Original Article

Effect of Infant Feeding On the Occurrence of Celiac Disease: A Case Control Study

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Abstract

Background: Celiac disease (CD), or gluten-sensitive enteropathy, is an immune mediated chronic enteropathy with variable presentation and severity in genetically predisposed population. The objective is to study the effect of the duration of breast feeding on the risk of occurrence of celiac disease. **Material and Methods:** This Case control study was conducted in the Pediatric Gastroenterology Division of the Department of Pediatrics of Chacha Nehru Bal Chikitsalaya, Delhi. The study enrolled consecutive patients diagnosed with celiac disease attending the Pediatric Gastroenterology clinic and age and sex matched controls from the general pediatrics OPD. **Results:** The median age of the entire study population was 66.5 ±34.0 months. The celiac patients had a median age of 67.0±34.0 and the controls had a median age of 66.3±34.1 and the difference being statistically non-significant (p=0.89). Female population was higher and they made up 83(64%) and 69(45.4%) of the celiac group and the control group respectively(p=0.006). The median age of onset of the classical and atypical disease is the same (26.7±18.3 vs 28.2±17.2 respectively, p=0.75). But the atypical cases were diagnosed at a significantly later age (61.8±32.2 vs 84.5±35.3 respectively, p=0.02). 62.6% subjects received exclusive breast feeding while 30.8% received mixed feeding during the first 6 months of life and 7.3% subjects did not receive any breast feeding. On comparing the celiac group with the controls it was observed that, 88% of the celiac disease patients received any breast feeding as compared to 94.7% in the control group (p=0.02). The median duration of any breast feeding in the celiac and control groups were 15.4±11.9 and 17.2±10.4 (p=0.24) respectively. In the celiac and the control groups, gluten containing cereals were added at median ages of 7.7±2.7 and 7.4±2.2 months respectively (p=0.33). Breast feeding was continued at the time of gluten containing cereal introduction in 80.2% of the subjects. A significantly lower proportion of subjects were introduced to dietary gluten containing cereals while being breast fed in the celiac group as compared to the control group (65.3% vs. 87.5%, p=0.0001). **Conclusion:** The incidence of the disease is more in girls than boys, the delayed diagnosis of atypical cases, the protective effect for partial and exclusive breastfeeding on the incidence of celiac disease and the introduction of cereals/solids at the background of breastfeeding has the most significant effect on the occurrence of celiac disease.

Keywords: Celiac disease, breastfeeding, gluten sensitive enteropathy.

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Introduction

Celiac disease is triggered by the ingestion of gliadin fraction of wheat gluten and similar alcohol- soluble proteins (prolamines) of barley and rye in genetically susceptible subjects with subsequent immune reaction leading to small bowel inflammation and destruction of villous architecture. Celiac Disease not only affects the gut, but it is a systemic disease that causes injury to the skin, liver, joints, brain, heart, and other organs. It is a complex genetic disorder, and HLA status appears to be the strongest genetic determinant of risk for celiac autoimmunity.[1]

Affected individuals have either DQ2 (HLA- DQA1*05- DQB1*02) or DQ8 (HLA- DQA1*03- DQB1*0302) haplotypes. Several non-HLA genetic risk factors are also being studied. It is the interplay between genes (both HLA and non- HLA) and environment (i.e. dietary gluten, infant feeding practices, gut infections) that leads to intestinal damage typical of the disease. Gluten peptides, modified by tissue transglutaminase, are able to elicit gluten specific immune response in the intestinal mucosa of genetically predisposed subjects, resulting in the infiltration of the epithelium with lymphocytes and tissue remodeling leading to villous atrophy.

The clinical classification of CD can be divided into classic (typical) and atypical. Some patients with CD have no symptoms or symptoms which were not initially attributed to CD until they improve on a gluten free diet (GFD), and are called ‘silent’. Those with the appropriate genetic background (HLADQ2/DQ8) and positive serology but normal or mildly abnormal small bowel histology are called ‘potential’. In addition, those who have previously been diagnosed but are now on a gluten containing

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diet with a normal small bowel biopsy are called 'latent'.

Breastfeeding is widely recognized as beneficial for children's health and exclusive breastfeeding for the first 4–6 months of life is recommended.[2,3] Apart from many other benefits, breast milk protects children from intestinal infections by enhancing passive immunity by factors such as IgA antibodies, lysozyme, lactoferrin, and various cytokines. This effect may be of importance because repeated gastrointestinal infections probably increase the risk of celiac disease. Moreover, some studies have shown decreased gut permeability in breast-fed infants. Modulation of gut immunity, less infections, and decreased gut permeability may be among the possible explanations for the protective potential of consuming human milk against developing celiac disease.[4,5] Additionally, human milk contains some gluten ingested by breastfeeding mothers, and this early but low grade exposure is hypothesized to lead to the development of gluten tolerance.[6,7]

Breast-fed infants differ from those receiving formula in terms of gut microbiota, and alterations in gut microbiota have been linked to the risk of having celiac disease.[7] The above listed points may be some of the possible reasons for the protective potential of human milk. Hence this study was conducted to study the effect of the duration of breast feeding on the risk of occurrence of celiac disease.

Materials and Methods

This Case control study was conducted in the Pediatric Gastroenterology Division of the Department of Pediatrics of Chacha Nehru Bal Chikitsalay, Delhi. The study enrolled consecutive patients diagnosed with celiac disease attending the Pediatric Gastroenterology clinic and age and sex matched controls from the general pediatrics OPD. Duration study was one year.

Sample Size: The number of cases needed for

- A case: control ratio of 1:2
- 80% power
- 0.05 significance level
- Difference in mean duration of breast feeding between the 2 groups of 1.5 months would be 76. Hence, the number of controls needed would be 152 bringing the size of the study population to 228.

Methodology: We enrolled consecutive patients diagnosed with celiac disease (as per ESPGHAN criteria) attending the pediatric gastroenterology clinic. Only incident cases will be enrolled. Controls will be age and gender matched, with no history of any feeding difficulty and attending the general pediatric OPD for non-gastrointestinal complaints. The ratio of the cases to controls will be 1:2 for optimal power. Data recorded from all subjects would include basic demographics, duration of exclusive and total breast feeding, age of introduction of dietary gluten, whether child was breast fed at the time of gluten introduction and the type of cereal used for gluten introduction by means of a structured questionnaire. The patients of celiac disease were also inquired about the age of onset, diagnosis and initiation of gluten free diet. The cases and controls were compared in terms of the above infant feeding parameters to look for any significant difference between celiac disease patients and controls. In the case group we will also analyse whether infant feeding patterns had an impact on the age of onset of celiac disease. Informed consent was taken from the parents of all study subjects. Confidentiality and privacy was ensured at all levels. People who will be found to have other health problems will be adequately treated.

Statistical Analysis: Comparisons between the two groups will be performed using t tests, Mann-Whitney U tests, and Pearson chi-square-tests depending on the characteristics of the variables. Differences will be reported as significantly different, if p values are <0.05. The effects of duration of breast-feeding and age at gluten introduction on the age of onset of symptoms were estimated simultaneously by fitting a multiple Cox regression model adjusted for age. ORs as relative risk estimates and the corresponding 95% confidence intervals (CI) were estimated by fitting multiple logistic regression models to the data.

Results

This prospective case control study was conducted in pediatric gastroenterology division of Chacha Nehru Bal Chikitsalaya, Delhi. Chacha Nehru Bal Chikitsalay is a pediatric superspeciality teaching hospital catering to patients from entire north India. The study enrolled 75 incident cases of celiac disease diagnosed between January to October 2017 and 152 age and gender matched healthy controls. Celiac disease was diagnosed as per the modified ESPGHAN criteria. The control patients were sourced from the immunization room and siblings of admitted patients.

The mean and median age of the entire study population was 66.5 ±34.0 months respectively. The celiac patients had a median age of 67.0±34.0 and the controls had a median age of 66.3±34.1 and the difference being statistically non-significant (p=0.89).

Females constituted a little over half (51.5%) of the study population. However, the made up 64% and 45.4% of the celiac group and the control group respectively (p=0.006).

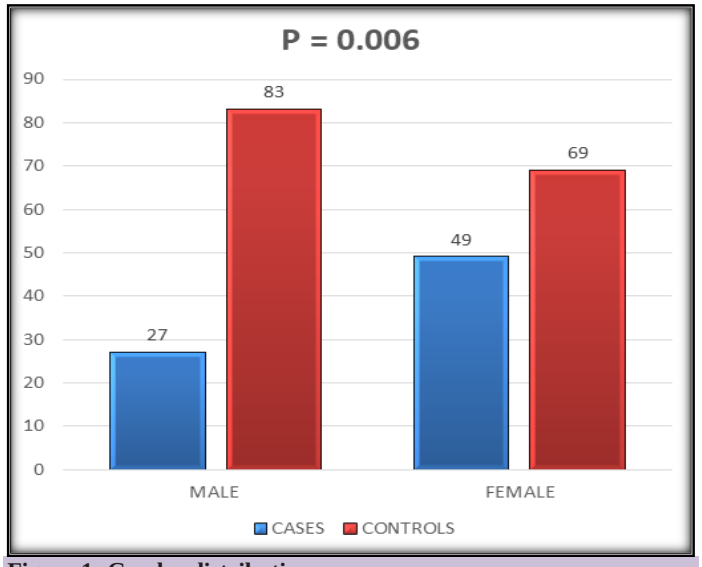


Figure 1: Gender distribution

Disease related variables: A total of 75 patients were diagnosed with celiac disease during the study period with a mean age of

67.0±34.0. The overall mean age of onset was 27.01±17.9 months. The patients were diagnosed at a mean age of 66.9±34.0 months and were started on gluten free diet soon after (67.1±34.1 months of age). Atypical celiac disease constituted 22.7% of the total. On comparing with the patients with classical celiac disease, the atypical cases had similar age of onset (26.7±18.3 months vs. 28.2±17.2 months, p=0.75 respectively). But the atypical cases were diagnosed at a significantly later age (61.8±32.2 vs. 84.5±35.3 p=0.02 respectively).

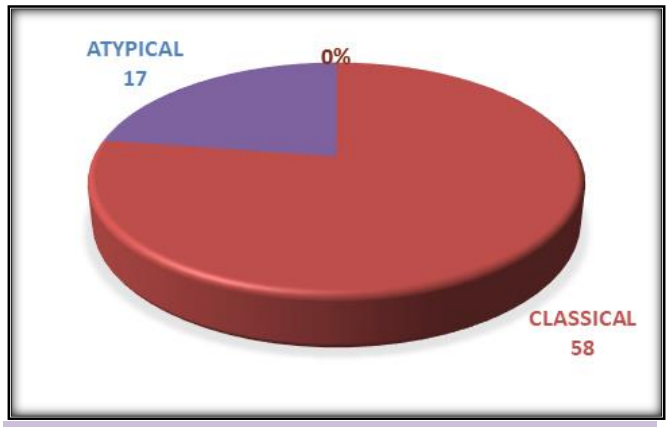


Figure 2: Distribution of celiac patients on the basis of clinical presentation

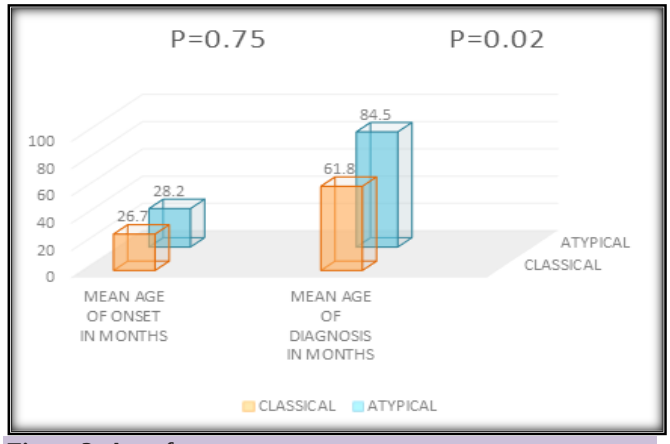


Figure 3: Age of onset

Variables pertaining to breast feeding: 62.6% subjects received exclusive breast feeding while 30.8% received mixed feeding during the first 6 months of life. 7.3% subjects did not receive any breast feeding. On comparing the celiac group with the controls it was observed that, 88% of the celiac diseases patients received any breast feeding as compared to 94.7% in the control group (p=0.04). The mean duration of any breast feeding in the celiac and control groups were 15.4±11.9 and 17.2±10.4 (p=0.24) respectively. The frequency of exclusive breast feeding was higher in the control group (exclusive breast feeding-68.4%, mixed feeding-27.0%) than in the celiac group (exclusive breast feeding-50.7%, mixed feeding-37.3%) with the difference being statistically significant (p=0.02). We categorized children who received breast feeds into three groups; those who were breast fed for less than 4 months, between 4 to 6 months and more than 6 months. Overall, 11.9% subjects were breast fed for less than 4 months of age, 10.1% fed till 4-6 months of age and 78% received breast feeding for more than 6 months. In the celiac group, 18.7% ceased breast feeding after 4 months of age, 14.7% received breast feeds till 4-6 months of age and 66.6% received breast feeds beyond 6 months of age. The corresponding percentages in the control group were 8.6, 7.9 and 83.6 respectively making the difference statistically significant (p=0.01).

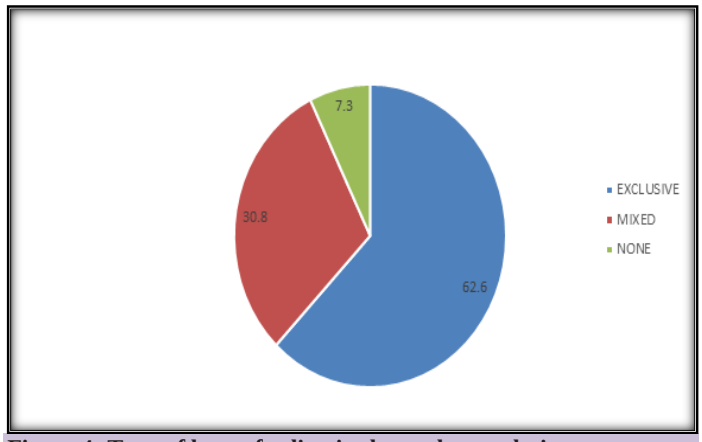


Figure 4: Type of breastfeeding in the study population

Variables pertaining to dietary cereal introduction: Dietary cereals were added at a mean age of 7.5±2.3 months. All subjects were weaned with wheat containing food items reflecting the prevailing dietary habits of north India. Breast feeding was continued at the time of gluten containing cereal introduction in 80.2% of the subjects. In the celiac and the control groups, gluten containing cereals were added at mean ages of 7.7±2.7 and 7.4±2.2 months respectively (p=0.33). A significantly lower proportion of subjects were introduced to dietary gluten containing cereals while being breast fed in the celiac group as compared to the control group (65.3% vs. 87.5%, p=0.0001).

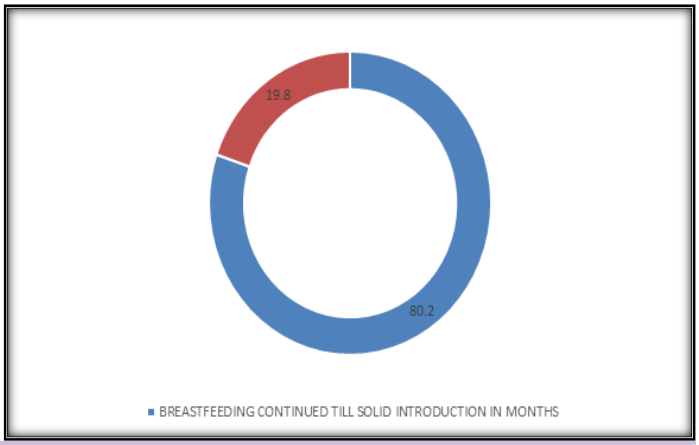


Figure 4: Breast feeding continued till solid introduction in months

Discussion

The results of my case control study is the mean age of onset of celiac disease in both classical and atypical cases are same which

is mostly less than two to three years but the age of diagnosis is delayed in atypical cases because of delay in identification of symptoms(p=0.02) and the proportion of the atypical cases is almost a quarter of all cases. It is found that there is an increase in incidence of the disease in girls when compared to boys in my study (p=0.006). In regarding to breastfeeding practices there is no difference in mean duration of breastfeeding between celiac patients and controls but the frequency of exclusive breastfeeding in controls group which is statistically significant(p=0.02), which shows the protective effect of exclusive breastfeeding against celiac disease. The total duration of breastfeeding has no effect on the disease but the categorisation into three groups as <4 months,4-6 months, >6months has effect on the onset of the disease(p=0.01). The most significant part of my study is breastfeeding at the time of cereal introduction has the most protective effect on the occurrence of celiac disease(p=0.0001). There is no effect of age of introduction of cereals on the onset of disease(p=0.33).

Table 1: Characteristics of Children in my study population

	Cases	Controls	P value
AGE AT THE TIME OF STUDY	MEDIAN AGE 67.0+/-34.0	MEDIANAGE: 66.3+/-34.1	0.86
AGE AT ONSET IN MONTHS CLASSICAL ATYPICAL	MEDIAN AGE: 26.7+/-18.3 MEDIAN AGE: 28.3+/-17.2		0.75
OVERALL AGE OF DIAGNOSIS IN MONTHS	MEDIAN AGE 66.9+/-34.0		
AGE AT DIAGNOSIS IN MONTHS CLASSICAL ATYPICAL	 MEDIAN AGE 61.8+/-32.2 MEDIAN AGE 84.5+/-35.3		0.02
AGE OF STARTING OF GFD IN MONTHS	MEDIAN AGE 67.1+/-34.1		
GENDER MALE FEMALE	 27(36%) 49(64%)	 83(54.6%) 69(45.4%)	 0.006
ARE THEY BREASTFED? YES NO	 66(88%) 9(12%)	 144(94.7%) 8(5.3%)	 0.04
TOTAL DURATION OF BREASTFEEDING	MEDIAN DURATION: 15.4+/-11.9	MEDIAN DURATION: 17.2+/-10.4	 0.24
TYPE OF BREASTFEEDING EXCLUSIVE MIXED NONE	 38(50.7%) 28(37.3%) 9(12%)	 13(8.6%) 12(7.9%) 7(4.6%)	 0.02
CATEGORED DURATION OF BREASTFEEDING <4MO 4-6MO >6MO	 14(18.7%) 11(14.7%) 50(66.6%)	 13(8.6%) 12(%) 127(%)	 0.01
AGE OF CEREAL INTRODUCTION	MEDIAN AGE:7.7+/-2.7	MEDIAN AGE:7.4+/-2.2	0.33
BREASTFEEDING AT THE TIME OF CEREAL INTRODUCTION YES NO	 49(65.3%) 26(34.7%)	 133(87.5%) 19(12.5%)	 0.0001

Study by Lionette et al,[7] concluded that overt celiac disease developed in the large majority of children within the first 5 years of life, and in 80% of those in whom celiac disease developed, it did so during the first 3 years, which is confirmed by my study were the mean age of onset is 27.01+/-10.9. The longitudinal study of HLA-DR characterized normal newborns from the Denver metropolitan general population by Hoffenberg provides evidence that approximately 1 in 100 children have evidence of CD by 5 years of age.

A study by Anneli Ivarsson et al,[8] in Swedish celiac population concludes that girls with a prevailing two-fold higher risk as compared to boys may be genetically more vulnerable to environmental exposures influencing the immunological processes towards coeliac disease, which goes in favour of my study. An Italian multicenter study by Cerutti F et. al. provided evidence that girls have a higher risk of having celiac disease than boys. Hoffenberg et al also shows increased risk of celiac disease in girls.

When coming to breastfeeding, any or no breastfeeding has effect in the onset of the disease. The statistical data is near significant value(p=0.04) but categorization into groups seems to have protective effect on the onset of the disease(p=0.001). Studies supporting the protective effect of any breastfeeding are Falth Magnusson et.al[9]. and Greco et al.[10]

But the total duration of breastfeeding has no protective effect over CD, which is supported by a Swedish study by Welander et al,[11] who prospectively collected data from the ABIS (All Babies in Southeast Sweden) study and detected no association between breastfeeding duration and subsequent development of CD.

Regarding the frequency of breastfeeding, my study shows that both partial and exclusive breastfeeding has protective effect, as previously suggested by Peter et al,[12] which shows significant protective effect on the incidence of celiac disease was suggested by the breast-feeding practices (partial breastfeeding as well as exclusive breast-feeding).

In TEDDY, the time to first introduction to gluten introduction was not an independent risk factor for developing CD which is found to favouring my study.[13] Another study favouring my

study is the RCT conducted by Lionette et al,[7] which says either the delayed introduction of gluten nor breast-feeding modified the risk of celiac disease among at-risk infants, although the later introduction of gluten was associated with a delayed onset of disease. But one study that showed an association between age at gluten introduction and CD is that by Norris et al.[14]

The most significant part of my study is breastfeeding at the time of gluten introduction, which suggests the protective effect of breastfeeding at the time of cereal introduction, which is favoured by Ivarsson et al,[15] study of 12 years two Swedish cohorts at 2013, which differed in infant feeding, and our findings suggest that gradual introduction of gluten in small amounts during ongoing breastfeeding is favorable. Moreover, prolonged breast feeding during the introduction of gluten-containing feeding has been associated with a reduced risk of developing CD in infancy as suggested by Shamir et al and Silano et al.[16]

Conclusion

Case-control studies are an efficient design for rare diseases, but methodological limitations must be considered. The results of this case-control study suggest that the incidence of the disease is more in girls than boys, The delayed diagnosis of atypical cases, the protective effect for partial and exclusive breastfeeding on the incidence of celiac disease and the introduction of cereals/solids at the background of breastfeeding has the most significant effect on the occurrence of celiac disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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