CASE REPORT

Central congenital hypothyroidism caused by maternal thyrotoxicosis

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SUMMARY

Central congenital hypothyroidism (CCH) is a rare and underdiagnosed disease that sometimes is caused by maternal Graves' disease. We report a case of CCH caused by undiagnosed, initially antibody-negative maternal thyrotoxicosis with possible disruption of fetal hypothalamic-pituitary-thyroid axis maturation. In CCH, maternal thyroid disease should be considered.

BACKGROUND

Central congenital hypothyroidism (CCH) is a rare and underdiagnosed disease with significant morbidity if not treated adequately.¹ The estimated prevalence of CCH in the Netherlands is 1:16 000 newborns.² The cause can be either genetic or non-genetic. One of the most important non-genetic causes of CCH is maternal thyroid disorder. We report a case of CCH caused by undiagnosed and initially antibody-negative maternal thyrotoxicosis.

CASE PRESENTATION

A 6-day-old female infant was admitted to the hospital because of poor drinking and lethargy. She was born after a largely uncontrolled pregnancy. The first medical consultation was at approximately 35 weeks' gestation. Maternal serological screening for HIV and hepatitis B was negative. Delivery was uneventful and Dubowitz scoring resulted in an estimated gestational age of 38 weeks. Her birth weight was 3090 g. The girl was discharged on day 4 of life and transferred to foster care. She was readmitted with symptoms of poor drinking and lethargy; physical examination findings were mild jaundice, lethargy and macroglossia.

INVESTIGATIONS

Laboratory testing showed normoglycaemia, normal complete blood cell count, a bilirubin level below the limit to start phototherapy and no signs of infection. Routine newborn screening results were known that same day: thyroid-stimulating hormone (TSH) 3 mIU/L (normal value ≤ 7 mIU/L), thyroxine (T4) 26 nmol/L (-3.3 SD, normal ≥ -1.6 SD) and thyroxine-binding globulin (TBG) 271 nmol/L (normal value TBG >40 nmol/L) (all screening results in units per litre of blood; multiplied with 2 to compare with serum results).³ Confirmation in the hospital laboratory showed a TSH of 7.2 mIU/L (normal range 0.32–12.27 mIU/L) and free T4 (fT4) of 6.7 pmol/L (normal range 8.9–33.6 pmol/L),

suggesting central hypothyroidism (inappropriately normal TSH in the context of fT4 below the normal range).⁴ Before initiation of levothyroxine replacement, other pituitary hormone axes were tested and found to be normal. The biological mother was diagnosed with primary hyperthyroidism with a TSH level <0.010 mIU/L and fT4 of 40.1 pmol/L, whereupon she was referred to an endocrinologist. Maternal family history was negative for thyroid disease. Thyroid-stimulating hormone receptor antibody (TRAb) levels in both the mother and the newborn were negative; antithyroid peroxidase was negative for the newborn and undetermined for the mother.

DIFFERENTIAL DIAGNOSIS

In general, the differential diagnosis of isolated CCH includes mutations in the TSHB, TRHR and IGSF1 gene, and maternal disease such as Graves' disease. CCH mostly occurs in the context of multiple pituitary hormone deficiencies, sometimes due to mutations in transcription factors that play a role in hypothalamic-pituitary development.

TREATMENT

Levothyroxine therapy was initiated at 25 µg/day (8 µg/kg/day). Based on TSH and fT4 levels, the dosage was initially increased to 31.25 µg/day (10 µg/kg/day). The dosage had to actively be lowered in the following weeks based on laboratory investigations. With the working diagnosis of undiagnosed maternal Graves' disease and transient CCH in the patient, treatment was discontinued at the age of 6 weeks. However, at 8 weeks of life, TSH was 11 mIU/L (normal range 0.58–5.57 mIU/L) with an fT4 level of 10 pmol/L (normal range 12.81–44.33 pmol/L), and levothyroxine therapy was restarted at 25 µg/day (6.5 µg/kg/day) and lowered to 18.75 µg/day (2.5 µg/kg/day).⁵

OUTCOME AND FOLLOW-UP

At the age of 2 years the infant showed normal psychomotor development and therapy was continued at 25 µg/day (2.5 µg/kg/day). Despite multiple attempts to refer the biological mother to an endocrinologist for further investigations, she refused treatment until her fT4 level was severely elevated (>100 pmol/L) with symptoms of tachycardia, weight loss, tremor and agitation. Repeat TRAb level in the mother, 5 months after delivery, was elevated (35 IU/L; normal value <9 IU/L),

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confirming the diagnosis of Graves' disease. TRAb levels were not repeated in our patient.

DISCUSSION

We report a case of CCH caused by maternal thyroid disease that could have been missed if primary TSH-based newborn screening was used. Thyroid hormone is critical for childhood growth and brain development. Undiagnosed hypothyroidism in infancy is the leading cause of intellectual impairment worldwide. Early diagnosis and treatment with levothyroxine can largely prevent this.⁶ In most European countries, newborn screening for primary congenital hypothyroidism due to dysgenesis or dyshormonogenesis of the thyroid is based on measurement of TSH.^{7,8} In the Netherlands, the newborn screening programme is T4-based with secondary TSH and thyroid-binding globulin measurements.

Isolated CCH is rare. The worldwide prevalence of CCH ranges from 1:16 000 newborns in the Netherlands to 1:180 000 newborns in the USA.^{2,9} Causes of CCH can be divided into genetic and non-genetic aetiology.¹⁰ One of the non-genetic disorders includes maternal hyperthyroidism due to the autoimmune disorder Graves' disease. Estimated prevalence of hyperthyroidism during pregnancy caused by Graves' disease is 0.1%–2.7%.^{11–14} Graves' disease is caused by TRAb that binds to the TSH receptor on follicular cells of the thyroid, resulting in autonomous thyroid hormone (T4) production and clinical signs and symptoms of hyperthyroidism. TSH-blocking antibodies bind to the TSH receptor but do not initiate intracellular signalling, resulting in hypothyroidism. These antibodies freely cross the placenta, particularly during the second half of gestation.¹⁵ Because the fetal thyroid is functionally mature around 25 weeks of gestation, the hypothalamic-pituitary-thyroid (HPT) axis can be affected in utero and/or postnatal.¹⁶

Congenital thyroid disease caused by maternal Graves' disease is rare and probably underdiagnosed; the prevalence is estimated at 1.5%–2.5%, although observational cohort studies report a prevalence up to 20.0%.^{14,17–26} Direct binding of TRAb to the pituitary gland with suppression of TSH production by a mechanism known as the autoregulatory ultra-short loop feedback control of TSH secretion might play a role.^{27,28} Cases in which CCH is caused by antibody-negative maternal thyrotoxicosis such as in our patient are very rare.²⁵

In our case, postpartum maternal TRAb levels were negative, but 5 months after delivery TRAb levels were highly elevated (35 IU/L). The initially antibody-negative maternal thyrotoxicosis with increasing antibodies postpartum may be explained by physiological changes in pregnancy.

Pregnancy is a state of general immunosuppression and TRAb levels decrease during pregnancy, reaching a nadir at term age.^{29,30} After delivery TRAb levels may increase again, resulting in aggravation or relapse of maternal Graves' disease.^{31,32} Seroconversion of TRAb levels has been described.³³

In our patient we speculate that CCH is caused by the increased transplacental transfer of maternal T4 and therefore disturbed maturation and regulation of the fetal HPT axis. Eight weeks after birth, when treatment was discontinued, the infant showed a low T4 with an elevated TSH. The elevated TSH might be due to an overcorrection of TSH production by the pituitary gland in response to (a recovering) CCH or by (transient) primary hypothyroidism. Primary hypothyroidism has been described in 2%–9% of newborns born to mothers with Graves' disease.^{30,34,35} It might also be an indication of altered thyroid growth and development since small volume thyroid

glands with inhomogeneous echotexture have been described in these patients.³⁶ Over time thyroid function tests remained stable with a low dose of levothyroxine (current dose 2.5 µg/kg/day). A new attempt to stop treatment will likely be done after the age of 3 years, beyond the critical phase of brain development. In rare instances, CCH can be prolonged and become permanent.³⁶

Learning points

- Physicians should be aware of the clinical signs of (central) hypothyroidism, including poor feeding, lethargy, prolonged jaundice, hypotonia, dry skin, large fontanelle, distended abdomen, umbilical hernia and poor weight gain.
- Central congenital hypothyroidism (CCH) can be missed in newborn screening programmes with primary thyroid-stimulating hormone measurements.
- In search of the cause of CCH, maternal thyroid disease should be considered.
- When thyroid-stimulating hormone receptor antibody (TRAb) levels are normal in combination with maternal primary hyperthyroidism, repeat measurement of maternal TRAb levels should be considered; TRAb levels may be decreased initially because of the immunosuppressive state during pregnancy.
- Long-term careful monitoring of thyroid function in these patients is very important in order to ensure the best possible neurodevelopmental outcome.

Contributors All four authors were directly involved in the patient's care. The first draft was written by DP, SvG, RL and DvdK, and DP critically reviewed the manuscript draft and approved it for final submission. DvdK was the paediatric endocrinologist who was consulted and who guided the writing process.

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REFERENCES

- 1 Léger J. Congenital hypothyroidism: a clinical update of long-term outcome in young adults. *Eur J Endocrinol* 2015;172:R67–R77.
- 2 Lanting CI, van Tijn DA, Loeber JG, *et al*. Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. *Pediatrics* 2005;116:168–73.
- 3 Afkap/beslissingscriteria Neonatale screening. RIVM, versie 1 juli 2016.
- 4 Verburg FA, Kirchgässner C, Hebestreit H, *et al*. Reference ranges for analytes of thyroid function in children. *Horm Metab Res* 2011;43:422–6.
- 5 Lem AJ, de Rijke YB, van Toor H, *et al*. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metab* 2012;97:3170–8.
- 6 Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis* 2010;5:17.
- 7 Büyükgöbüz A. Newborn screening for congenital hypothyroidism. *J Clin Res Pediatr Endocrinol* 2013;5(Suppl 1):8–12.
- 8 Léger J, Olivieri A, Donaldson M, *et al*. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab* 2014;99:363–84.
- 9 Brown RS, Bellisario RL, Botero D, *et al*. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. *J Clin Endocrinol Metab* 1996;81:1147–51.
- 10 Schoenmakers N, Alatzoglou KS, Chatterjee VK, *et al*. Recent advances in central congenital hypothyroidism. *J Endocrinol* 2015;227:R51–R71.
- 11 Korelitz JJ, McNally DL, Masters MN, *et al*. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid* 2013;23:758–65.

- 12 Rivkees SA, Mandel SJ. Thyroid disease in pregnancy. *Horm Res Paediatr* 2011;76 Suppl 1(suppl 1):91–6.
- 13 Chen CH, Xirasagar S, Lin CC, *et al*. Risk of adverse perinatal outcomes with antithyroid treatment during pregnancy: a nationwide population-based study. *BJOG* 2011;118:1365–73.
- 14 Wang W, Teng W, Shan Z, *et al*. The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. *Eur J Endocrinol* 2011;164:263–8.
- 15 Pitcher-Wilmott RW, Hindocha P, Wood CB. The placental transfer of IgG subclasses in human pregnancy. *Clin Exp Immunol* 1980;41:303–8.
- 16 Polak M, Legac I, Vuillard E, *et al*. Congenital hyperthyroidism: the fetus as a patient. *Horm Res* 2006;65:235–42.
- 17 De Groot L, Abalovich M, Alexander EK, *et al*. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543–65.
- 18 Ogilvy-Stuart AL. Neonatal thyroid disorders. *Arch Dis Child Fetal Neonatal Ed* 2002;87:165F–71.
- 19 Mitsuda N, Tamaki H, Amino N, *et al*. Risk factors for developmental disorders in infants born to women with Graves disease. *Obstet Gynecol* 1992;80(3 Pt 1):359–64.
- 20 Peleg D, Cada S, Peleg A, *et al*. The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. *Obstet Gynecol* 2002;99:1040–3.
- 21 Besançon A, Beltrand J, Le Gac I, *et al*. Management of neonates born to women with Graves' disease: a cohort study. *Eur J Endocrinol* 2014;170:855–62.
- 22 Higuchi R, Kumagai T, Kobayashi M, *et al*. Short-term hyperthyroidism followed by transient pituitary hypothyroidism in a very low birth weight infant born to a mother with uncontrolled Graves' disease. *Pediatrics* 2001;107:e57–30.
- 23 Lee YS, Loke KY, Ng SC, *et al*. Maternal thyrotoxicosis causing central hypothyroidism in infants. *J Paediatr Child Health* 2002;38:206–8.
- 24 Liebrand CA, A.C.de Mol MJE, Kempers en C.Noordam. Centrale congenitale hypothyreoïdie door ziekte van Graves bij de Moeder. *Ned Tijdschr Geneesk* 2006;150:2229–32.
- 25 Matsuura N, Harada S, Ohya Y, *et al*. The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. *Pediatr Res* 1997;42:29:214–8.
- 26 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.
- 27 Zwaveling-Soonawala N, van Trotsenburg P, Vulsma T. Central hypothyroidism in an infant born to an adequately treated mother with Graves' disease: an effect of maternally derived thyrotrophin receptor antibodies? *Thyroid* 2009;19:661–2.
- 28 Prummel MF, Brokken LJ, Wiersinga WM. Ultra short-loop feedback control of thyrotropin secretion. *Thyroid* 2004;14:825–9.
- 29 Kamijo K. TSH-receptor antibodies determined by the first, second and third generation assays and thyroid-stimulating antibody in pregnant patients with Graves' disease. *Endocr J* 2007;54:619–24.
- 30 Balucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res* 2013;2013:1–15.
- 31 Amino N, Izumi Y, Hidaka Y, *et al*. No increase of blocking type anti-thyrotropin receptor antibodies during pregnancy in patients with Graves' disease. *J Clin Endocrinol Metab* 2003;88:5871–4.
- 32 Kung AW, Lau KS, Kohn LD. Epitope mapping of tsh receptor-blocking antibodies in Graves' disease that appear during pregnancy. *J Clin Endocrinol Metab* 2001;86:3647–53.
- 33 Nishihara E, Fukata S, Hishinuma A, *et al*. Prevalence of thyrotropin receptor germline mutations and clinical courses in 89 hyperthyroid patients with diffuse goiter and negative anti-thyrotropin receptor antibodies. *Thyroid* 2014;24:789–95.
- 34 Uenaka M, Tanimura K, Tairaku S, *et al*. Risk factors for neonatal thyroid dysfunction in pregnancies complicated by Graves' disease. *Eur J Obstet Gynecol Reprod Biol* 2014;177:89–93.
- 35 McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. *Thyroid* 2013;23:14–24.
- 36 Kempers MJ, van Trotsenburg AS, van Rijn RR, *et al*. Loss of integrity of thyroid morphology and function in children born to mothers with inadequately treated Graves' disease. *J Clin Endocrinol Metab* 2007;92:2984–91.

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