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50 Years Ago in *The Journal of Pediatrics*

Recognizing Familial Thyroid Dysgenesis

Orti E, Castells S, Qazi QH, Inamdar S. Familial thyroid disease: lingual thyroid in two siblings and hypoplasia of a thyroid lobe in a third. J Pediatr 1971;78:675-7.

In 1971, Orti et al described thyroid dysgenesis in 3 siblings. Two siblings had a lingual thyroid, and the third had a hypoplastic thyroid lobe. Other family members did not have thyroid disorders. The authors recognized that normal thyroid development may be genetically controlled, and that inherited defects could lead to abnormal thyroid development.

Thyroid dysgenesis, the failure of normal thyroid gland development, is the most common cause of primary congenital hypothyroidism and occurs in 1 in 3000 infants.[1] During embryogenesis, the thyroid gland primordium develops from the foregut endoderm, near the base of the tongue. These cells migrate from the pharyngeal floor through the anterior midline of the neck. The thyroid is connected to the pharynx by the thyroglossal duct during descent. The nascent thyroid reaches below the thyroid cartilage by week 7 of embryonic development and is completely formed by week 10.[2] Disruption of these developmental steps can lead to thyroid dysgenesis.

Most cases of thyroid dysgenesis occur sporadically, but the authors correctly recognized familial forms. Thyroid dysgenesis is attributed to genetic mutations in 2%-5% of cases.[3] Over the past 2 decades, several genes involved in thyroid gland development have been identified, including PAX8, NKX2-1, FOXE1, NKX2-5, GLIS3, JAG1, and CDCA8 (BOREALIN). Partial inactivation of the TSHR gene can also present with thyroid hypoplasia. Many of these genes are associated with developmental abnormalities in other organs as well. Familial thyroid dysgenesis often shows an autosomal dominant mode of inheritance with incomplete penetrance and variable disease expressivity.

Although there has been growth in understanding the genes responsible for thyroid development, the greatest advancement in the diagnosis of congenital hypothyroidism over the past 50 years has been the role of universal newborn screening. The authors described 1 sibling with an intellectual disability owing to congenital hypothyroidism. Universal newborn screening, implemented in the early 1970s, has led to the prevention of intellectual disability due to severe congenital hypothyroidism and is a major achievement of preventive medicine.

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