

Craniosynostosis: The Potential Contribution of Thyroid-Related Mechanisms

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Abstract Craniosynostosis, the premature fusion of one or more cranial sutures, leads to abnormal craniofacial form and function. Its causes remain largely unknown. One of the strongest clues regarding non-syndromic craniosynostosis etiology is its association with thyroid-related disorders, which is based on a mix of epidemiologic and experimental findings. This paper reviews evidence for the contribution of thyroid-related mechanisms to craniosynostosis and makes recommendations for how to improve this knowledge.

Keywords Thyroid · Craniosynostosis · Birth defects · Genetics

Introduction

Craniosynostosis (CS), the premature fusion of one or more cranial sutures, leads to abnormal craniofacial form and function. It is often associated with increased intracranial pressure

leading to abnormal neurocognitive development, and most affected infants require extensive reconstructive surgery [1–3]. It affects approximately 5 per 10,000 births and incurs substantial emotional and financial costs [4]. For about half of CS cases, the sagittal suture is affected; for 15 %, the metopic suture; for 20 %, the coronal suture; for 3 %, the lambdoid suture; and for 7 %, multiple sutures [5]. Based on reports of prenatal diagnoses and autopsies, it is thought that CS occurs as early as the second trimester [6–8]. Although most CS cases have a prenatal onset and are diagnosed at or soon after birth, postnatal craniosynostosis can occur and in most cases, are less severe [9, 10]. Normally, suture closure does not begin until 3 to 9 months of age for the metopic suture and not until the third decade of life for the other sutures [9, 11].

The etiology of CS is presumed to be multifactorial, with multiple contributing genetic and environmental factors [12]. Studies suggest various risk factors for CS, such as smoking, advanced maternal age, in utero constraint, male sex, and Caucasian race-ethnicity [13–16], but its actual causes remain largely unknown. This is particularly true of non-syndromic CS, i.e., cases for which no genetic cause has been identified, which comprise about 90 % of all cases.

One of the strongest clues regarding non-syndromic CS etiology is its association with thyroid-related disorders. For example, several case-only studies have reported CS among offspring born to women with thyroid-related disorders or neonates themselves diagnosed with thyroid disease [17–23]. This paper reviews evidence for the contribution of thyroid-related mechanisms to CS and makes recommendations for how to improve this knowledge. It is hoped that improved understanding of the contribution of thyroid function to CS will eventually lead to clinical advances in the prevention, detection, and treatment of this significant congenital disorder in skull development.

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Maternal-Fetal Thyroid Function and Hypotheses

Thyroid function involves a complex interplay among multiple hormones, including thyroid-stimulating hormone (TSH), thyroxine (T_4), and triiodothyronine (T_3). Hypothyroidism (high TSH, low free T_4) and hyperthyroidism (low TSH, high free T_4) affect up to 4 % of women of reproductive age if subclinical disease is included [24•]. In addition, transient hyperthyroidism affects up to 3 % of women during early pregnancy, due to the TSH-like activity of placental human chorionic gonadotropin (hCG). Thyroid autoantibodies are present in about 10–20 % of women of reproductive age and serve as markers of thyroid autoimmunity [24•, 25]. The presence of these antibodies in the absence of overt thyroid dysfunction is predictive of the development of thyroid disease, and their production may continue even after effective treatment. Hypo- and hyperthyroidism, as well as the presence of thyroid antibodies in the absence of thyroid disease, are associated with increased risk of adverse pregnancy outcomes such as spontaneous abortion and preterm delivery [26–28]. Risk factors for thyroid disease include maternal age >30, family history of autoimmune thyroid disease, infertility, diabetes, morbid obesity, and iodine deficiency, some of which have been suggested to be associated with risk of CS [29].

During pregnancy, levels of T_3 and T_4 increase by around 50 % [24•]. They tend to be highest during the first trimester, due to cross-reactivity of hCG with the TSH receptor leading to lower levels of TSH. Thyroid autoantibodies decline due to immunosuppression that occurs during pregnancy. These changes complicate approaches to screening and treatment of thyroid disease during pregnancy, and recommendations vary. In general, overt hypothyroidism is treated with levothyroxine, hyperthyroidism is treated with anti-thyroid drugs that block thyroid hormone synthesis, and all of these medications can cross the placenta. Among non-pregnant women, hyperthyroidism may be treated with radioactive iodine or thyroidectomy and may be the reason for subsequent hypothyroidism and treatment with levothyroxine.

The embryo depends entirely on transplacental passage of maternal thyroid hormones until endogenous synthesis begins at about 12 weeks of gestation [30]. Maternal thyroid function continues to affect fetal thyroid function even after that point, based on studies demonstrating concordance of maternal and cord blood levels of thyroid hormones [31]. Interestingly, one recent study identified that cord blood levels of T_4 were abnormally high among 50–60 % of infants born to mothers who had been diagnosed with hyperthyroidism or hypothyroidism [32]. All of these mothers were undergoing treatment during pregnancy. Like thyroid hormones, thyroid antibodies [24•] and anti-thyroid drugs [33] pass freely from mother to fetus throughout gestation.

There are multiple mechanisms by which fetal thyroid function may be affected by maternal thyroid function. Fetal

thyroid function could be disrupted by transplacental passage of maternal thyroid-related hormones, autoantibodies, or medications. The accompanying clinical features of the mother may be highly variable, however, depending on her current state of thyroid function and treatment. Given this complexity, our primary hypothesis is therefore framed in relatively general terms—that risk of CS may be increased among newborns whose mothers or themselves exhibit potential indicators of thyroid dysfunction, including particularly high or low levels of thyroid hormones or the presence of thyroid autoantibodies.

Epidemiologic Evidence

Case Reports In 1969, Robinson et al. [21] reported CS in a young boy who was hyperthyroid. Subsequent case reports described CS among newborns, infants, and young children who were hyperthyroid [19, 20, 34–36] or hypothyroid and being treated with levothyroxine [17, 37]. Another case report described a newborn with CS who had thyroid agenesis and a mother without thyroid disease [23]. The most severe cases tend to be those that present at birth or during early infancy, due to the rate of brain growth in the late fetal and early postnatal period [20].

Observational Studies We are aware of only two observational studies (i.e., studies that include a comparison group of non-cases) that have examined the association of maternal thyroid dysfunction with CS, and their results are mixed [38, 39]. The first case–control study did not observe an increased risk of CS among offspring born to mothers who reported a history of thyroid disease, but the study had limited power (it included 63 CS cases, 4 of whom reported a history of thyroid disease), and exposure assessment occurred up to 15 years after delivery [38]. The second study was based on the National Birth Defects Prevention Study, a population-based case–control study [39]. It reported a 2.5-fold increased risk of CS among offspring born to women with thyroid disease (based on 431 case mothers, 19 of whom reported a history of thyroid disease) [39]. Most women reported hypothyroidism, though the etiology could not be definitively established in all subjects. The association of maternal hypothyroidism with CS could be explained by passage of exogenous levothyroxine (as a maternal medication) or maternal thyroid autoantibodies to the fetus, especially stimulating thyroid receptor antibodies (TRAbs) in women who are currently hypothyroid due to past treatment for Graves' hyperthyroidism (e.g., thyroidectomy).

A large cohort study reported lower T_4 levels in newborns with CS [40]. A potential explanation for this finding is that maternal hyperthyroidism results in a hyperthyroid in utero environment and at the same time impedes physiologic maturation of fetal hypothalamic-pituitary-thyroid regulation, resulting in central congenital hypothyroidism in the newborn

[41–43]. These results suggest that both maternal thyroid dysfunction and fetal thyroid dysfunction via placental transmission of maternal anti-thyroid antibodies or treatment of maternal hypothyroidism contribute to the pathogenesis of CS [40]. Stimulating maternal antibodies or exogenous levothyroxine can also lead to hypothyroidism in the infant due to negative feedback regulation [43, 44].

Thyroid and Insulin-Like Growth Factor Pathway Interactions

Interactions between insulin-like growth factor (IGF) signaling and thyroid hormones in bone development are well described [45–48]. The thyroid and IGF1 pathways are closely related and enhance each other’s bioactivity. For example, hyperthyroidism is associated with increased IGF1 levels [49], as are certain *DIO1* variants [50], and rodents treated with exogenous thyroid hormone demonstrate markedly enhanced *IGF1* expression [51, 52]. The IGF1 receptor (*IGF1R*) is highly expressed in developing cranial sutures and is known to promote cellular proliferation, differentiation, and migration, likely by mediating activity of insulin-receptor substrate 1 (*IRS1*) via IGF1 and IGF2 binding to IGF1R [53]. Genetic models supporting the role of IGF signaling in CS include the association of CS with *IGF1R* trisomy/tetrasomy [54, 55], and our recent identification of *IGF1R* gain-of-function mutations in CS patients [56]. We have determined that osteoblast cell lines derived from patients with CS with high *IGF1/IGF1R* expression demonstrate enhanced signaling, though the *IRS1*/Akt pathway implicating IGF1 signaling as a potential biomarker for CS (Fig. 1). *IGF1* is expressed in rat calvaria osteoblasts [46, 57] and is induced in the sagittal suture of a hyperthyroid rat model [51]. T₃ enhances the

effects of IGF1 in osteoblasts by increasing *IGF1* and *IGF1R* expression, IGF1 binding, and IGF1-induced cell proliferation, suggesting thyroid hormone potentiates signaling of IGF1 at the receptor level [52, 58, 59]. These observations suggest that thyroid hormone leads to increased IGF1 signaling and may be critical in the pathogenesis of CS. In fact, we have preliminary data indicating that *IGF1/IGF1R* expression in CS osteoblasts is strongly correlated with expression of thyroid-related genes (e.g., *THRA*, *THRB*, *PDE8B*) (Fig. 2).

Genetics

Many syndromic cases of CS have an underlying genetic cause, but the specific genes causing syndromic CS have not been identified as major contributors to non-syndromic CS [56, 60, 61]. Studies demonstrating concordance in twins and familial recurrence do, however, support a contribution of genetics to non-syndromic CS [12, 62]. Although genome-wide association studies and candidate gene resequencing efforts have identified genes that may be associated with increased risk, our understanding of genetic susceptibility to non-syndromic CS is limited [47, 56, 63].

A variety of genes affect circulating thyroid hormone levels or their intracellular availability and activity [49]. For example, iodothyroinine deiodinases 2 and 3 (*DIO2*, *DIO3*) and *FOXE1* regulate tissue-specific biologic activity of thyroid hormones; *DIO1* and *PDE8B* affect circulating levels of thyroid hormones; and thyroid hormone receptors (*THRA*, *THRB*) directly affect thyroid hormone signaling. Functional variants have been identified in many of the genes that code for these proteins, and they have been associated with altered thyroid function [49, 50, 64]. A recent study examined the association of variants in 24 thyroid hormone pathway genes with newborn TSH values; the strongest associations from that study were for

Fig. 1 Differential gene expression in synostosis osteoblasts with high and low IGF1 signatures exposed to T₃. Seven-day exposure of human CS osteoblasts to 10⁻⁷ M (T₃) results in ≥1.5-fold increased expression of *AHSG*, *BMP3*, *CD36*, *CHRD*, *FLT1*, *ITGB1*, *COL2A1*, *SPP1*, *TGFBR1*, and *TNF* in cells with a “high” IGF1/IGF1R signature relative to the those with a “low” IGF1 signature. Data presented as log₂ΔΔCt. Green outline >2-fold change in gene expression, orange outline 1.5–2-fold change in gene expression

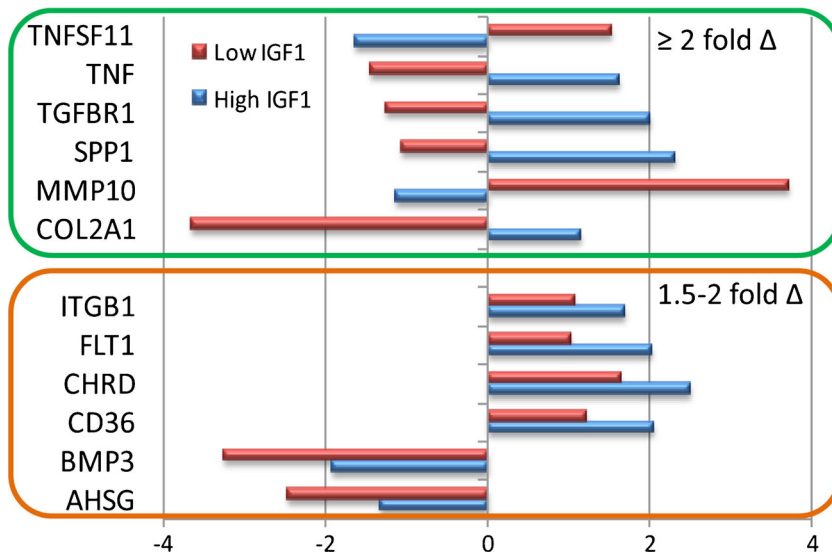
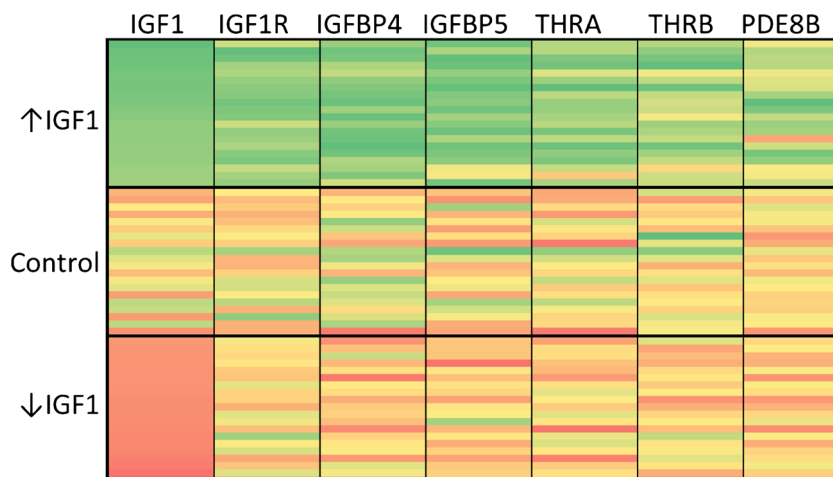


Fig. 2 Osteoblast expression profile from 20 cases with the highest IGF1 expression contrasted with 20 control lines and 20 cases with the lowest IGF1 expression. Colors represent robust multi-array average normalized signal intensities in log₂



PDE8B and *FOXE1* [65]. Similarly, a meta-analysis examining the association between variants in 68 thyroid hormone pathway genes and TSH and T₄ levels in adults identified candidates in *PDE8B*, *FOXE1*, *DIO1*, and *THRB* [64].

To our knowledge, no studies have focused on examining the contribution of variants in thyroid regulatory genes to the risk of developing CS. Examination of the association of CS with variants in genes that are most proximal to thyroid hormone synthesis and biologic activity, such as those mentioned above, would certainly be informative. Bioinformatic approaches that examine gene expression correlation structures may also be useful [53]. As a preliminary demonstration of this approach, we examined publicly available data that reflect changes in gene expression subsequent to T₄ exposure (Gene Expression Omnibus “GEO” GSE32444, 47517, and 15458). Two of the top ten up-regulated genes were *POR* and *IGFBP4*. *POR* is of interest given that *POR* mutations cause the CS syndrome Antley-Bixler. *IGFBP4* is a binding protein that increases the bioavailability of IGFs [66]. As a third approach to identifying additional genes of interest from the thyroid pathway, we recently conducted preliminary studies investigating differential expression of genes in osteoblasts derived from patients with CS in response to T₃ exposure and stratified by the level of IGF1 expression (Fig. 1). These preliminary data suggest that several transcripts related to osteoblast differentiation demonstrate differential expression in response to the combination of high IGF1 expression and T₃ exposure.

Experimental Evidence

There are many lines of experimental evidence supporting the biologic link between thyroid hormone exposure and the development of CS. Osteoblasts express thyroid receptors which upon binding T₃ reduce proliferation and enhance differentiation [67]. Exposure of mouse calvarial pre-osteoblasts to thyroid hormone results in enhanced osteogenesis and upregulation of genes

known to play a role in CS including *Fgf1*, *Fgf2*, and *Igf1* [52]. These in vitro results are further substantiated by in vivo experiments exposing rat pups to T₃ resulting in enhanced bone formation at the osteogenic front of the calvaria [68]. Furthermore, transgenic models of hyperthyroidism serve as ideal in vivo experiments to understand the biologic response to thyrotoxicosis. Mice engineered to harbor a loss of function mutation in thyroid hormone receptor beta (*THRB*) are resistant to thyroid hormone and thus become hyperthyroid. They demonstrate increased endochondral and membranous ossification resulting in both growth retardation and CS [69]. Taken together, these experiments provide strong evidence that hyperthyroidism enhances osteogenesis, and in in vivo models, it induces CS.

Conclusions and Recommendations for Future Studies

There is strong epidemiologic and basic science evidence that abnormal thyroid function is associated with an increased risk of CS, but the exact mechanism(s) by which thyroid-related dysfunction may affect risk of CS is uncertain. Evidence to date suggests that thyroid hormones or antibodies may directly influence gene expression at the developing suture, and that IGF may potentiate the osteoblast response. Additional research is needed to advance our understanding of these associations, beyond the existing useful but limited case reports and epidemiologic and experimental studies on this topic. For example, the identification of a genetic predisposition to CS influenced by maternal thyroid disease is an ideal model for meaningful gene-environment interaction studies that could lead to translational research impacting this subset of patients, although admittedly it may require relatively large cohorts. Similarly, identification of high-risk pregnancies based on the presence of maternal biomarkers of aberrant thyroid function or IGF signaling could potentially contribute to prevention among at-risk infants.

Based on existing evidence, our primary hypotheses are that maternal subclinical or overt hyperthyroidism or thyroid

autoimmunity (especially stimulating maternal TRAbs) or low newborn TSH are associated with increased risk of having an infant with CS because they are all indicators of a hyperthyroid environment in the fetus. Secondary hypotheses to take into account include the complexities of thyroid dysfunction and its treatment. We hypothesize that increased CS risk may occur in the presence of maternal subclinical or overt hypothyroidism (e.g., due to transplacental passage of thyroid antibodies among women previously treated for Graves disease) or newborn hypothyroidism (a consequence transplacental transfer of thyroid hormone in cases of maternal hyperthyroidism). Our premise is that exposure of the fetus to abnormal thyroid hormone levels or anti-thyroid antibodies during gestation induces aberrant thyroid signaling in the fetus.

After diabetes, thyroid disorders are the second most common endocrine disorder among women of childbearing age. Improved knowledge of potential harmful effects of aberrant thyroid function will contribute to the development of optimal approaches to the screening and management of thyroid disease among pregnant women and infants. Appropriate screening for thyroid dysfunction and thyroid autoimmunity in pregnant women are a topic of on-going debate [24•]. A better understanding of the association between thyroid function and CS will be informative to this debate, especially as it relates to the potential risks associated with unresolved hyperthyroidism or overtreatment of hypothyroidism during pregnancy.

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Compliance with Ethics Guidelines

Conflict of Interest SL Carmichael, CM Clarke, and ML Cunningham all declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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