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CASE REPORTS

Maternal Levothyroxine Treatment as an Etiologic Factor in the Development of Infantile Craniosynostosis

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Abstract Craniosynostosis (CS) is a condition characterized by premature fusion of one or more calvarial sutures. Numerous studies have demonstrated a correlation between CS and maternal hypothyroidism (MH), but research into this relationship has been scarce. A six-day-old male patient presented for initial neurosurgical consultation with trigonocephaly and prominent metopic ridging. A CT scan of the head confirmed the diagnosis of metopic CS, and it was revealed during the examination that the mother suffered from hypothyroidism during her pregnancy. Two theories provide a potential etiologic basis for the development of CS in infants born to hypothyroid mothers treated with levothyroxine. It is possible that the transplacental delivery of levothyroxine results in fetal thyrotoxicosis. Alternatively, intermittent periods of maternal hypothyroxinemia may encourage fetal thyroid hyperactivity to compensate for insufficient maternal thyroid hormones. Regardless, both theories must be formally investigated in order to elucidate the true association between CS and MH.

Keywords Craniosynostosis · Maternal hypothyroidism · Levothyroxine · Fetal thyrotoxicosis · Hypothyroxinemia

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Introduction

Craniosynostosis (CS) is a condition characterized by abnormal fusion of one or more calvarial sutures, which separate the paired frontal, parietal, and temporal bones, and the singular occipital bone of the skull vault. Premature fusion will prevent growth perpendicular to the fused suture(s) and encourage compensatory overgrowth at the open sutures, resulting in distorted head shape [1, 2]. The condition has been found to correlate with maternal hypothyroidism (MH), the most common form of pregnancy-related thyroid dysfunction [3, 4]. In spite of this, the majority of investigations have focused on the association between CS and hyperthyroidism [5]. We present a unique case of an infant with metopic CS born to a hypothyroid mother, whose treatment during pregnancy may have contributed to the premature fusion of the metopic suture.

Case Report

A six-day-old Caucasian male was referred for initial neurosurgical consultation by his primary care physician for concerns about trigonocephaly with prominent metopic ridging. The twenty-three-week prenatal ultrasound revealed a typical lemon-shaped cranium (Fig. 1), as commonly caused by metopic craniosynostosis [6]. Conception was unassisted, and the mother denies a history of smoking. The pregnancy was complicated by diet-controlled gestational diabetes and pre-gestational, non-autoimmune hypothyroidism, for which the mother was prescribed 100 µg of Synthroid daily, to be taken orally. Two months post-conception, a thyroid panel showed a thyroid stimulating hormone (TSH) level of 2.37 mIU/L and a free thyroxine (FT_4) level of 1.3 ng/dL, both of

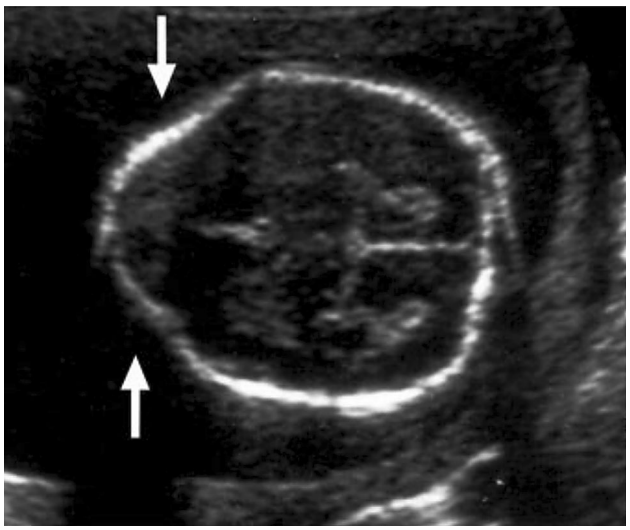

Fig. 1 Typical prenatal sonogram of a lemon-shaped cranium, also referred to as the "lemon sign", at the level of the ventricles. White arrows indicate the biconcavity of the frontal bones, resulting in a distinct lemon-like configuration [6]

which were within the normal range for the first trimester. The patient was born full-term via a planned C-section. A CT scan of the head with 3D reconstruction was completed one day after birth (Fig. 2), and the newborn discharge summary makes note of the prominent ridge along the metopic suture.

The patient presented with a ridge in the center of the forehead and a triangulated, retracted infraorbital rim. The anterior fontanelle was small but open. The patient's head circumference was 13.58 in., which corresponds to the eighteenth percentile for his age. His neurologic and motor examinations were normal. The fetal spine was normal, and there were no other associated structural abnormalities. The CT scan was reviewed with the family and confirmed to reveal partial fusion of the metopic suture, consistent with a diagnosis of metopic CS. There was flattening of the left and right frontal bones, and the orbital roof was more posterior than the floor of the orbit. The frontonasal and zygomatic sutures did not appear to be fused, and it was clear that the coronal, lambdoid, squamosal, and sagittal sutures were open. Therefore, single-suture involvement was indicated.

Discussion of treatment options included endoscopic strip craniectomy followed by the use of a cranial molding orthotic, as well as fronto-orbital advancement and reshaping. The details of both techniques were discussed with the parents, including comparative risks and benefits of the two surgeries. They ultimately opted for the endoscopic technique. The parents were also referred to genomic medicine for a craniosynostosis panel and SNP microarray analysis, both of which were negative for any genetic mutations or genes of interest.

Discussion

The two thyroid hormones (THs), triiodothyronine (T_3) and thyroxine (T_4), play a significant physiological role in skeletal development, influencing both endochondral and intramembranous ossification. The latter is the process that occurs along the margins of the calvarial sutures and is believed to be more sensitive to the effects of THs [7, 8]. Researchers speculate that THs are primarily involved in bone formation, with excess hormone resulting in the acceleration of skeletal maturation [9]. T_3 is known to increase insulin-like growth factor (IGF) signaling, which promotes cellular proliferation in numerous tissue types, including that of the calvarial sutures [10]. It is for this reason that T_3 is regarded as a critical regulator of bone turnover in the calvarium, stimulating skull osteogenesis and modulating intramembranous ossification [11].

A recent study of the effect of THs on rat calvarial growth demonstrated that the exposure of pre-osteoblasts to T_3 enhances osteogenesis and increases the expression of *FGFR1* and *FGFR2*, two genes known to play a significant role in CS [11, 12]. Accordingly, CS is a recognized and well-documented complication of high TH levels during the neonatal period [12]. This association has been proved in animal models, with premature narrowing of the sagittal sutures observed in juvenile female Wistar rats injected with excess T_3 [8]. In infants, excess TH is most often attributable to neonatal thyrotoxicosis or excessive thyroid replacement during early treatment of congenital iodine deficiency syndrome (CIDS) [8, 13].

It was previously assumed that maternal THs only crossed the placenta in negligible quantities [4, 5]. However, more recent studies have shown that the embryo/fetus relies entirely upon the transplacental passage of maternal THs until the twelfth week of gestation, when the fetus is able to endogenously synthesize its own THs [4, 14]. Even after this period, maternal TH continues to cross the placenta and regulate fetal thyroid function until the time of birth, as demonstrated by the concordance of maternal and cord blood levels of thyroxine [10, 15]. This relationship has raised questions about the correlation between MH and CS.

One compelling theory concerns the transplacental passage of levothyroxine administered during pregnancy. Dosage requirements are often steadily increased by about 30% between the fifth and twentieth weeks of gestation to match increased demand for TH [3]. It is believed that levothyroxine, similar to endogenously synthesized thyroxine, is capable of diffusing across the placental barrier and entering the fetal circulation. Considering that most infants born to hypothyroid women are euthyroid, additional TH in the form of levothyroxine could induce mild

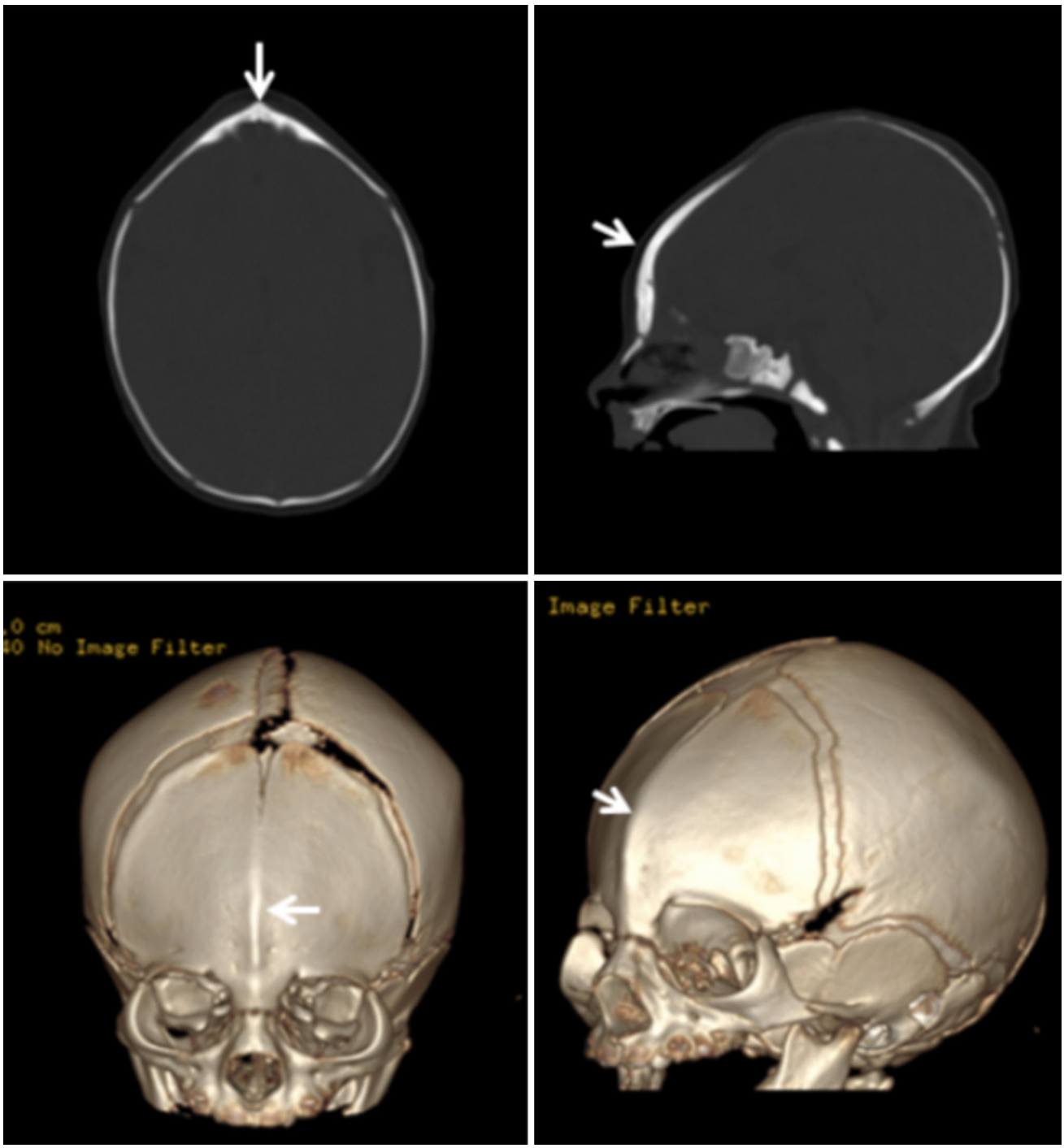

Fig. 2 White arrows indicate the fused metopic ridge; the coronal, sagittal, squamosal, and lambdoid sutures remain open

fetal thyrotoxicosis [5, 10]. A similar phenomenon has been observed when children with CIDS are treated with excessive amounts of levothyroxine, with some infants developing iatrogenic hyperthyroidism and/or CS [12]. Thus, in euthyroid infants with hypothyroid mothers who underwent treatment during pregnancy, such as our patient, it is possible that sutural fusion is at least partly attributable to the incidental transplacental delivery of levothyroxine.

The second theory concerns fetal thyroid function in response to levothyroxine treatment regimens. Fluctuations in maternal serum TSH and FT_4 concentrations throughout pregnancy serve as the basis for levothyroxine dosage increases in expectant hypothyroid mothers. These increases, however, cannot always be synchronous with

increased demand for maternal THs, despite routine monitoring of these values. Therefore, hypothyroid mothers may undergo intermittent periods of maternal hypothyroxinemia. Diminished TH transfer to the fetus could induce a corresponding increase in endogenous TH synthesis by the fetal thyroid. When maternal TH levels are ultimately corrected by dosage increases, fetal overcompensation could induce a form of iatrogenic hyperthyroidism, with excessive TH signaling triggering premature sutural fusion. Possible support for this theory includes the fact infants born to hypothyroid mothers tend to have smaller head circumferences, a common feature of hyperthyroid newborns [16].

Implications for Clinical Practice

Prenatal diagnosis, small head circumference, and treatment with Synthroid during pregnancy make both of the aforementioned theories compelling as potential explanations for the development of CS in our patient. These theories call into question the safety of levothyroxine regimens for expectant hypothyroid mothers. While the possibility remains that the diagnosis of CS and MH are unrelated in this particular case, it demonstrates the need for further investigation into the etiologic relationship between these two conditions. Novel hypothesis-testing and clinical research will allow maternal–fetal medicine specialists to make informed decisions regarding the prescription of levothyroxine during pregnancy.

Author Contributions Mr. BRB conceptualized and designed the project, performed the review of relevant literature, drafted the initial manuscript of the case report, and reviewed and revised the manuscript. Dr. CAM conceptualized and designed the project, critically revised the manuscript for important intellectual content, and supervised the writing process. Dr. JJC collected the data for the project and critically revised the manuscript for important intellectual content. Dr. JCR analyzed and interpreted the data and critically revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent to Publish The parents of the patient have signed informed consent regarding the publication of their data and photographs in this case report.

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