

## A case of Hirschsprung disease: does thyroid hormone have any effect?

Makbule Eren<sup>1</sup>, Mustafa Çelik<sup>2</sup>, Sibel Kınık<sup>3</sup>, İrfan Serdar Arda<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Osmangazi University Faculty of Medicine, Eskişehir, and Departments of <sup>2</sup>Pediatric Surgery, and <sup>3</sup>Pediatrics, Başkent University Faculty of Medicine, Ankara, Turkey

**SUMMARY:** Eren M, Çelik M, Kınık S, Arda İS. A case of Hirschsprung disease: does thyroid hormone have any effect? Turk J Pediatr 2009; 51: 94-96.

Hirschsprung disease, the colonization defect of neural crest cells through the colon, is one of the reasons for functional obstruction in neonates. Furthermore, hypothyroidism has been known to be one of the causes of bowel hypomotility and pseudoobstruction. These two diseases are generally considered in the differential diagnosis. Although defective thyroid function has been found to be responsible for inappropriate neuronal migration in the brain, the effect of thyroid hormone on neural crest cell migration to the bowel has not yet been evaluated. Here, we report a case with Hirschsprung disease and congenital hypothyroidism, which may point to the need for future studies evaluating the interaction of colonic neural crest cell colonization and thyroid hormone.

*Key words:* thyroid hormone, Hirschsprung disease, neural migration.

Hirschsprung disease (HD), the congenital absence of ganglion cells in the myenteric and submucosal plexus, is caused by the failure of the enteric nervous system (ENS) precursors to colonize the distal intestine. As a result, the affected segment of the colon fails to relax, causing a functional obstruction.

Approximately 15% of patients with HD present with at least one congenital anomaly, including cardiac, genitourinary, and skeletal anomalies, and 12% of HD cases are associated with chromosomal anomalies, with Down syndrome the most prevalent<sup>1,2</sup>. However, to date, HD and hypothyroidism have been considered in the differential diagnosis rather than their concomitant existence. Ongoing researches have clarified that alterations in thyroid function during embryogenesis and fetal development are known to produce extensive damage to the central nervous system, including severe mental retardation<sup>3</sup>. Thyroid hormone is necessary for appropriate neuronal migration and lamination during brain development<sup>4</sup>. Although hypothyroidism impairs the colonic motility and function, whether or not deficient thyroid hormone can lead to arrest of neural crest cell migration through the bowel has not

yet been studied. Here, we report a case of HD together with congenital hypothyroidism, whose mother was subclinical hypothyroid.

### Case Report

A two-hour-old boy, weighing 3740 g at birth, was referred to our hospital with the complaint of poor sucking and agitation. Other than absence of sucking reflex, his physical examination was normal. On the first day of his admission, he developed vomiting followed by abdominal distension. He did not pass meconium for the first 48 hours.

Plain abdominal films and contrast studies demonstrated dilated bowel loops with air-fluid levels. However, a transitional zone could not be observed. He was followed with intravenous antibiotics. Due to ongoing abdominal distension and developing hypotonia, his thyroid function was checked on the third day and elevated thyroid stimulating hormone (TSH: 29 mIU/ml) and normal total thyroxin (T4: 9.74 µg/dl) and free thyroxin (fT4: 1.3 ng/dl) levels were detected. His complete blood count and serum sodium, potassium, chloride, calcium and glucose levels were normal. His mother's TSH, T4 and fT4 were

0.46 uIU/ml, 5.32 µg/dl, and 0.58 ng/dl, respectively (lower limits: TSH: 0.7 uIU/ml, T4: 4.2 µg/dl, fT4: 0.8 ng/dl). His mother's urine iodine level was 14 µg/dl (range: 10-20 µg/dl). After hemodynamic stabilization, a diverting colostomy was performed. Histopathological examination of serial biopsies taken during colostomy operation demonstrated absence of ganglion cells until splenic flexura. TSH increased over 100 uIU/ml with a decrease in T4 (6.39 µg/dl) and fT4 (0.93 ng/dl) levels on the 10<sup>th</sup> day. He was discharged with oral thyroxin treatment and with a future plan of definitive repair for HD.

### Discussion

Hirschsprung disease is the congenital absence of ganglion cells in the myenteric and submucosal plexus. It is thought to be caused by the failure of neural crest cells precursors to colonize the gut between 5- 12 weeks of gestation. Approximately 10% of children have positive family history, especially those with longer segment disease. Since the penetrance of HD varies, gene mutations may not predict the disease, but they increase the probability of having HD.

Multiple signals are known to affect neural crest cell migration. At least eight genetic mutations have been identified<sup>5</sup>. Among the identified HD susceptibility genes, the most commonly studied is the RET proto-oncogene, encoding the RET protein, which is a receptor tyrosine kinase that transduces growth and differentiation signals in several developing tissues, including those derived from the neural crest. More than 20 different mutations in the RET proto-oncogene have been described<sup>5</sup>. Glial-cell-line-derived neurotrophic factor (GDNF), expressed by the mesenchyme, has been identified as the ligand for RET. RET and GDNF receptor family (GFR<sub>α</sub>-1) are expressed by ENS precursors as they migrate through and colonize the gut during embryogenesis<sup>6</sup>. Mutations of RET, GDNF and its receptor (GFR<sub>1-α</sub>) cause deficient colonization of the distal gut.

Mutations in other genes include endothelin 3 (EDN3), endothelin receptor B (EDNRB), endothelin converting enzyme (ECE1), and the gene encoding the Sry-related transcription factor (SOX10)<sup>5</sup>. EDN3 is the ligand of EDNRB.

ECE1 is responsible for activation of EDN3. EDNB and EDN3 are expressed by the early ENS and surrounding mesenchyme, respectively. The former controls cellular differentiation. SOX10 is a transcription factor that is expressed in the early ENS and support of their survival may be by controlling apoptosis<sup>5,6</sup>.

Hypothyroidism is one of the most recognized causes of intestinal hypomotility, and it is considered in the differential diagnosis of HD<sup>7</sup>. The examination of 78 children with suspected HD revealed congenital hypothyroidism in three of them<sup>8</sup>. Although great progress has been made in understanding the effect of thyroid hormone on appropriate neuronal migration during brain development, to our best knowledge, the interaction of thyroid hormone and neural crest cell migration has not yet been documented. Neuronal migration in the central nervous system and the effect of thyroid hormone deprivation on it has been studied extensively in animal models. It has also been seen that thyroid hormone is essential in histogenesis, cellular migration and cytoarchitecture of the central nervous system<sup>9</sup>. For example, defective thyroid hormone has been shown to affect the normal migratory pattern in the auditory, somatosensory and visual cortex. It is also a major factor in regulating the timing of proliferation and differentiation in a number of neural and non-neural cell populations including retinal progenitors, oligodendrocytes and erythroid precursors<sup>10-12</sup>.

Until the recognition of the role of thyroid hormone in early and mid pregnancy in recent years, there was a consensus that thyroid hormone is necessary for brain development only during the third trimester. Present studies support that thyroid hormone of maternal origin is also necessary for normal brain development during the first and second trimesters; beyond hormone replacement normal function cannot be recovered<sup>13</sup>. It has been reported that maternal hypothyroidism before mid-gestation leads to mental retardation or attention deficit syndrome<sup>14</sup>.

Three theories for the cause of HD are proposed. The most commonly accepted is that there is a defect in the cranio-caudal migration of neuroblasts. The other two theories include: defects in the differentiation of neuroblasts into ganglion cells and accelerated ganglion

cell destruction within the intestine<sup>6</sup>. If thyroid hormone has any effect on HD development, it may exert its regulatory action by controlling the directly above- mentioned gene expressions, ligands, receptors, apoptotic factors or extracellular matrix protein affecting cellular migration or differentiation.

Cranio-caudal migration of neuroblasts originating from the neural crest occurs during the first 12 weeks of gestation. Although synthesis and secretion of T4 and triiodothyronine (T3) starts at approximately 12 weeks of gestation, maturation of the hypothalamic-pituitary-thyroid axis occurs during the second half of gestation. Thus, at the time of active fetal thyroid hormone secretion, gut colonization by neural crest cell precursors should be completed. This means that in order to interfere with neuroblast migration and gut colonization, thyroid hormone must act within the first half of pregnancy. As it is known that the effective thyroid hormone in the first half of gestation is maternally originated, the mother's thyroid hormone status seems more important than that of the fetus in that half of pregnancy. Although T4 level was normal, fT4 and TSH levels in our patient's mother were found to be low. It may thus be speculated that this maternal hypothyroxinemia may have led to a defect in gut colonization. The most frequent cause of maternal hypothyroxinemia is iodine deficiency; however, the urine iodine level of our child's mother was normal. If we consider the other two theories about HD, fetal thyroid hormone levels seem more important than the mother's. In this case, fetal hypothyroidism may have led to HD by affecting cellular differentiation or apoptosis.

In conclusion, with the present case, we propose that thyroid hormones may have a role in the development of HD. Even though this hypothesis cannot be assessed in humans for ethical reasons, studies with animal models may shed further light on this issue.

## REFERENCES

1. Ryan ET, Ecker JL, Christakis NA, Folkman J. Hirschsprung's disease: associated abnormalities and demography. *J Pediatr Surg* 1992; 27: 76-81.
2. Brown RA, Cywes S. Disorders and congenital malformations associated with Hirschsprung's disease. In: Holschneider AM, Puri P (eds). *Hirschsprung's Disease and Allied Disorders*. Amsterdam: Harwood Academic Publishers; 2000: 137-145.
3. Auso E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocortico-genesis alters neuronal migration. *Endocrinology* 2004; 145: 4037-4047.
4. Martinez-Galan JR, Escobar del Rey F, Morreale de Escobar G, Santacana M, Ruiz-Marcos A. Hypothyroidism alters the development of radial glial cells in the term fetal and postnatal neocortex of the rat. *Brain Res Dev Brain Res* 2004; 153: 109-114.
5. Inoue K, Shimotake T, Iwai N. Mutational analysis of RET/GDNF/NTN genes in children with total colonic aganglionosis with small bowel involvement. *Am J Med Genet* 2000; 93: 278-284.
6. Imseis E, Garipey CE. Hirschsprung disease. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR (eds). *Pediatric Gastrointestinal Disease* (4<sup>th</sup> ed). United States: B.C. Decker Inc.; 2004: 1031-1054.
7. Goto S, Billmire DF, Grosfeld JL. Hypothyroidism impairs colonic motility and function. An experimental study in the rat. *Eur J Pediatr Surg* 1992; 2: 16-21.
8. Mustafin AA, Sultanova LM. Differential diagnosis of Hirschsprung's disease and congenital hypothyroidism in children. *Vestn Khir Im I I Grek* 1985; 134: 89-91.
9. Alvarez-Dolado M, Ruiz M, Del Rio JA, et al. Thyroid hormone regulates reelin and dab1 expression during brain development. *J Neurosci* 1999; 15: 6979-6993.
10. Lemkine GF, Raj A, Alfama G, et al. Adult neural stem cell cycling in vivo requires thyroid hormone and its alpha receptor. *FASEB J* 2005; 19: 863-865.
11. Tokumoto YM, Tang DG, Raff MC. Two molecularly distinct intracellular pathways to oligodendrocyte differentiation: role of a p53 family protein. *EMBO J* 2001; 17: 5261-5268.
12. Billon N, Tokumoto Y, Forrest D, Raff M. Role of thyroid hormone receptors in timing oligodendrocyte differentiation. *Dev Biol* 2001; 235: 110-120.
13. Utiger HD. Maternal hypothyroidism and fetal development. *N Engl J Med* 1999; 34: 601-602.
14. Vermiglio F, Lo Presti VP, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 2004; 89: 6054-6060.