



HIRSCHSPRUNGS DISEASE WITH HYPOTHYROIDISM AND CARDIAC DEFECT

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ABSTRACT

There are some case reports of *Hirschsprungs disease (HD)* and its association with hypothyroidism. *Hirschsprungs disease* is defect in abnormal neuroblast migration.^[1] Normal thyroid function is required for appropriate neuronal migration in the brain. Effect of thyroid hormone on neural crest cell migration has not been adequately studied.

KEYWORDS: *Hypothyroidism, Hirschsprungs disease, neuroblast migration, cardiac defect.*

INTRODUCTION

Hirschsprungs disease, hypothyroidism and cow milk are the three common causes of constipation in early infancy. Hirschsprung disease (HD) is the absence of ganglion cells in the myenteric and submucosal plexus due to failure of the enteric nervous system (ENS) precursors to colonize the distal intestine. The affected aganglionic segment of the colon fails to relax and lead to functional obstruction. Hypothyroidism is also one of the cause of bowel hypomotility and pseudoobstruction. Normal thyroid function is required for appropriate neuronal migration in the brain. Effect of thyroid hormone on neural crest cell migration has not been adequately studied. Hirschsprungs disease and hypothyroidism are rare association in children. Only few case has been reported worldwide^[2] and only one case from india.^[3] We are reporting a child with coexisting HD, hypothyroidism and ASD without any dimorphism.

Case Presentation

A 5 months female child was brought to our pediatrics department with complaints of abdominal distension, which was rapidly progressive over 1 month, high grade fever and labored breathing. Baby was unable to pass stools since last 3 days. Before that baby used to pass small amount of stools, the frequency of which was twice or thrice a week and liquid in consistency suggestive of chronic constipation. This was associated with poor feeds, vomiting, excessive cry and poor weight gain. The baby was exclusively on breast feed.. There was no history suggestive of convulsions and no urinary complaints. There is history of on and off high grade fever in the past 2 months. The mother had an uneventful antepartum and intrapartum course with vaginal delivery with a birth weight of 2.7 kgs. The elder female child was running a healthy course. On examination the baby was dehydrated and febrile with dry and rough skin. The anterior fontanelle was widely separated & the posterior fontanelle was also open. The pulse rate was 118/min and respiratory rate 32/min. On auscultation of chest there were bilateral fine crepitations. On per abdomen examination abdominal distension was present with prominent veins and visible intestinal peristalsis and there was tender hepatomegaly. On per rectal examination, rectum was empty. External anal sphincter tone was normal. Rest of the systemic examination was within normal limits. On investigating the patient, total leucocyte count was raised with predominant neutrophils, renal & liver function tests were normal. Thyroid function test was abnormal with T₃ of 10ng/ml, T₄ of 0.6ng/ml & TSH in a very high range (149 μ IU/ml) suggestive of hypothyroidism. Echocardiography revealed atrial septal defect (secundum type) with left to right shunt. Abdominal X ray-radiography showed dilated gas filled bowel loops. On barium enema examination the proximal colonic loop was dilated, rectum was empty and funneling of bowel between dilated rectum and constricted loop. After achieving hemodynamic stability a colostomy and colonic biopsy done. Histopathology of the biopsy showed aganglionic segment confirming Hirschsprung disease. On genetic analysis there was no chromosomal abnormality with 46XX genotype. Mother thyroid function test were normal.

DISCUSSION

Normally neuroblasts are found in the esophagus in 5th week of gestation, and they migrate to small intestine by 7th week and colon by 12th week. Hirschsprung disease (HD) is the congenital absence of ganglion cells in the myenteric and submucosal plexus that may be limited to the rectosigmoid area (75%) or may involve any length of colon^[1] 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.^[4,5] There are some genetic disorders those are associated with hypothyroidism, hirschsprung's disease and cardiac defect e.g. down syndrome, Cartilage hair hypoplasia (CHH)^[6], Mowat-Wilson syndrome (MWS)^[7], 22q11.2 deletion^[8] syndrome but are also associated with facial dysmorphysm. In our case there was no facial dysmorphysm. Our case presented with chronic constipation, distended abdomen and inability to pass stool with poor weight gain which suggest presentation of HD. Possible etiology for development of hirschsprung disease may include arrest of cranio-caudal neuroblast migration, neuroblast apoptosis, failure of proliferation and differentiation, absence or dysfunction of fibronectin, laminin, neural cell adhesion molecule (NCAM), and neurotrophic factor.^[9] There are 622 genes mutations in eight genes discovered with anomalous expression in aganglionic tissue including RET, GDNF, GFR α 1, NRTN, HAND2, ET3, SOX10, SHH.^[10] Thyroid function abnormality may affect motility and transport function of the gastrointestinal tract.^[11,12] Hypothyroidism may cause hypomotility and pseudoobstruction. It is being known that thyroid hormone is critical for neuronal multiplication, migration, myelination and structural organisation of brain. There are 3 theories for the association of congenital hypothyroidism with HD. First theory is defective cranio-caudal migration of neuroblasts due to thyroid hormone deficiency. Cranio-caudal migration of neuroblasts is complete by the 12th week of gestation while fetus start secreting thyroid hormone at 12 week so only maternal thyroid deficiency can affect the migration not the fetal deficiency. In most of the reported cases maternal thyroid functions were normal. Same is our case. The second and third theories are defects in the differentiation of neuroblasts into ganglion cells.^[13] and accelerated ganglion cell destruction within the intestine are situations in which fetal thyroid hormone levels seem more important. So the 2nd and 3rd theories are more convincing to explain the association as compared to 1st theory. Role of thyroid hormone in neuroblast migration and development of enteric nervous system (meissners plexus and Auerbachs plexus) are yet to be established. No literature found for association of Hirschsprungs disease, hypothyroidism with atrial septal defect without dysmorphysm. So ASD may be coincidental finding.

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