Journal of the Endocrine Society, 2021, Vol. 5, No. 6, 1–7
doi:10.1210/jendso/bvab044
Case Report

Case Report

Management of Severe Graves' Hyperthyroidism in Pregnancy Following Immune Reconstitution Therapy in Multiple Sclerosis

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Abbreviations: ALZ, alemtuzumab; ATD, antithyroid drug; CBZ, carbimazole; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GW, gestational week; HR, hear rate; MS, multiple sclerosis; PTU, propylthiouracil; TSH, thyroid stimulating hormone; TRAb, TSH receptor stimulating antibody.

Received: 14 December 2020; Editorial Decision: 14 March 2021; First Published Online: 17 March 2021; Corrected and Typeset: 15 May 2021.

Abstract

Context: Alemtuzumab (ALZ), a CD52 monoclonal antibody, is highly efficacious in multiple sclerosis; however, side effects are common. Autoimmune thyroid disease (Graves' disease and Hashimoto thyroiditis) is a well-known complication of ALZ. Treatment of ALZ-induced Graves' disease can be challenging, and even more difficult during pregnancy.
Case description: We present a case of severe ALZ-induced Graves' disease with a rapid increase in thyrotropin receptor antibodies (TRAb 240 IU/L) and thyrotoxicosis in early pregnancy. Treatment with high doses of antithyroid medication was needed. There was high risk of both fetal and neonatal thyrotoxicosis. Serial fetal sonography showed normal development. The newborn baby presented high levels of TRAb (240 IU/L) and developed neonatal thyrotoxicosis on day 8. Adequate monitoring, treatment, and follow-up of the newborn baby ensured normal thyroid function until disappearance of TRAb 6 weeks after birth.
Conclusion: Multiple sclerosis patients treated with ALZ may develop severe Graves' disease with an increased risk of both fetal and neonatal thyrotoxicosis. Close follow-up with a multidisciplinary approach is needed to ensure a healthy outcome.

Key Words: Graves' disease, multiple sclerosis, neonatal thyrotoxicosis, pregnancy, alemtuzumab

ISSN 2472-1972

Multiple sclerosis (MS) is a chronic neurological disorder with onset in young adulthood. Several highly effective treatments have become available during the last years, altering the course of the disease. Alemtuzumab (ALZ), a CD52 monoclonal antibody, is highly efficacious; however, side effects are common. Indeed, autoimmune thyroid diseases (AITD) is 1 the most common forms of complication of ALZ treatment [1-3].

The incidence of hyperthyroidism during pregnancy is low 0.65 (0-2.5%) [4], Graves' disease (GD) accounting for most of the cases. AITD occurs in up to 40% of the patients [1-3] treated with ALZ [1-3], of which GD accounts for 60% to 70% [3]. During pregnancy, a mild form of GD may improve, allowing for discontinuation of antithyroid drugs (ATDs) in the third gestational trimester in some patients [5]. However, in severe cases, transplacental transfer of thyrotropin (TSH) receptor stimulating antibodies (TRAb) may induce fetal and neonatal thyrotoxicosis with potential life-threatening consequences. Poor control of thyrotoxicosis inn pregnancy is associated with pre-eclampsia, miscarriage, prematurity, intrauterine growth restriction, fetal hyperthyroidism and hypothyroidism, preterm labor low birth weight, thyroid storm, heart failure, and still birth [6-8].

Treatment of ALZ-induced GD can be challenging [9], even more difficult in pregnancy. In this report, we present a case of severe ALZ-induced GD during pregnancy demonstrating the need for a multidisciplinary approach to ensure a healthy outcome.

Material and Methods

Case Presentation

A 36-year-old woman was diagnosed with MS at the age of 29. She was initially treated with interferon for a short time and then for 2 years with fingolimod (Gilenya-sphingosine-1-phosphate receptor modulator). Due to disease activity, ALZ was administered in 3 courses at the ages of 32, 33, and 35 years. GD was diagnosed during a routine control 4 weeks after the third treatment course. She did not present any symptoms of hyperthyroidism or endocrine ophthalmopathy. TRAb level was 13 IU/L (ref. range <1.8) and she was treated with carbimazole (CBZ). Five months later, thyroid function tests were normal and TRAb levels were 2.2 IU/L (ref. range <1.8). Due to pregnancy desire, the treatment was switched to propylthiouracil (PTU). She conceived shortly after in vitro in fertilization, but had a miscarriage.

She conceived again (in vitro in fertilization), 8 months after the third ALZ course while using PTU 100 mg daily.

After conceiving, free thyroxine (FT4) was normal 19 pmol/L. The TRAb level was slightly elevated (3 IU/L; ref. range <1.8). She did not present any symptoms of hyperthyroidism (blood pressure 100/65, heart rate [HR] 79/minute) or any clinical features of endocrine ophthalmopathy. The thyroid gland volume was assessed as normal by clinical examination. According to American Thyroid Association (ATA) guidelines [6], treatment with PTU 100 mg daily was continued. Human chorionic gonadotropin–induced thyrotoxicosis may occur early in pregnancy. However, in human chorionic gonadotropin–induced thyrotoxicosis, the TRAb level is normal and the levels of FT4 are often slightly elevated but return to normal within few months.

At the onset of pregnancy and through pregnancy, hematological parameters including differential cell count were normal.

Materials and Methods

TRAb were measured in the hormone laboratory at Oslo University Hospital using the BRAHMS KRYPTOR compact PLUS Kit (Thermo Fisher Scientific) [10] (ref. range <1.8 IU/L), TSH [11] and FT4 [12] (DELFIA kit; Wallac Oy, Finland) (ref. range TSH 0.5-3.6 mUI/L, FT4 8-21 pmol/L), and free triiodothyronine (FT3) [13] (Cobas e601 kit, Roche diagnostic, IN, USA) (ref. range 2.8-7 pmol/L).

Results

Case Management—Outcomes

Thyroid function tests and the results for fetal development by serial sonography are shown in Fig. 1A–1F. At gestational week (GW) 4, thyroid function showed elevated FT4 27 pmol/L and a clear increase in TRAb level (23 IU/L). (Fig. 1A and 1B) PTU dose was increased to 300 mg daily. In GW 8, both FT4 and FT3 were normalized. In GW 13 PTU was switched to CBZ (10 mg/day). However, the thyroid disease activity and TRAb increased rapidly during the following weeks. An enlargement of the thyroid gland was notable. The dose of CBZ was gradually increased up to 30 mg daily in GW 20, which she used for 2 weeks; thereafter, the dose was gradually reduced. Although thyroid function tests rapidly normalized (FT4 18 pmol/L in GW 22), TRAb levels continued to rise, reaching 240 UI/L in GW 22 (Fig. 1B).

However, it was possible that in addition to high levels of circulating thyroid hormones, the high levels of TRAb could potentially stimulate the thyroid gland of the fetus inducing fetal thyrotoxicosis [14]. The use of a high dose of CBZ can induce congenital malformation (early in pregnancy), liver toxicity, increase the risk of agranolucytosis, or affect fetal thyroid function inducing hypothyroidism. ALZ-induced TRAb could be stimulating and/or blocking antibodies. Serum samples were analyzed by specific assay showing that >90% of the antibodies were stimulating Abs

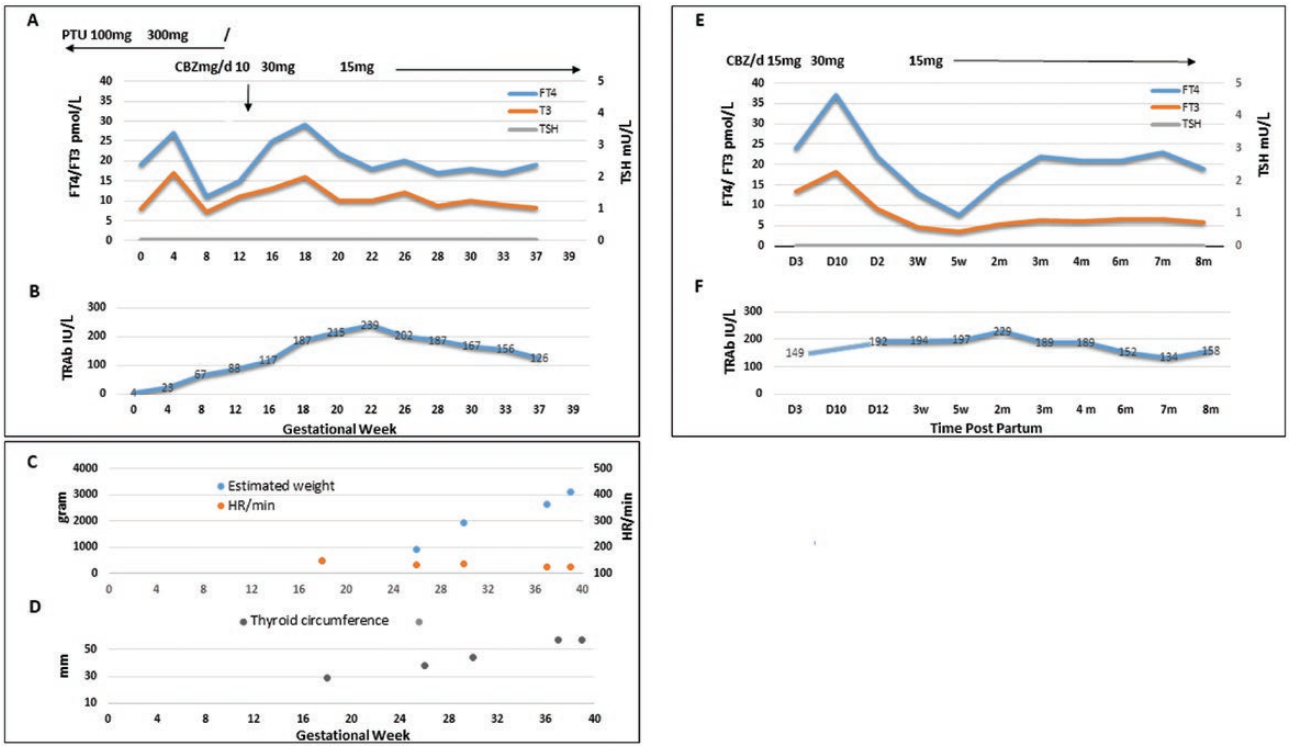

Figure 1. Thyroid function in pregnant women. Thyroid function (A), and TRAb (B) during pregnancy; serial fetal ultrasonography: estimated weight g (gram), heart rate (HR) (C), and thyroid circumference (mm) (D). Postpartum thyroid function (E), and TRAb (F). GW, gestational week; TSH, thyroid stimulating hormone (ref. range 0.5-3.6 mIU/L); FT4, free thyroxin (ref. range 8-20 pmol/L); FT3, free triiodothyronine (ref. range 3.5-6.6 pmol/L); TRAb, TSH receptor stimulating antibody (ref. range <1.8 IU/L); PTU, propylthiouracil; CBZ, carbimazole; HR, heart rate.

(courtesy of Prof. Dr. G.J. Kahaly, Johannes Gutenberg University Medical Center, Mainz, Germany).

Based on perceived risks, thyroidectomy as an alternative therapy was discussed with the endocrine surgeon. Thyroid ultrasonography showed a highly vascularized enlarged gland (volume 20 mL), which could increase the risk for bleeding and postoperative hypocalcemia. Furthermore, TRAb could persist for weeks, inducing fetal thyrotoxicosis after surgery.

Thyroid function tests (Fig. 1A) were kept close to the upper reference range (CBZ 15 mg/day), and she did not present any symptoms of hyperthyroidism. After GW 22, TRAb levels slowly decreased, but remained high during the entire pregnancy (128 mU/L at GW 37). (Fig. 1B)

Fetal monitoring

There was a high risk for fetal thyrotoxicosis and regular follow-up by a fetal medicine specialist was necessary to monitor the fetus. Serial fetal sonography showed normal development, normal heart rate, normal thyroid gland size and no sign of fetal thyrotoxicosis. Estimated weight in GW 18, 22, 29, and 37 was 460 g, 929 g, 1940 g, and 2649 g respectively; HR 149, 132, 138, and 127/minute; and thyroid circumference 29 mm (15 percentile), 38 mm, 44 mm, and 57 (60th percentile).(Fig. 1C and 1D)

In GW 39, estimated weight was 3100 g. However, 1 week later the growth curve declined and induction of labor was scheduled. The newborn baby was at high risk for perinatal thyrotoxicosis, and therefore the neonatal intensive care unit was informed prior to labor. However, she had spontaneous labor, vacuum-assisted due to risk of asphyxia (GW 40). No complications occurred, and the patient gave birth to a small but healthy girl (Apgar score 9 + 9 + 9, weight 2600 g and 47 cm length).

Except from slightly dysmaturity (assigned to low birth weight), there were no clinical signs of hyper- or hypothyroidism. At birth, blood pressure was 70/30, HR 142, temperature 34.9-36.2°C, SaO_2 99%, respiration frequency 26, and s-glucose 5.2 mmol/L.

The newborn baby

Thyroid function in the newborn baby was assessed in blood tests after birth. Initially, a normal physiological surge in serum TSH (32.8 mU/L) (ref. range <8 mU/L, age 0-12 months) was noted while FT4 and FT3 were within reference ranges (15.5 pmol/L and 3.0 pmol/L respectively) (Fig. 2A). Due to high levels of TRAb (240 IU/L) (Fig. 2B), there was a risk of perinatal thyrotoxicosis, and the newborn baby was submitted to the intensive care unit for close monitoring. During the first week,

she received milk supplements in addition to breast milk because of the low birth weight and in case thyrotoxicosis occurred.

FT4 started to increase from day 8. On day 10, the newborn baby presented symptoms of thyrotoxicosis, weight gain stopped, and HR increased (140-160/minute). A decrease in TRAb (149 IU/L) was noted. The blood sample showed increasing FT4 (47.9 pmol/L) and FT3 (16.7 pmol/L) (Fig. 2A). Treatment with a CBZ mixture (0.5 mg/kg/day) and propranolol (2 mg/kg/day) was initiated, with normalization of symptoms within 1 week. (Fig. 2A and 2B). After 3 weeks, thyroid function tests returned to normal with a clear decrease in TRAb (32 IU/L). The CBZ dose was gradually tapered and stopped after 6 weeks when thyroid function tests and TRAb were normalized. By 3 months of age, thyroid function remained normal and the baby showed normal growth and development.

Postpartum

The mother's thyroid function tests and TRAb increased shortly after birth (FT4 37 pmol/L, TRAb 192 IU/L) (Fig. 1E and 1F), and the dose of CBZ was increased (30 mg/day). Eight months after birth, TRAb levels were still high (119 IU/L) while using CBZ. Thyroidectomy was recommended, but postponed by the patient.

Discussion

MS and GD are both common autoimmune diseases mainly affecting young women of fertile age. ALZ (CD52 monoclonal antibody) is an efficient therapy in MS. ALZ leads to a rapid depletion and gradually reconstitution predominantly of CD52-bearing B and T cells with reprogramming effects on immune cell composition. We have found that many young women have a desire to get pregnant shortly after improvement of MS symptoms. However, these women are at high risk for development of autoimmune thyroid diseases, mainly GD [1-3]. Several cases with blocking TRAb and hypothyroidism have also been reported in patients treated with ALZ [3]. Secondary autoimmunity is likely due to homoeostatic T-cell proliferation, generating constantly activated and highly proliferative CD4+ and CD8+ populations which promote further inflammation [15].

The risk of thyroid dysfunction being high in patients receiving ALZ, TSH, and FT4 should be tested before conception, and early in pregnancy, and supplemented with TRAb. We present a case of ALZ-induced GD with a rapid increase in TRAb and thyroid function early in pregnancy. Hematological parameters including differential count were normal. The increased activity appeared 8 months after ALZ treatment. The median (range) onset is reported to be 23 (2-107) months [3]. The course of the disease may fluctuate, adding to the treatment challenges [16].

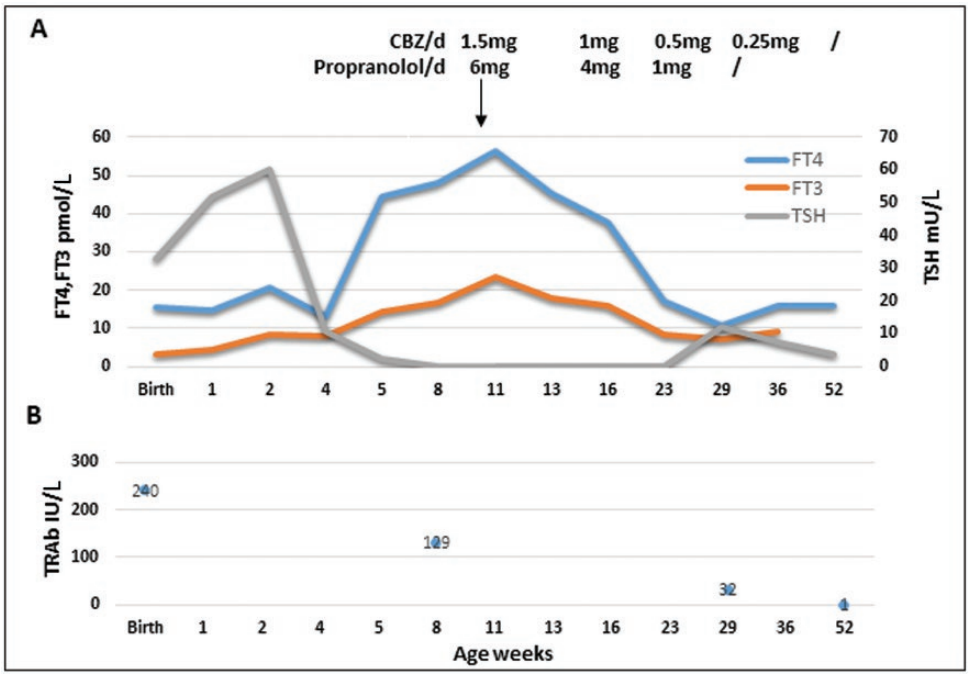

Figure 2. Perinatal thyrotoxicosis in the newborn baby. Thyrotoxicosis was observed on day 8. TRAb levels that were high after birth, returned to normal values after 6 weeks. **(A)** FT4, free thyroxin (ref. range 8-20 pmol/L); FT3, free triiodothyronine (ref. range 3.5-6.6 pmol/L); TSH, thyroid-stimulating hormone (ref. range 0-12 months <8 mIU/L); (B) TRAb, TSH receptor stimulating antibody (ref. range <1.8 IU/L); CBZ, carbimazole.

Hyperthyroidism during pregnancy may induce maternal, fetal, obstetrical, and neonatal complications. Other than maternal hyperthyroxinemia, transplacental transfer of TRAb can induce fetal and neonatal hyperthyroidism. ATD is the first choice of treatment of GD during pregnancy [6]. PTU is recommended during the first trimester and CBZ/methimazole during second and third trimesters [6], due to risk of hepatotoxicity of PTU [17, 18] and lower rate of congenital malformation than CBZ/methimazole early in pregnancy (respectively 3% and 5%) [19, 20]. FT4 levels were closely monitored and kept close to the upper reference range. According to ATA guidelines, the initial dose of ATD depends on severity of symptoms and levels of FT4 (CMZ 10-40 mg and PTU 100-600 mg daily) [6].

Given the high levels of TRAb, the fetus was at high risk for fetal thyrotoxicosis, and high doses of ATD have been associated with a number of side effects [21]. Therefore, other treatment strategies were considered. Thyroidectomy in the second trimester is an alternative therapy in the case of severe GD or intolerance to medication [6]. The risk of postoperative hypocalcemia, bleeding, or recurrent laryngeal nerve palsy is higher in patients with a hypervascularized and enlarged thyroid gland as in this case. Furthermore, TRAb usually will be normalized within a year in 50% of patients [22]. High levels of circulating TRAb could persist for several weeks after thyroidectomy [23] (stimulating fetal thyroid gland), and together with discontinuation of antithyroid medication in pregnant women, the risk of fetal thyrotoxicosis would still be high. The use of potassium iodide (Lugol's solution) prior to surgery is recommended by the ATA [6]. However, the use of potassium iodide during pregnancy is usually considered to be contraindicated as it can potentially induce fetal hypothyroidism. A few studies in Japan have tested the safety and efficacy of this treatment during pregnancy [24].

The use of corticosteroid was not considered in this case. However, given the high levels of TRAb, a low dose of prednisolone could have a beneficial effect. Corticosteroid other than in ophthalmopathy is used in the resistant form of GD [25, 26], and also during pregnancy [27].

The incidence of fetal and neonatal hyperthyroidism is 1% to 5% in women with GD. TRAb should be measured in pregnant women with GD or past history of GD (through pregnancy and GW 20-28) to assess the risk of fetal hyperthyroidism. A maternal TRAb level >5 IU/L or 3 times the upper reference range is associated with a higher risk for neonatal hyperthyroidism [28, 29]. ALZ-induced GD patients may present considerably high levels of TRAb as in the current case (TRAb 240 IU/L, mainly stimulating antibodies) with a high risk of fetal thyrotoxicosis. Serial ultrasound and close follow-up by experienced fetal medicine specialist is necessary in patients with severe GD and high levels of TRAb, in order to assess signs of fetal hyperthyroidism: fetal goiter, tachycardia, growth restriction, accelerated bone maturation, heart failure, and hydrops [30]. Although no sign of hyperthyroidism was noted by serial ultrasound, the birthweight was below the third percentile according to the national growth standard. Delivery should have been induced at gestational week 37 if fetal weight had been estimated correctly [31].

Moreover, high levels of maternal TRAb late in pregnancy increase the risk of neonatal thyrotoxicosis, which usually appears few days after birth as in our case. Neonatal thyrotoxicosis is transient but serious, and if undetected and untreated the newborn baby will present severe symptoms. The pediatrician should be informed regarding the high risk before labor, and close monitoring after birth is necessary. The newborn baby presented a physiological transient increase in TSH with normal thyroxin level at birth. In spite of high levels of TRAb at birth, the signs of hyperthyroidism appeared a week later after clearance of maternal ATD (half-life of CBZ 5 hours). Neonatal thyrotoxicosis might not be diagnosed by the thyroid screening program. It is recommended to test TRAb after birth, and to monitor thyroid function on days 3-5 and on day 10 [32]. On day 8, the TRAb level was 45% lower than at birth, which gradually returned to normal 6 weeks after birth, supporting the reported half-life of TRAb being 1-2 weeks [6].

Adequate monitoring, treatment with CBZ (PTU is not recommended because of the increased risk of hepatotoxicity) and propranolol, and close follow-up of the newborn baby ensured normal thyroid function until clearance of maternal TRAb, 6 weeks after birth (reported to be up to 3 months).

TRAb blocking is less common; however, it should be identified as it results in a transient hypothyroidism. Biological assays are available to distinguish between stimulating and blocking TRAb. Distinguishing between transient and permanent neonatal hypothyroidism is difficult [33, 34]. The clinical decision is usually replacement with L-thyroxin [34]. The withdrawal of treatment should be considered in a longer run if permanent cause of congenital hypothyroidism is not established [34, 35].

Conclusion

MS patients treated with ALZ have an increased risk of developing autoimmune thyroid diseases and mainly GD [2, 3]. Disease activity may be higher than "the classic Graves' disease," and may escalate rapidly, requiring meticulous follow-up mainly during pregnancy [3]. Hyperthyroidism during pregnancy may induce maternal, fetal, obstetrical, and neonatal complications. Antibodies in this case were

mainly stimulating with high risk for fetal and neonatal thyrotoxicosis. However, overt hypothyroidism due to blocking TRAb inducing hypothyroidism may occur.

All women treated with ALZ and with a stated pregnancy desire should be tested for TSH, FT4, and TRAb before conception, early in pregnancy, and in GW 20-28. Thyrotoxic women should be euthyroid before attempting pregnancy. In case of severe ALZ-induced GD and pregnancy desire, definitive treatment (radioiodine therapy or surgery) prior to conception should be considered. Increased disease activity with high levels of TRAb appeared 8 months after the last dose of ALZ. It is generally recommended to avoid pregnancy for 4 months after last course of ALZ treatment. Larger studies are needed to explore if this period should be extended.

In summary, multidisciplinary management with collaboration between endocrinologist, neurologist, endocrine surgeon, fetal medicine specialist, pediatrician, and the laboratory medicine service is important to ensure adequate treatment of both the mother and the baby, as shown in this case report.

Acknowledgments

Financial Support: This study was financed by the authors' institutions and South-Eastern Norway Regional Health Authority to S.S.H.

Additional Information

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***Disclosures*:** The authors have no potential conflict of interest to declare.

Data Availability: All date data used in this study are presented or available from the corresponding author upon reasonable request.

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