Original Article

Parietal Cell Antibodies in Type 1 Diabetes Mellitus and Its Implications for Iron Deficiency: A Tertiary Centre Experience from North India

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Abstract

Introduction: Parietal cell antibody (PCA)-mediated auto-immune gastritis is known to increase the risk of iron-deficiency and pernicious anaemia in adults with type 1 diabetes mellitus. However, in children and young adults with type 1 diabetes, these data are scarce. We aimed to study the prevalence of parietal cell antibodies (PCAs) and its clinical associations in people with type 1 diabetes with onset below 30 years. **Methods:** In a cross-sectional study, 224 children and young adults with type 1 diabetes and 171 healthy controls were enrolled. We measured haemoglobin, serum ferritin, vitamin B12, PCA, thyroid peroxidase, and anti-tissue transglutaminase antibodies in all patients. Mann–Whitney U test for continuous data and Chi square test for categorical data were used. Linear regression analysis was performed with haemoglobin as a dependent variable. **Results:** The prevalence of PCA was significantly higher in patients than in controls (22% vs 10.2%; $P = 0.002$). Patients with PCA had a higher frequency of anaemia (60% vs 30%, $P < 0.001$), lower haemoglobin [7.3 (1.6) vs 7.8 (1.1) mmol/L; $P = 0.002$], and lower serum ferritin [46.9 (70.8) pmol/L vs 66.0 (105.3) pmol/L; $P = 0.04$], as compared to those without PCA. On multivariate analysis, haemoglobin was associated with PCA ($\beta = -0.174$, $P = 0.005$) and serum ferritin ($\beta = 0.247$, $P < 0.001$). **Conclusion:** Presence of PCA was an independent risk factor for iron deficiency and anaemia in children and young adults with type 1 diabetes.

Keywords: Anaemia, gastric auto-immunity, iron deficiency, parietal cell antibody, type 1 diabetes, vitamin B12 deficiency

Introduction

Type 1 diabetes is a T-cell mediated auto-immune disorder characterised by insulitis and antibodies against various islet antigens.[1,2] The disorder is associated with an increased prevalence of other auto-immune disorders such as auto-immune thyroid disease, celiac disease, Addison's disease, and auto-immune gastritis/pernicious anaemia.[3,4] Antibodies against tissue-specific antigens often serve as markers for these disorders.[5]

Auto-immune gastritis is known to result in decreased secretion of intrinsic factor from the parietal cells and consequent vitamin B12 deficiency. In addition, it also affects H^+K^+ATPase in the gastric parietal cells and leads to achlorhydria, impaired absorption of iron in the intestine, and iron deficiency anaemia.[6] Thus, identification of gastric auto-immunity should lead to further testing for iron and vitamin B12 deficiency and anaemia in patients with type 1 diabetes. Cytoplasmic parietal cell antibodies (PCAs) are a marker of gastric auto-immunity. Most studies suggest that the PCA frequency is increased in patients with type 1 diabetes (3–37%) in comparison to healthy control subjects (2.5–12%).[7,8] The frequency of PCA positivity increases with age and duration of diabetes.[9]

While some authors have suggested that all patients with type 1 diabetes should be screened for gastric auto-immunity at diagnosis,[10-12] recommendations of professional societies such as the International Society for Pediatric and Adolescent

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diabetes (ISPAD) and American Diabetes Association (ADA) do not provide any clear guidelines in the regard.[13,14] The association of PCA with iron deficiency, vitamin B12 deficiency, and anaemia, while well established in older patients with type 1 diabetes, has not been adequately studied in children and young adults.[11,15]

The aim of the current study is to study the prevalence of parietal cell antibody and its relevant clinical associations in children and young adults with type 1 diabetes.

Materials and Methods

Study design

Selection and Description of Participants: In this cross-sectional observational study, we recruited 224 children and young adults with type 1 diabetes [Median (IQR) age 17 (13.8) years; 123 (55%) males; median (IQR) duration 4 (6) years] who presented to the diabetes clinic of our hospital, which is a referral centre in North India. Type 1 diabetes mellitus was diagnosed by severe hyperglycaemia (plasma glucose > 300 mg/dl) at onset and continuous insulin requirement from the time of diagnosis. In adolescents, chronic pancreatitis was ruled out by abdominal ultrasonography. One hundred and seventy-one healthy children and young adults [median (IQR) age 16 (14) years; 105 males] who presented to our clinic were recruited as controls. All the control subjects were in good health, as assessed by clinical history and family history and physical examination, and did not take any medications.

Technical information: Height and weight Z-scores were calculated using Centre for Disease Control (CDC) growth charts for subjects ≤ 20 years of age.[16] Anaemia was defined as per World Health Organization (WHO) criteria as haemoglobin less than the lower limit for age and sex.[17] We measured haemoglobin, haemoglobin indices, serum ferritin, vitamin B12, and PCA in all participants (type 1 diabetes and controls) and additionally antibodies against thyroid peroxidase (TPO) and tissue transglutaminase (TTG) in all people with type 1 diabetes. All people with type 1 diabetes were requested to provide a stool sample for examination of parasites and occult blood, but this was provided by only 116 patients.

PCA positivity was detected by indirect immunofluorescence using cryo-preserved rat gastric mucosa as a substrate. Serum was added at 1:40 dilution and detected using an FITC-tagged polyclonal rabbit anti-human antibody (DAKO, Glostrup, Denmark). Each slide was read by two investigators and scored as negative or 1 + to 3 + positive. Patients with PCA 2 + or 3 + were taken as positive for the purpose of the study. Haemoglobin and red cell indices were measured using an automated analyser (Sysmex, Kobe, Japan). Serum ferritin was measured by particle-enhanced immuno-nephelometry (N Latex Ferritin Kit, Siemens, Malvern, USA). Serum B12, TSH, and TPO antibody were measured by chemiluminescence immuno-assay (Immulite 1000, Siemens Diagnostics, Tarrytown, NY, USA). Anti-TTG antibody was measured using an immune-enzymatic method (Diesse Diagnostica, Monteriggioni, Siena, Italy). Creatinine clearance was calculated using the bedside Schwartz equation [0.413× (height/serum creatinine)] in children.

Statistics

Continuous data were presented as mean ± SD or median (inter-quartile range), while categorical data were expressed as n (%). The 95th percentile confidence interval was calculated. Comparison between groups for continuous variables was performed using Mann–Whitney U test, while Chi square test was used for comparing categorical data. Univariate and multivariate linear regression analysis was done with haemoglobin as a dependent variable. A two-tailed *P* value of < 0.05 was considered significant. The statistical software package SPSS 21.0 (IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA) was used for analysis.

Ethical aspects

Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study was approved by the institutional ethics committee, SGPGIMS, Lucknow (Letter number: PGI/BE/487/2015; dated 29/04/2015).

The procedures in the study follows and are in compliance with the guidelines laid down in the Declaration of Helsinki 2013.

Results

The baseline clinical characteristics of the patients (participants with type 1 diabetes) are shown [Table 1]. Parietal cell antibody positivity was detected in 50 patients [22% (95% CI 17–28%)], significantly higher than that in the control participants [10.2% (95% CI 6–16%); *P* = 0.002]. There was no significant difference in the age of onset, duration of diabetes, or gender among patients with or without PCA. However, the prevalence of PCA positivity increased with advancing age as shown in Figure 1. Patients with PCA had a significantly higher frequency of anaemia than PCA-negative patients (60% vs 30%; *P* < 0.001). Even after excluding patients with creatinine clearance < 90 ml/minute/1.73 m^2 from the analysis (n = 28), anaemia was more frequent among those positive for PCA (57% vs 30%; *P* = 0.001). Patients with PCA also had lower haemoglobin [median (IQR), 7.3 (1.6) vs 7.8 (1.1) mmol/L; *P* = 0.002] and serum ferritin [median (IQR) 46.9 (70.8) vs 66.0 (105.3) pmol/L; *P* = 0.04], as compared to the patients without PCA. The presence of PCA increased the odds of having anaemia by 3.3 (95% CI 1.7–6.4) and iron deficiency by 2.0 (95% CI 1.0–3.8). Haemoglobin [median (IQR), 7.8 (1.1) mmol/L] and ferritin levels [median (IQR) 64.9 (109.8) pmol/L] and prevalence of anaemia (31.7%) in controls did not differ from that in type 1 diabetes participants without PCA. Serum vitamin B12 level did not differ between PCA-positive and PCA-negative participants with type 1 diabetes. However, the serum vitamin B12 level was significantly lower among controls compared to both PCA-positive and PCA-negative participants with type 1 diabetes [median (IQR), 146.8 (127.2), 171.9 (154.9) and 193.4 (164.5) pmol/L respectively;

Table 1: Comparison of participants with type 1 diabetes according to parietal cell antibody status (*n*=224)

Variable	All patients	PCA present (*n*=50)	PCA absent (*n*=174)	*P*
Age (years)	17 (11-24)	18 (14-18)	16 (11-16)	0.06
Age of onset (years)	11.7 (7-17)	12.5 (7.7-17.2)	11 (6.8-16.2)	0.46
Duration (years)	4.0 (2-8)	5.7 (2-10.2)	4 (2-7)	0.09
Onset <18 years	177 (79%)	39 (78%)	138 (79%)	0.81
Males	123 (55%)	23 (46%)	100 (57%)	0.15
Anaemia	84 (37.5%)	30 (60%)	54 (30%)	<0.001
Haemoglobin (mmol/L)	7.7 (7.01-8.25)	7.3 (6.5-8.0)	7.8 (7.2-8.3)	0.002
Serum ferritin (pmol/L)	63.8 (28.9-130.3)	46.9 (25.6-96.3)	66 (32.8-138.5)	0.04
Iron deficiency	79 (35.3%)	24 (48%)	55 (31.6%)	0.02
Serum vitamin B12 (pmol/L)	190.0 (202.9-290.0)	171.9 (112.2-267.8)	193.3 (142.4-297.4)	0.43
Vitamin B12 deficiency	44 (19.6%)	14 (28%)	30 (17%)	0.09
TPO antibody present	80 (35.7%)	24 (48%)	56 (32%)	0.04
TTG antibody present	35 (15.6%)	7 (14%)	28 (15%)	0.72

P values for comparison between PCA positive and negative patients; Median (inter-quartile range) or *n* (%). Iron deficiency (serum ferritin <26.9 pmol/L for age <5 years and <33.7 pmol/L for age >5 years). Vitamin B12 deficiency (serum vitamin B12 <118 pmol/L)

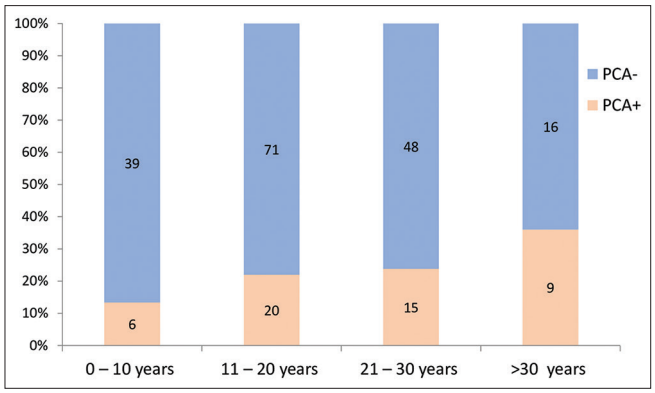

Figure 1: Prevalence of PCA in various age groups of type 1 diabetes participants (N = 224)

P = 0.001]. Ferritin and vitamin B12 levels were not different among controls when subjected to sub-analysis according to age (≤10 or > 10 years).

Anti-TPO antibodies were detected in 80 (36%) patients. Patients with PCA had a higher TPO antibody frequency compared with those without PCA (48% vs 32%, *P* = 0.04). Fourteen percent of patients had overt hypothyroidism. There was no difference in the prevalence of anaemia in those having overt hypothyroidism. The frequency of TTG antibodies was not increased in patients with PCA (14% vs 16%). The frequency of anaemia was also similar in patients with or without TTG antibodies.

Anaemia was noted in 38% (95% CI 31–44%) of participants with type 1 diabetes and 31.7% in control participants. The prevalence was similar in males (33%) and female participants with type 1 diabetes (44%). The anaemia was mild, moderate, and severe in 52%, 42%, and 6% of patients, respectively. Among patients with anaemia, 19% had iron deficiency, 3% had vitamin B12 deficiency, and 4% had combined deficiency, while 12% had normal iron and vitamin B12 levels. Among participants with PCA positivity, 32% had iron deficiency, 12% had vitamin B12 deficiency, and 16% had combined deficiency, while 40% had normal iron and vitamin B12 levels. The frequency of anaemia in various age groups is shown in Figure 2; it was the highest (51%) in females > 15 years of age.

Weight and height Z-scores did not differ based on PCA positivity among participants with type 1 diabetes. However, patients with anaemia had significantly lower height Z-scores as compared to patients without anaemia (-1.6 vs -0.9; *P* = 0.004), though weight Z-scores did not differ. Stool examination, available in 116 patients, was abnormal in only one patient (who had cysts of Giardia lamblia). On multivariate analysis, haemoglobin level was associated with PCA positivity (β = -0.174; *P* = 0.005), serum ferritin level (β = 0.247; *P* < 0.001), and creatinine clearance (β = 0.160; *P* = 0.012) [Table 2].

Discussion

We report a high prevalence of PCA in children and young adults with type 1 diabetes. Presence of PCA was associated with anaemia, iron deficiency, and low ferritin levels, thus emphasising the relevance of its clinical measurement. Independent contributing factors to anaemia were low ferritin and the presence of PCA.

The prevalence of PCA (22%) in our type 1 diabetes participants was significantly higher than that in matched control participants. The prevalence of PCA in type 1 diabetes patients varies markedly in previous studies, ranging from 3% to 37%.[7,8,15,18,19] This variability is partly dependent on the age of patients studied and iron deficiency and the method of detection of PCA.[20] Presence of PCA has been found in 10–15% of children and 15–25% of adults with type 1 diabetes.[5,21,22] We did not find any significant difference in PCA prevalence in our patients with age, duration of disease, or gender, similar to results reported in some previous studies.[4,8]

Patients with PCA had an increased prevalence of anaemia, low serum ferritin, and iron deficiency anaemia compared to

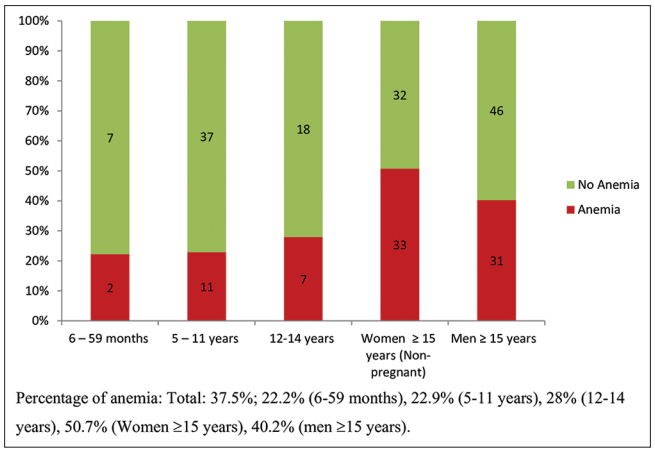

Figure 2: Prevalence of anaemia in various age groups of type 1 diabetes participants (N = 224)

Table 2: Multivariate analysis of risk factors for haemoglobin concentration

Baseline variables	Beta (Standardized regression Coefficients)	*P*
PCA	-0.179	0.005
Serum vitamin B12	-0.124	0.05
Serum ferritin	0.247	<0.001
Creatinine clearance	0.160	0.012

r=0.37, r^2=0.141, adjusted r^2=0.125, SE=1.793

PCA-negative patients. The PCA-negative type 1 diabetes participants were not significantly different from our healthy controls in terms of percentage of anaemia, haemoglobin, and ferritin levels. There is a paucity of literature on the association of iron deficiency with PCA positivity.[5] We could find only one reference in the paediatric literature which reported significantly lower ferritin levels among PCA-positive type 1 diabetes patients as compared to PCA-negative subjects.[23]

In contrast to some studies in older participants with type 1 diabetes, where the frequency of pernicious anaemia was increased in type 1 diabetes patients, the prevalence of vitamin B12 deficiency was not increased among our patients with PCA.[5,24,25] This may be explained by the fact that our patients were young (median 11.7 years) and had a short duration of illness at the time of testing (median 4 years). Vitamin B12 deficiency and pernicious anaemia have been reported to develop at a later stage in the progression of gastric auto-immunity.[14] Alonso *et al*.[26] reported an increase in frequency of vitamin B12 deficiency from 27 to 45% on follow-up after 5 years. A study in 2005 reported a high prevalence of latent pernicious anaemia (assessed by lower serum pepsinogen levels) in type 1 diabetes patients as compared to healthy controls. Serum pepsinogen I is considered as a sensitive marker gastric atrophy.[10] Taking the high prevalence of latent pernicious anaemia in type 1 diabetes patients into account, the authors raised the need of regular screening of latent pernicious anaemia using pepsinogen levels in addition to parietal cell antibodies. Nevertheless, it would be important to follow these patients at regular intervals for cobalamin levels and treat deficiency when it occurs. This is even more relevant in India where a high prevalence of cobalamin deficiency in the general population (16–77%) has been reported.[10,27]

We found a higher frequency of vitamin B12 deficiency in the healthy control population than our type 1 diabetes patients (both PCA-positive and PCA-negative). Similar to our findings, a previous study on adult type 2 diabetes mellitus from India reported a higher prevalence of vitamin B12 deficiency among the general population as compared to people with diabetes.[28] This was attributed to the fact that people with diabetes are more likely to remain in constant touch with the healthcare system and are more likely to be supplemented.[28,29] Vitamin B12 deficiency in multi-factorial and vegetarian diet, increased requirement during adolescence, and use of proton pump inhibitors have been postulated as some risk factors in the previous studies.[29] We did not quantify vitamin B12 intake in our study.

Anaemia was noted in 38% of type 1 diabetes patients, and in nearly half of the subjects, it was of moderate to severe grade. Anaemia has serious implications for cognitive function and exercise tolerance. The permanent physical handicap in terms of short stature was documented in our patients and in the literature.[30]

Patients with type 1 diabetes and gastric auto-immunity were more likely to have thyroid auto-immunity. This association has been previously reported, and therefore, detection of one disorder should lead to the testing for other.[4,27] In contrast, an association with anti-TTG antibodies has not been reported.

Strengths and limitations

The main strength of the present study is that it assessed the prevalence of PCA and also its associated functional consequences in children and young adults with type 1 diabetes, a group not well studied thus far. The limitations of the present study are that the other factors known to affect ferritin levels or vitamin B12 levels like *Helicobacter pylori* infection, dietary intake, or vitamin supplements were not studied. Gastric auto-immunity can be adequately assessed by gastric mucosal biopsy, which was not undertaken for the study subjects.

Future research directions

Further longitudinal and multi-centre studies with a large number of patients are needed to generate a strong recommendation for the need of routine screening for gastric auto-immunity in patients with T1D. Future studies shall also include the evaluation of gastric auto-immunity by assessment of gastric mucosal biopsy.

Conclusion

PCA was associated with an increased risk of anaemia and iron deficiency in children and young adults with type 1 diabetes. Anaemia was associated with the functional consequences such as short stature. Screening for PCA will identify a group of patients who will benefit from screening for identification and treatment of iron deficiency and anaemia and should be emphasised in regular screening protocols. Further longitudinal studies with a large number of patients are needed to evaluate the need of screening for gastric auto-immunity.

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Authors' contribution

Khurshid Ahmed Bhat, Eesh Bhatia, Vijayalakshmi Bhatia and Siddhnath Sudhanshu contributed in conceptualization, design, literature search, methodology and data analysis and manuscript review and editing. Manuscript preparation was done by Khurshid Ahmed Bhat, Sonali Verma and Siddhnath Sudhanshu. Siddhnath Sudhanshu is also guarantor of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The authors of this manuscript are willing to share the data supporting the results of this manuscript upon request.

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