Indian J Med Res 145, January 2017, pp 4-6
DOI: 10.4103/ijmr.IJMR_1223_16

Quick Response Code:

Commentary

Celiac disease & type 1 diabetes mellitus: Connections & implications

Type 1 diabetes mellitus (T1DM) in children is an important public health problem in India and worldwide. India is estimated to have more than 100,000 children with diabetes[1]. The disease imposes a significant financial and psychological strain on the families of the affected children due to lifelong requirement of insulin replacement as well as the dietary restrictions. The incidence is increasing worldwide with the increase being much higher in the low-income countries of Africa and Asia[2].

Being autoimmune in aetiology, T1DM is known to coexist with other autoimmune disorders such as celiac disease (CD), Hashimoto's thyroiditis, Grave's disease, pernicious anaemia and Addison's disease. Of these, the association with autoimmune thyroid disorder is the most common, seen in 17-50 per cent of patients with T1DM in different populations[3,4]. The prevalence of CD in patients with T1DM has been reported to range from 1 in 6 to 1 in 103 in different populations[5]. Like T1DM, the risk of CD is also increased by certain alleles of human leukocyte antigen (HLA) DQA1 and HLA DQB1. There are also certain non-HLA genes that are common to T1DM and CD. These include *RGS1* on chromosome 1q31, *IL18RAP* on chromosome 2q12 and *TAGAP* on chromosome 6q25[6].

Though the role of routine screening for CD in T1DM patients is somewhat controversial, most consensus guidelines favour it[7-9]. Patients with CD may be asymptomatic or have intestinal/extraintestinal manifestations such as poor growth, delayed puberty, osteopenia and anaemia[10]. The clinical picture may overlap with that of other co-existing hormonal disorders such as thyroiditis or Addison's disease and routine screening eliminates the risk of potentially preventable and treatable complications.

The recommendations regarding the timing and frequency for screening are also variable. In a prospective study conducted by Barera *et al*[11] the prevalence of CD in Italian children with T1DM at the time of diagnosis was 3.6 per cent which increased to 6.2 per cent over a follow up of six years. In a recent systematic review, it was identified that most cases of CD were diagnosed within five years of diagnosis of T1DM and hence it was recommended that all children with T1DM should be screened for CD at the time of diagnosis, between two and five years, and whenever symptomatic[12].

The 2014 position statement of the American Diabetes Association (ADA) states that screening for thyroid dysfunction, vitamin B12 deficiency and CD should be considered in T1DM patients based on signs and symptoms. The ADA does not give a definite recommendation on screening in asymptomatic individuals stating that although recommended, the effectiveness and optimal frequency of periodic screening in asymptomatic individuals are unclear[7]. The 2014 International Society for Pediatric and Adolescent Diabetes guidelines are more lucid, stating that screening for CD should be performed at the time of diagnosis of T1DM, and every 1-2 year thereafter, with more frequent assessment if suggested by clinical situation or if a first-degree relative has CD[8]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends that all patients with T1DM should be offered testing for CD, but it does not specify if there is any role of repeating the test in those who are asymptomatic at first[9]. The recommendation in all the above guidelines is to screen by serology and confirm by biopsy[7-9].

Those against routine screening argue that CD is usually symptomatic and should be suspected clinically. Poor growth, anaemia and delayed puberty should be identified by the clinician looking after the patient, rather than screening the entire population. A

positive serology would not confirm the diagnosis, and biopsy is an invasive test. In addition, the reporting of a biopsy may vary between different centres. The benefits of putting asymptomatic children on a gluten-free diet are also not fully established[13]. One should also keep in mind that putting asymptomatic T1DM patients on gluten-free diet might further complicate their nutritional management and increase the financial and psychological burden on the family.

The problem of establishing routine screening guidelines would be further complicated by the variation in the prevalence of both T1DM and CD in different regions and different ethnicities. Hence, it is important to study the prevalence and clinical features of CD in children with type 1 diabetes in specific populations as has been done in the study by Singh *et al*[14] in this issue. In this study, all children with T1DM presenting to a tertiary care referral centre were screened by serology, and the diagnosis was confirmed by biopsy. Such studies are important in different regions of the country. However, the children diagnosed with CD in the study by Singh *et al*[14] were not asymptomatic. Fifteen of 17 children diagnosed with CD had the clinical presentation of frequent hypoglycaemia. The odds for short stature and hypothyroidism were also significantly higher in the children with CD[14]. This reinforces the clinical knowledge that testing for CD is a must in T1DM patients with unexplained recurrent hypoglycaemia, short stature or thyroiditis[15,16]. Anaemia and delayed puberty are other relatively common symptoms that should serve as red flags to screen for CD[16]. However, these have not been reported in the present study.

The scope of this study was inherently limited due to it being a retrospective analysis. The important question of whether screening for CD is required in all children with T1DM even if they do not have any of the common non-gastrointestinal symptoms, such as poor growth, hypoglycaemia or anaemia has not been answered by the present study. An adequately powered prospective cohort study in children with T1DM is needed for answering this question. In such a study, children who are asymptomatic but seropositive for CD can be prospectively followed for the development of symptoms or complications in the form of impairment of growth, fall in haemoglobin or worsening of glycaemic control. This would be useful to understand the natural course and clinical implication of seropositivity in the absence of symptoms, and provide insights into the need for screening all asymptomatic diabetic children for CD, subjecting them to biopsy, and initiating gluten-free diet. Further, children with T1DM who are initially seronegative for CD can be followed up with annual or biennial screening tests to understand the need for, and frequency of periodic re-screening of asymptomatic children. At the same time, the role of biopsy and testing for HLA DQ2 and HLA DQ8 for the diagnosis of CD in patients who are seronegative, but have poor glycaemic control or other symptoms potentially attributable to CD, can also be investigated.

It is important for the physicians caring for children with both T1DM and CD not to overlook the psychological dimension of the diagnosis. It becomes difficult for the children to share their food with friends, to have the same meals as the rest of the family and to enjoy social dining, which can lead to emotional problems and poor compliance. Hence, apart from referring these patients to expert dieticians, who can guide the parents in making the meals not only healthy, but also interesting and varied, it is also important to arrange psychological counselling to help the child and family in dealing with the dual dietary restriction. Regular follow up and monitoring will go a long way in achieving optimal outcomes in terms of growth, development and glycaemic control in these children.

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Received July 25, 2016

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