CASE REPORT

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Worsening of Congenital Hypothyroidism After Start of Carob-bean Gum Thickened Formula: Is There a Link? A Case Report

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What is already known on this topic?

Infant formulas containing soya bean extracts, as well as soy-containing baby foods, some drugs used to manage infants with recurrent regurgitation and specific medications for infant colic, are related to altered thyroid function in early childhood. Moreover, carob-beans used to thicken formula milk are reported to increase its viscosity and thickened formula with locust (carob) bean gum, slows gastric emptying in infants.

What this study adds?

This is the first case report to provide evidence of a possible effect of carob-bean gum thickened formula on the absorption of levothyroxine. We recommend caution and frequent thyroid function evaluation if these products are given to young patients with congenital hypothyroidism.

Abstract

Congenital hypothyroidism (CH), if not correctly treated with levothyroxine (L-T4), may cause permanent intellectual disability. If patients treated with L-T4 do not achieve good thyroid stimulating hormone (TSH) control, the possibility of poor compliance and/or poor absorption of L-T4 should be investigated. We describe an infant with CH whose thyroid hormone levels worsened after she started a carob-bean gum thickened formula. A baby girl was diagnosed with CH by newborn screening [confirmatory venous blood TSH was 496.0 µIU/mL and free thyroxine (fT_4) was 0.13 ng/dL]. Five weeks after beginning replacement L-T4 treatment (10.6 µg/kg per day), thyroid function normalized (TSH 2.72 µIU/mL, fT_4 2.08 ng/dL). However, five weeks later, thyroid function test results had worsened (TSH 31.1 µIU/mL, fT_4 1.27 ng/dl), which worsened further (TSH 44.8 µIU/mL, fT_4 1.16 ng/dL) even after L-T4 dose was increased (10.9 µg/kg per day). Anamnesis disclosed that she had started a carob-bean gum thickened formula to combat gastroesophageal reflux disease rather than regular type 1 formula milk. The anti-reflux milk formula was discontinued. Fourteen days later her TSH level dropped to 0.38 µIU/mL and fT_4 increased to 2.68 ng/dL, allowing the L-T4 dose to be reduced (from 10.9 µg/kg per day to 8.0 µg/kg per day). These findings suggest that carob-bean gum thickened formula may affect absorption of L-T4. If such formulas are used, we recommend a more frequent evaluation of thyroid function. In CH infants, inexplicably high TSH levels may be caused by gastrointestinal disorders or the interference from drugs or other substances, including some types of milk formula, which impair L-T4 absorption.

Keywords: Congenital hypothyroidism, L-thyroxine, treatment, carob-bean gum thickened formula, gastro-intestinal absorption, gastroesophageal reflux, case report

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Introduction

Congenital hypothyroidism (CH) is a relatively frequent endocrine disorder in which thyroid hormone (TH) deficiency, if not promptly diagnosed and correctly treated with L-thyroxine (L-T4) replacement, may lead to permanent intellectual disability (1). Below three years of age, adequate TH levels are essential for normal brain development. In CH patients treated with L-T4, poor compliance and/or poor absorption of L-T4 may cause a poorer developmental outcome compared to patients with satisfactory compliance and uncompromised absorption (2).

To achieve better developmental outcome, THs should return to normal range rapidly, preferably within the first 14 days of therapy (2). Screening programs for CH are used in many countries, allowing L-T4 treatment to be started early, generally when the disease is still asymptomatic (1). High starting doses of L-T4, between 10 and 15 mg/kg are the treatment of choice and determine both auxological (3) and neurological improvement (4). Nevertheless, initial L-T4 dose should vary based on formulation used, thyroid stimulating hormone (TSH) and TH levels (5). In the presence of poor TSH control, it is advisable to first investigate the correct method of administration and intake of L-T4, since caregivers make mistakes that can often be identified (2). However, it has been shown that gastrointestinal disorders, as well as several medications and other substances, may affect L-T4 absorption in infants (2,6).

Proton-pump inhibitors, aluminium-containing antacids, iron and calcium salts, herbal remedies and nutritional supplements may worsen L-T4 absorption, modifying gastric pH or binding with L-T4 to create insoluble complexes (2,7,8,9). Although few data have been reported, there may also be interference from infant milk formula, which, due to its composition rich in fats, proteins and lactose, inhibits the absorption of L-T4 in the small intestine (10). In a small number of historic case reports, soy infant formulas and soy-containing baby foods were shown to alter L-T4 absorption in the first years of life (11). After weaning, if L-T4 is taken with food, a higher dose may be needed to maintain euthyroidism (5,8).

The liquid formulation of L-T4 is currently the most widely used in children with CH, given the greater absorption of oral solutions compared to tablet form L-T4 (12). Moreover, some L-T4-treated children with CH achieve euthyroidism only if they are treated with a combined therapy of L-T4 and liothyronine (L-T3), probably because of insufficient peripheral conversion of thyroxine (T4) to thyronine (T3) (13).

Endocrinologists and pediatricians must ensure that parents are appropriately informed about the correct method of L-T4 administration and the possible interference of some drugs, supplements and foods. Parents also need to be made aware of the potential negative consequences for growth and especially neurological development of their child in case of insufficient replacement (10). Thickened formulas are increasingly used in patients with gastroesophageal reflux. The availability of calcium, iron, and zinc tends to be significantly impaired by products thickened with locust (carob) bean gum compared to non-thickened infant formulas (14).

In this case report, an infant with CH whose TH levels worsened after a carob-bean gum thickened formula was introduced for gastroesophageal reflux disease (GERD) is presented for the first time. The possible interference of infant milk formula with L-T4 treatment is discussed.

Case Report

A baby girl was referred for diagnosis with by newborn screening with a blood spot TSH of 186.57 µIU/mL. At the first evaluation, anamnesis showed that the patient was born to non-consanguineous, healthy, young parents. There was no family history of thyroid disorders. Pregnancy was uncomplicated and the child was born by cesarean delivery at 39 weeks of gestation. Her birth weight was 3.140 g [-0.36 standard deviation score (SDS), according INeS chart, 2010], length 49.0 cm (-0.41 SDS, according INeS chart, 2010) and head circumference 34.5 cm (0.44 SDS, according INeS chart, 2010). Apgar scores were 9 at one minute and again 9 at five minutes. Clinical examination at 8 days of age revealed icterus, little spontaneous motor activity, a hoarse cry and cool, dry, rough and thick skin. Her abdomen was distended with an umbilical hernia. At that time she was fed breast milk supplemented with regular type 1 formula milk (80 mL for seven meals a day). On confirmatory blood evaluation, also on day 8, TSH was 496.0 µIU/mL (normal value for age: 0.70-11.0 µIU/mL), free T4 (fT_4) was 0.13 ng/dL (normal value for age: 1.24-3.89 ng/dL), and free T3 (fT3) was 1.05 ng/dL (normal value for age: 2.73-8.46 ng/dL), confirming the diagnosis of CH. Further testing showed anti-thyroid peroxidase, anti-thyroglobulin and TSH receptor antibodies (TRAbs) were negative. Urinary iodine excretion was normal. Ultrasound examination of the neck was consistent with thyroid agenesis (Figure 1).

The patient immediately started therapy with 32.2 µg/day (10.6 µg/kg per day) of liquid L-T4. After five weeks of L-T4 treatment, TSH values had normalized at 2.72 µIU/mL

(normal value: 0.40-4.0 µIU/mL) with fT_4 values of 2.08 ng/dL (normal value for age: 1.24 - 3.89 ng/dL). However, five weeks later, blood tests revealed lower fT_4 values (1.27 ng/dL) associated with an increase in TSH to 31.1 µIU/mL, without any clinical findings of hypothyroidism and anamnesis suggested good compliance. Furthermore, parents reported that they waited at least 30 minutes between the milk meal and the administration of L-T4. Consequently, the L-T4 dose was raised to 50.0 µg/day (10.9 µg/kg per day) in line with the increase in body weight. One week later, TSH had again increased to 44.8 µIU/mL (normal value: 0.40-4.0 µIU/mL), while fT_4 had decreased further to 1.16 ng/dL although it remained in the normal range for age of 0.8-1.9 ng/dL. The patient was not taking any medications other than L-T4. Anamnesis revealed that to supplement breast milk, the patient had been given a carob-bean gum thickened formula (170 mL for 7 meals a day) rather than regular type 1 formula milk for approximately three weeks as treatment for GERD. When this anti-reflux milk was discontinued, after only two weeks, the TSH level dropped to 0.38 µIU/mL, and her fT_4 level increased to 2.68 ng/dL. L-T4 treatment was reduced to 8.0 mg/kg per day, with normalization of thyroid function (Figure 2).

Discussion

This case suggests that carob-bean gum thickened formula may influence the absorption of L-T4. We therefore suggest additional caution when the use of these products in patients with CH is necessary. If such formula is used, we recommend evaluating thyroid function more frequently. To the best of our knowledge, this is the first published report of a potential interference of this type of anti-reflux milk on the absorption of L-T4. Therefore, further studies are needed to confirm these findings.

Some drugs used to manage infants with recurrent regurgitation, such as acid lowering agents or increasing gastric pH, reduce the intestinal absorption of L-T4 (15). With different mechanisms, specific medications for infant colic, such as simethicone, alter the bioavailability of L-T4 (16).

Various thickening agents derived from cereals, such as polysaccharide from glass rice and carob-bean gum, which are all sources of dietary fibre, are commonly used in the treatment of GERD and failure to gain weight in infants and children (17). Cow's milk formulas with added thickening agents, again including carob-beans or galactomannan, have long been commercially available. Carob-beans thicken formula milk, increasing its viscosity. The beans have a high sugar content (48-56%: mainly sucrose, glucose, and fructose), and a low protein (3-4%) and fat content (0.2-0.6%). They are also rich in dietary fibre and minerals, including calcium and iron (18). Milk thickening agents with carob-bean gum improve clinical symptoms of GERD in infants (19), even if data from rat studies have suggested a reduction in gastric emptying rate with a slowed passage of food from the stomach to the upper small intestine (20). In one study on infants with gastroesophageal reflux, a thickened formula with commercially available concentrations of locust (carob) bean gum slowed gastric emptying (21). Another study revealed a 1000-fold increase in meal viscosity, with a significant delay in gastric emptying (22). However, in a study involving 20 full term Thai infants without pathological gastroesophageal reflux there was no significance difference in gastric emptying half time (17). In adult humans, the addition of locust bean gum to a semisolid meal significantly delayed the gastric emptying rate (23).

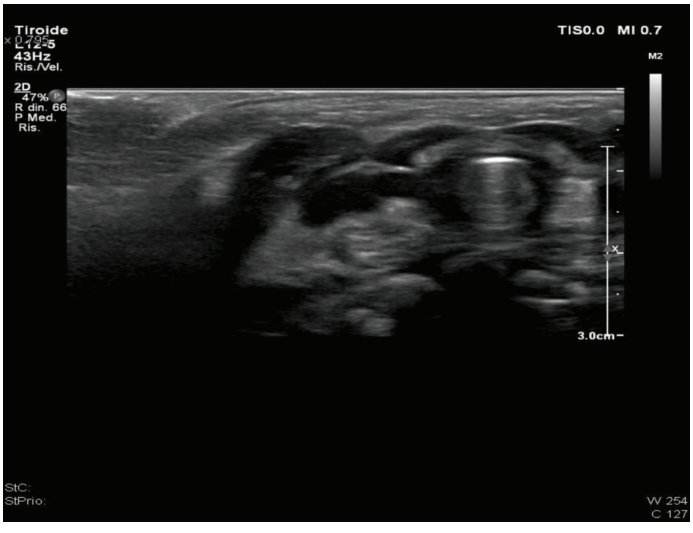

Figure 1. Ultrasound of the thyroid gland showing the absence of thyroid tissue

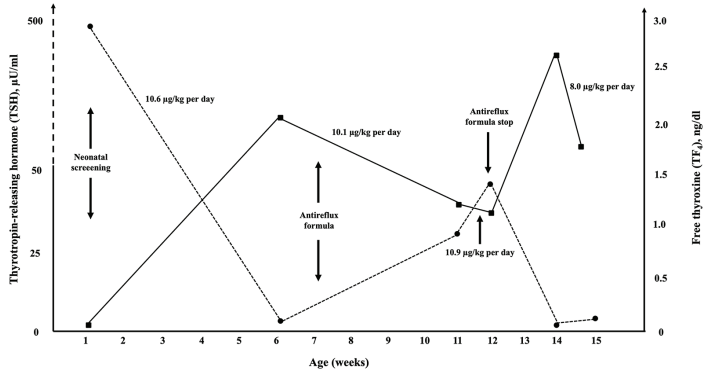

Figure 2. Trend in fT_4 and TSH, illustrating the effect of anti-reflux formula on their values

fT_4: free T_4, TSH: thyroid stimulating hormone

To date the correlation between formula milk and L-T4 absorption is not well clarified, but it would seem that composition of infant formula milk, rich in fat, protein and lactose, may reduce it. Consequently larger L-T4 doses are required to maintain euthyroidism (7). One study reported that in adults, cow's milk may reduce L-T4 absorption by nearly 8%. There are no data in the literature regarding breast milk, although it is possible that it also decreases L-T4 bioavailability (24,25).

The effect of soy bean-containing infant formulas, as well as soy-containing baby foods, on thyroid function in early childhood is better understood (11,26,27,28,29,30,31). Soy-based formula is often an alternative to milk protein formula in cases of allergies or intolerances. Two historic case reports described two infants fed with soy-based formula, one of whom had cretinism and goitre at 10 months of age, and the other was asymptomatic but with persistently high TSH levels despite high doses of L-T4. In both cases, thyroid function normalized after discontinuation of the soy-based diet and appropriate L-T4 dose adjustment (11,28). Other cases of soy-induced goitre in infants have been reported (29,30). Infants fed soy formula have prolonged increase of TSH when compared to infants on non-soy formula and they may need more frequent TSH measurements and increased L-T4 doses to achieve good control of thyroid function (31).

Of note, certain herbal remedies and nutritional supplements contained in formula milk, including iron, calcium and fibre, may also impair L-T_4 absorption (2,9), although these were not used in the presented case.

Conclusion

Carob-bean gum thickened formula appears to impair the absorption of L-T4. Therefore, we recommended caution and frequent thyroid function evaluation if these products are given to patients with CH. In infants who need increasing doses of L-T4, it is essential to investigate the method of administration first, as this is usually the cause of poorer thyroid function test results, and the medical history, including current medicines and diet, before modifying the drug dosage. Furthermore, parents and caregivers should be educated about factors that may interfere with L-T4 therapy in order to prevent or reduce potential irreversible neurodevelopmental damage.

Ethics

Informed Consent: Written and signed consent has been obtained from the patient's parents.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Stefano Stagi, Concept: Stefano Stagi, Design: Claudia Signorino, Data Collection or Processing: Marta Ferrari, Analysis or Interpretation: Marta Ferrari, Literature Search: Stefano Stagi, Claudia Signorino, Giovanna Municchi, Writing: Claudia Signorino.

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