and there was no medical history of note.

From the second day of life a persistent grade 3/6 continuous murmur was auscultated over her left upper sternal border. An echocardiogram (ECHO) showed a non-restrictive haemodynamically significant PDA with left ventricular overload. Medical management of the PDA with paracetamol and ibuprofen was unsuccessful. A chest X-ray showed evidence of respiratory distress syndrome. Twin 1 had weekly TSH level screening as part of the national newborn bloodspot screening. This was normal from day of life 3 until after her PDA ligation.

Twin 1 failed extubation and the decision was made to proceed with PDA ligation in a tertiary cardiology unit on day of life 28. Topical iodine was used as an antiseptic prior to this procedure. Nine days later the newborn screening showed an elevated TSH. Serum thyroid function tests (TFTs) taken on the same day showed a low Free T4 level of less than 0.05 ng/dL and a high TSH level of 228 mIU/L. Urine sample was analysed for urinary spot iodine 9 days postexposure, which showed a significantly high level of iodine of 178 mg/L (reference range 0.30–1.97 mg/L). Renal function was within normal limits. Thyroid ultrasonography was normal. Twin 1 was started on 10 μg/kg of levothyroxine immediately. TFTs had normalised following 2 weeks of Levothyroxine treatment but it was held on day of life 15 secondary to tachycardia. However, it was restarted due to rising TSH levels. Twin 1 was admitted until 34 weeks corrected. Serial cranial ultrasounds were normal but the admission was complicated by chronic lung disease, anaemia of prematurity and retinopathy of

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prematurity. Twin 1 was discharged home on levothyroxine with follow-up arranged with a paediatric endocrinologist.

INVESTIGATIONS

- Heal prick test for newborn screening.
- Full blood count.
- Peripheral blood film.
- Urea and electrolytes.
- Liver function test.
- TFT.
- Blood cultures.
- Thyroid ultrasound.
- Cranial ultrasound.
- ECHO.

DIFFERENTIAL DIAGNOSIS

Primary congenital hypothyroidism secondary to dysgenesis or dyshormogenesis were two initial differential diagnosis. Thyroid dysgenesis was ruled out following a thyroid ultrasound which confirmed a normal sized and positioned thyroid. Given the sudden change in thyroid stimulating hormone and the history of recent PDA ligation, a urinary iodine level was analysed to differentiate between dyshormogenesis and iatrogenic hypothyroidism. A significantly elevated level of urinary iodine of 178 mg/L (reference range 0.30–1.97 mg/L) confirmed the diagnosis.

Thyroid dysfunction secondary to transplacental passage of excess iodine or drugs was ruled out given that neonatal thyroid levels were normal in the first 4 weeks of life and there was no indications from her medical or obstetric history.

TREATMENT

A paediatric endocrinologist consultation was sought and thyroxine was started immediately. TFTs were checked every 2 weeks for 6 weeks and then every 4 weeks until discharge at 34 weeks corrected.

OUTCOME AND FOLLOW-UP

Twin 1 was discharged at 34 weeks corrected. Thyroid function never recovered fully during this time. Therefore, on discharge, the dose of levothyroxine remained the same and the plan was for 6 weekly serum TFTs along with 6 weekly endocrine clinical reviews. Her parents were counselled that treatment would continue until exogenous thyroxine was no longer required to maintain normal thyroid function. Follow-up appointments were arranged with a paediatric endocrinologist and in our neonatology outpatient clinic. At 16 months, she remains on levothyroxine with a plan to trial off at 2 years of age, in keeping with European Society for Paediatric Endocrinology recommendations.[2]

DISCUSSION

Prenatal, perinatal or postnatal exposure to iodine can cause thyroid gland dysfunction such as transient hyperthyrotropinaemia, hypothyroidism or hyperthyroidism in neonates.[3 4] Excess iodine exposure is known to result in a rapid decline of thyroid hormone synthesis termed the Wolff and Chaikoff effect.[5] However, some patients are unable to escape such effect, which can lead to iodine induced hypothyroidism.[6] Even though, the onset of fetal thyroid synthesis is approximately at 11 weeks gestation, maturation of thyroid axis does not occur until the third trimester, thus premature infants are extremely susceptible to iodine induced hypothyroidism.[7] This, along with a small surface area, very thin epidermis and less subcutaneous fat all place very low birth weight (VLBW) premature infants at increased risk of hypothyroidism.[8]

Topical iodine-induced hypothyroidism has been observed in neonates and cited in the literature since the 1970s.[9] However, much of the literature reports a transient hypothyroidism but VLBW and very premature infants appear to be underrepresented. This may be underestimating the significant effect of iodine on particularly vulnerable premature infants. The first trial focusing of VLBW infants, published in the Lancet in 1989, showed premature infants absorbed a large amount of iodine and 25% of those exposed to iodine during routine procedure went on to develop a transient hypothyroidism. This study concluded that iodine containing antiseptics should be avoided in VLBW neonates.[8] However, the mean gestation of infants studied was 28 weeks and the mean weight was over 1 kg. Therefore, this study still underestimated the effect of iodine on younger gestations. Further trials and case reports, observing the link between topical iodine and hypothyroidism, report transient hypothyroidism but focus on older infants.[4 10 11] A randomised controlled trial compared the use of topical iodine versus non-iodinated preparation prior to cardiac surgery, however, this trial was based on term infants, including only one infant undergoing PDA ligation and of all the neonates included, the lowest weight was greater than 3 kg.[12] A systematic review looking at neonates less than 32 weeks who were exposed to topical iodine concludes that 12–33 infants per 100 infants will go on to have thyroid dysfunction but there is a lack of conclusive evidence.[13] No randomised control trials were available and of the 15 studies included, 6 studies included infants greater than 1.5 kg or greater than 32 weeks.

The British National Formulary advises that the use of povidone-iodine is contraindicated in neonates less than 32 corrected gestation and less than 1.5 kg. The use of chlorhexidine is favoured over iodine in neonatal units in this gestation. However, the use of topical iodine remains standard as an antiseptic in a surgical setting for PDA ligation, but not in PDA device closure. In the past, the number of infants who underwent cardiac surgical procedures at less than 32 weeks' gestation and less than 1.5 kg were minimal and the literature reflects this when reporting cases of hypothyroidism in VLBW neonates undergoing cardiac surgery.[12 14] As ongoing advances are made in surgery at this younger gestation and the mortality rates of premature infants continue to improve, guidelines regarding the use of iodine during surgery need to be established. Especially considering the importance of thyroid hormone in critical early brain development.

In conclusion, premature neonates are more prone to developing thyroid dysfunction following exposure to iodine.

Patient's perspective

Mother of the patient:

I was so worried after Twin 1 had her cardiac surgery as she seemed to have so much going on. I was disappointed that Twin 1 had a problem with her thyroid and to be honest I was also annoyed that this had happened. I wondered could it have been avoided. I'm so happy that Twin 1 is doing so well now. But after everything that Twin 1 has been through the only medication she is still on is Eltroxin. I am so grateful for everything that was done for Twin 1 but if this can be avoided for any other baby I think it should be.

Learning points

- Premature neonates are extremely susceptible to the effects of iodine on thyroid function including topical exposure.
- Topical iodine should be considered as a possible risk factor in the development of iatrogenic primary hypothyroidism and an alternative should be used.
- Any neonates exposed to iodine should have close monitoring of thyroid function tests to avoid the adverse neurodevelopmental outcomes associated with hypothyroidism.
- The current body of literature may underestimate the effect of iodine on extremely premature infants.

Although some literature suggests that this thyroid dysfunction may be transient, this case emphasises the severity of hypothyroidism that can result from topical iodine exposure and that it may be prolonged and persistent. There is a lack of high-quality evidence representing extremely low birthweight and premature infants less than 32 weeks. Therefore, further research is needed in this area. However, in the meantime this is an avoidable cause of thyroid dysfunction and its potential adverse neurodevelopmental outcomes. Identifying these high-risk infants and standardising TFTs after the use of iodine is of paramount importance. Ultimately, there is a need to establish clear guidance regarding the avoidance of iodine in VLBW and premature infants.

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ORCID iD
Catherine Mary Breen http://orcid.org/0000-0002-6621-5587

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