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Coexistence of celiac disease & type 1 diabetes mellitus in children

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***Background & objectives*: Type 1 diabetes mellitus (T1DM) and celiac disease (CD) tend to co-exist due to similar underlying genetic predisposition. Failure to recognize CD in patients with T1DM predisposes them to complications. The present study was aimed to assess children with T1DM for the presence of CD.**

***Methods*: This was a retrospective analysis of the records of children with T1DM attending paediatric endocrinology clinic at a tertiary care hospital in north India from January 2006 to May 2014. All children were screened for CD at the time of diagnosis of T1DM using IgA anti-tissue transglutaminase (anti-tTG) levels in serum. Seropositive children were subjected to upper gastrointestinal endoscopy and duodenal biopsy for histopathological confirmation. The children also underwent thyroid function testing (TFT); those with deranged TFT were evaluated for thyroid-specific antibodies.**

***Results*: Positive serology for CD was present in 43 of 126 children with T1DM whose records were reviewed [34.1%; 95% confidence interval (CI): 25.9-43.1]. Confirmed CD was diagnosed in 17 (13.5%; CI: 8.1-20.7) of the children screened and 17 of 40 (42.5%; CI: 27.1-59.1) seropositive participants. Four out of 17 children with coexisting CD and T1DM also had autoimmune thyroiditis with overt hypothyroidism. The children with confirmed CD were more likely to have short stature [odds ratios (OR)-3.16; 95% CI: 1.09-9.20, *P*<0.05] and hypothyroidism (OR-6.4; 95% CI: 1.52-26.90, *P*<0.05).**

***Interpretation & conclusions*: Our study showed a higher proportion of CD in children with T1DM as compared to that reported in general population. Regular screening of children with T1DM for CD is needed to improve metabolic control and prevent long-term complications.**

Key words Anti-tissue transglutaminase antibody - celiac disease - children - hypothyroidism - type 1 diabetes mellitus

Celiac disease (CD) is an immune-mediated multisystem disorder seen in genetically susceptible individuals triggered by gluten and related prolamins in wheat, rye and barley. The coexistence of type 1 diabetes mellitus (T1DM) and CD is due to intricate interaction between the environmental factors and genetic susceptibility. There is evidence of common genetic basis for disease expression as both the diseases are associated with the major histocompatibility complex class II antigen DQ2 encoded by the alleles, DQA1∗501 and DQB1∗201 and seven shared non-human leucocyte antigen (HLA) loci[1]. Globally, the estimated prevalence of CD in the general population is around 1 per cent[2] which rises 5 to 7 folds in association with T1DM[3-5]. This variation in coexistence is determined by geographical/genetic predisposition

and diabetes duration. In north India, the prevalence of CD in general population has been reported as 1.04 per cent[6], while in south India, the disease has been infrequent and its prevalence has not been established. The prevalence of CD in association with T1DM was reported as 11[7] and 17 per cent[8] from two studies from north India.

CD has protean manifestations, but majority of patients with coexisting T1DM do not have classical gastrointestinal symptoms of CD. They are either asymptomatic or manifest with atypical features such as short stature, refractory anaemia, delayed puberty, osteopenia and other autoimmune disorders such as thyroiditis and autoimmune hepatitis[3,9]. Clinical clues suggestive of CD in T1DM include unpredictable blood glucose levels, recurrent episodes of hypoglycaemia and growth failure[10]. These symptoms are often attributed to poor glycaemic control *per se*. Failure to recognize co-existing CD may predispose the individuals to increased risk of growth failure, osteoporosis, infertility and gastrointestinal lymphoma[11]. It is also speculated that continuous exposure to gluten may facilitate development and progression of other autoimmune diseases apart from CD[12]. It therefore, becomes important to actively screen for CD in patients with T1DM at the time of diagnosis of T1DM and also during follow up later in life. This will help optimize insulin therapy, achieve good glycaemic control and avert the risk of complications both due to T1DM and CD[13]. The present study was conducted to assess the coexistence of CD in children with T1DM in a tertiary care hospital in north India.

Material & Methods

This was a retrospective analysis of the records of children with T1DM attending the paediatric endocrinology clinic on a regular basis for atleast one year, at Lady Hardinge Medical College, a tertiary level teaching hospital in New Delhi, India, from January 2006 to May 2014. As per the clinic's protocol, all children diagnosed with T1DM were screened for CD at enrolment by IgA anti-tissue transglutaminase (anti-tTG) levels in the serum. The samples for IgA anti-tTG were analyzed using ELISA kits based on solid-phase enzyme immunoassays (Kit: tTG-A ELISA REF EIA - 31003, 31004; Euroimmune, Germany) with a sensitivity of 95 per cent and specificity of 96 per cent. Children meeting the reference cut-off level of anti-tTG IgA ≥15 U/ml were considered as seropositive. Among the seropositive group, those with anti-tTG levels ≥3 times the reference cut-off were advised endoscopic biopsy as per the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition criteria[14]. Serum IgA levels were measured in children with negative celiac serology to detect IgA deficiency. Seronegative children were considered for re-testing over subsequent visits in the presence of poor metabolic control and frequent hypoglycaemic episodes. Upper gastrointestinal (UGI) endoscopy and biopsy were performed after obtaining written informed consent. The severity of inflammatory process was graded on histopathology using modified Marsh classification[15]. A diagnosis of CD was established when the biopsy showed Marsh Grade 2 or 3 in the presence of seropositivity. The children were regularly followed up in the clinic as per protocol that included monitoring growth parameters, insulin compliance and blood glucose levels. Children with height for age below −2 standard deviation for age as well as gender-related norms were considered to have short stature. All children underwent thyroid function testing (TFT) while thyroid-specific antibodies were analyzed only in those with deranged thyroid function. Children with CD and hypothyroidism were managed as per the standard protocol. The study protocol was approved by the Institutional Ethics Committee.

Statistical analysis: The data were analyzed using SPSS software version 16.0 (SPSS Inc., Chicago, USA). Proportion of children with seropositivity and confirmed CD was calculated and 95 per cent confidence interval (CI) was determined by exact method[16]. Simple logistic regression[17] was applied to study the association of variables (like age, sex, height, BMI, HbA_{1c} levels) in type 1 DM with celiac seropositivity and confirmed CD. The odds ratios (ORs) with 95 per cent CI were calculated for the same.

Results

Records of 126 children and adolescents (62 boys and 64 girls) with T1DM were reviewed. The mean age at enrolment was 8.2±4 and 8.1±3.8 yr for boys and girls, respectively. Forty three children (34.1%; 95% CI: 25.9-43.1) were seropositive for CD with anti-tTG levels >3 times of the reference cut-off. None of the participants with negative serology were found to be IgA deficient. There was no significant difference among seropositive and seronegative individuals in age at presentation (OR-2.21; CI: 0.64-7.75, *P*=0.20), gender (OR-0.64; CI: 0.30-1.34, *P*=0.24), body mass index (BMI) (OR-2.18; CI: 0.91-5.20, *P*=0.08), baseline glycated haemoglobin (HbA_{1c}) (OR-1.08; CI: 0.95-1.23, *P*=0.22) and prevalence of co-existing

hypothyroidism (OR-2.60; CI: 0.66-10.23, *P*=0.17). However, the probability of finding short stature was more among seropositive as compared to seronegative children (OR-2.26; CI: 1.06-4.79, *P*<0.05).

Duodenal biopsy was performed in 40 seropositive children. The remaining three children did not give consent for UGI endoscopy as they were asymptomatic with a good metabolic control. Histopathologically confirmed CD was diagnosed in 17 of 126 children (13.5%, 95% CI: 8.1-20.7). Eight children had a normal biopsy, 12 showed non-specific duodenitis and the remaining three had Marsh Grade I. In two cases, CD was diagnosed before they developed features of T1DM. In the remaining cases, the diagnosis of CD was made either concurrent or within two years of the diagnosis of T1DM. None of the children with CD exhibited typical gastrointestinal symptoms. Concomitant autoimmune thyroiditis with hypothyroidism was diagnosed in nine (7.1%) children, while four (3.1%) had coexistence of CD, T1DM and autoimmune thyroiditis. There was no difference in age at presentation (OR-2.68; CI: 0.31-23.35, *P*=0.37), sex (OR-0.52; CI: 0.18-1.49, *P*=0.52) and BMI (OR-0.76; CI: 0.20-2.86, *P*=0.68) among patients with and without CD. However, concomitant short stature (OR-3.16; 95% CI: 1.09-9.20, *P*<0.05) and hypothyroidism (OR-6.4; 95% CI: 1.52-26.90, *P*<0.05) were associated with significantly higher odds of CD.

Fifteen children in whom CD was diagnosed on screening exhibited poor metabolic control in spite of good compliance with insulin and diet before institution of gluten-free diet (GFD). They experienced frequent postprandial and early morning hypoglycaemia on an average of 8-10 episodes/month over three months before the diagnosis of CD was established. Following the institution of GFD in this subgroup, there were no further hypoglycaemic episodes without significant change in insulin requirement and HbA_{1c} levels.

Discussion

The coexistence of CD and T1DM reported in our study was comparable to that reported in other studies from north India[7,8]. The reported prevalence of CD in the general population in north India is 1.04 per cent[6]. The global prevalence of biopsy-proven CD in children with TIDM varies from 2.4 per cent in Finland to 16.4 per cent in Algeria[18]. The difference in the prevalence of CD across geographical locations was found to be due to difference in distribution of the HLA genotypes and its complex interaction with the environment and host immunological factors[19]. The association of T1DM and CD in north Indian population may be attributed to microsatellite polymorphism in major histocompatibility complex class I chain[20]. A multicentre study from Italy has demonstrated a positive association between young age at diabetes onset, female gender and the development of CD[21]. The global prevalence of IgA deficiency is variable, and a low prevalence reported in north Indian population[22] can possibly explain the absence of IgA deficiency in our study group.

The sequence of appearance of T1DM and CD cannot be predicted. A large proportion of CD cases are diagnosed within two years of T1DM and majority within 10 yr of screening in paediatric setting; however, the diagnosis can be made beyond this period[23]. The diagnosis of T1DM usually precedes CD[23,24] though the order can also be reversed[25]. In a prospective study, 2.4 per cent children with T1DM had CD at the outset and another 2.8 per cent seroconverted over a median interval of 3.6 yr[26]. In our study only 13.5 per cent children were found with T1DM and biopsy-proven CD, with a large pool of potential celiac patients to monitor for the future development of disease. This mandates screening for CD in T1DM at presentation as most children are asymptomatic and continued regular monitoring after every 1-2 years[13].

The observation of short stature being significantly associated with coexisting T1DM and CD in the current study was in agreement with reports from Indian[7,27] and other studies[28]. In addition, coexisting hypothyroidism increased the odds of CD in children with T1DM, and a similar association of autoimmune diseases with T1DM has been reported in literature[29,30]. Hypoglycaemia has been anecdotally described as a warning sign of CD in diabetes due to erratic absorption of nutrients[10]. Even though we reported reduced hypoglycaemic events after institution of GFD in children with CD and T1DM, its effect on clinical/metabolic parameters has been variably reported[26,31,32]. The limitation of the present study was its retrospective design and variable duration of follow up.

In conclusion, our findings showed a high proportion of CD in children with T1DM, the odds of which increased in the presence of short stature and hypothyroidism. Cohort studies with a robust study design are warranted for drawing firm conclusions.

***Conflicts of Interest*:** None.

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