Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2017, 6(5): 24-26

Gene Environment Interaction: A Trigger Point of Developing Polyglandular Autoimmunity in A Minor Girl from Rural India

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ABSTRACT

*A six-year-old girl from rural Bengal was admitted in our hospital with complaints of thirst, frequent micturition, pain in abdomen and constipation. Polyglandular endocrinopathies were identified in the girl thorough clinical and biochemical examination. Hashimoto's thyroiditis along with Type 1 diabetes mellitus made her a candidate of Polyglandular Autoimmune disease type IIIA. Patient's history revealed that she was on cow milk since birth. Presence of high risk alleles for T1DM HLA DQA1*0101-DQB1*0302 and DQA1*0301-DQB1*0501 in the girl was disclosed by genetic study. The effect of environmental factors along with genetic susceptibility might contribute to the aggravation and early expression of these rare autoimmune diseases in this girl. This could be a classic example of gene environment interaction in case of unexplained endocrinopathies.*

Keywords: Polyglandular autoimmune syndrome, Hashimoto's thyroiditis

CASE DESCRIPTION

A six-year-old girl of height 126 cm, weight 23 kg and BMI 14.55 kg/m^2 presented with increased frequency of micturition, weight loss, abdominal pain (on and off) along with constipation. She also suffered from urinary tract infection for two weeks and fever for one week prior to her admission in our hospital. Her blood pressure was 100/88 mm of Hg and pulse 130/min. She was on cow milk since birth and came from a remote village of Burdwan district in West Bengal. She had euthyroid and non-diabetic parents but her paternal grandfather was diabetic.

Biochemical investigations disclosed highly elevated fasting (FBS-210 mg/dl) and post prandial blood sugar levels (PPBS-243 mg/dl). Her HbA1c was 6.2% whereas C-peptide was sub normal (0.38 ng/ml). Urinalysis showed the presence of sugar in her urine though ketone was absent in it. Low C-peptide and high blood sugar satisfied the criterion to be diagnosed as Type 1 diabetes mellitus which was further confirmed by high titre of GAD 65 (Glutamate decarboxylase) antibody (531.5 IU/ml).

On clinical examination swelling of throat was visible after one week. Subclinical hypothyroidism with serum TSH level (4.87 mIU/ml) and abnormally high anti thyroid peroxidase (Anti TPO) antibody demonstrated autoimmune Hashimoto's thyroiditis in the girl along with T1DM. She was severely vitamin D deficient (Serum 25 (OH) vitamin D 8 ng/ml) with normal vitamin B12 (600 pg/ml) and cortisol (20.2 µg/dl). Genetic study revealed the presence of DQA1-DQB1 haplotypes which are reported to have a very strong association with T1DM. She was conservatively treated with insulin and LT4 and the girl responded well to the treatment.

DISCUSSION

Polyglandular autoimmune syndrome (PAS) is characterized by a diverse cluster (at least two) of auto immune endocrinopathies. The coexistence of type I DM and Hashimoto thyroid disease suggests PAS in her. PAS is classified into three groups: Type I, II and III. Absence of Addison's disease ruled out the possibility of type I and type II PAS in her. The girl did not develop pernicious anaemia (IIIB) or alopecia/vitiligo (IIIC) in combination with autoimmune

thyroid disease which are the major requisites for PAS IIIB and IIIC respectively, so she was more precisely categorized in PAS IIIA.

PAS IIIA is a rare autoimmune disorder and its exact prevalence in the world is still unknown. Studies have been conducted in Italy [1], Turkey [2], Greece [3,4] and other European countries where T1DM is more prevalent. In India, there are only a few studies are reported [5,6]. PAS IIIA was common among children under the age of 5 years but its incidence was lowest in the age group of 6-10 years [7].

A close association of type I DM with AITD has been deciphered in various studies. The frequency of occurrence of thyroid auto immunity in type I DM patients is observed to be two to four-fold higher than their normal counterpart [3,8]. This has also been reflected in a recent study conducted in Eastern India [7]. The effect of female gender, the age at which diabetes is diagnosed and glutamic acid decarboxylase (GAD) antibody towards development of thyroid auto immunity has already been recognized in adult type I DM patients [7,9]. GAD antibody positive type I DM patients are more prone develop thyroid auto immunity which can be evidenced by the presence of glutamate acid carboxylase antibody in pancreas and thyroid gland apart from brain tissue [10,11]. Generally thyroid autoantibodies started to appear in T1 DM patients after a diabetic duration of 3-4 years [12,13] and with increasing age. In this particular case, the simultaneous development of Hashimoto's thyroiditis along with diabetes led us to consider the profound role of severe vitamin D deficiency in the early expression of two coexistent autoimmune diseases.

Several meta-analysis and cross sectional studies deciphered a close link of vitamin D deficiency (VDD) with numerous auto immune disease including type 1 diabetes mellitus and Hashimoto's thyroiditis. Our early study on these diseases implicated a significant negative correlation of serum 25 (OH) vitamin D with the diseases [14]. VDD stimulates the production of proinflammatory cytokines, interferon and interleukin 6 which ultimately infiltrates the pancreas and thyroid causing apoptosis of β cells in pancreas and thyrocytes in thyroid gland ultimately leading to type I DM and Hashimoto's disease in this girl at her early infancy.

Another interesting feature of this case is prolonged exposure of the girl to cow milk which is thought to be an accelerating factor to develop type I DM in genetically predisposed persons due to the cross reactivity of bovine serum insulin antibodies with human insulin [15] responsible for β cell destruction. This girl already having high risk alleles (chromosomes with DQA1*0101-DQB1*0302 and DQA1*0301-DQB1*0501 along with DRB1*0401) makes her genetically vulnerable to have diabetes. Coexistence of thyroid auto immunity could be attributed to the presence of common HLA class II genes responsible for both the diseases. In addition to her genetic predisposition to auto immunity various environmental factors like vitamin D deficiency and cow milk exposure might be responsible to develop polyglandular auto immunity in her at this very early age.

Study of gene environment interaction could lead the researchers in to right direction for unravelling many unanswered queries in unexplained polyglandular diseases in the days ahead.

CONCLUSION

In-depth genetic analysis should be encouraged to indicate early predisposition of an individual towards autoimmunity. Exploration of gene environmental interplay in unresolved polyglandular endocrinopathies will open new avenue in current medical research.

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