مجلة جامعة بنغازي العلمية (2018) مجلد 31(2): صفحة 193-207

Scientific Journal of University of Benghazi (2018) vol. 31 (2):pp 194-208

http://sjuob.uob.edu.ly

Clinical presentation of Celiac disease among Libyan children :

The effect of Exclusive Breastfeeding

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Abstract

Celiac disease (CD) is a chronic small intestinal immune-mediated enteropathy triggered by exposure to dietary gluten in genetically susceptible individuals. It is claimed that prolonged breastfeeding is associated with a reduced incidence of symptomatic disease or alteration of its classical presentation. Aims, to explore the effect of EBE during the first 6 months of life on the presentation of celiac disease. Case series study was adopted, the sample was collected from Gastroentrology clinic of Benghazi Pediatric Hospital between 1st November 2011 up to April 2012. The data was collected using a validated questionnaire, Libyan children with proven intestinal biopsy were exclusively included. The data were entered into SPSS version 21. A sample of 100 child with mean age 10.5 years (± 4.45 years), 29% male and 71 % female, 37% have positive family history, age of symptoms extends from 4 months to 15 years. The duration of exclusive breastfeeding varies between few days to 18 months, earlier age of starting of gluten was 2 months. At diagnosis the most frequent symptoms were diarrhea and short stature (30% and 25% respectively). Age of diagnosis and mode of presentation do not significantly varies between the breastfed and other children. EBF has no significant correlation neither with age of disease symptoms, age of diagnosis nor with type of disease presentation. Conclusions, The results suggest that EBF does not modify CD in its presentation, neither the age of symptoms nor the age of diagnosis, the sample of this study presented more frequently with diarrhea and short stature.

Key-words: Celaic, exclusive breastfeeding, autoimmune, gluten

الملخص:-.

يعتبر مرض السيليك من أمراض الأمعاء الدقيقة المناعية والذي يحدث نتيجة لتناول الجلوتين في الأشخاص الذين لديهم استعداد وراثي للمرض. يعتقد أن الرضاعة الطبيعية المطلقة مرتبطة بتغيير أعراض المرض أو إخفاء اعراضه لفترة طويلة . الهدف من الدراسة هو بحث مدى تأثير الرضاعة الطبيعية المطلقة في الست أشهر الأولى من حياة الطفل على طريقة ظهور الأعرض. ولتحقيق هذا الهدف تم تجميع عينة من مرضى السيليك يبلغ عددهم 100 طفل من مستشفى الأطفال ببنغازي من بداية نوفمبر 2011 الى ابريل 2012. متوسط عمر الأطفال كان 10 سنوات ونصف (± 4.45 سنة). 29 % ذكور و 71% إناث, 37 % منهم لديهم تاريخ مرضي في الأسرة , ووقت ظهور الاعراض تراوح بين 4 شهور الى 18 سنة , تم تناول الجلوتين من عمر شهرين كحد أدنى . واستمرت الرضاعة الطبيعية المطلقة مدة تتراوح بين أيام قليلة الى 18 شهر كحد أعلى. وتم توزيع استبيان على مرضى السيليك أو ذويهم لجمع البيانات. بعد التحليل الاحصائي للبيانات أظهرت الدراسة حسب العينة المدروسة أن الرضاعة الطبيعية المطلقة لا تؤثر في المرض من حيث ظهور الأعراض ولا وقت التشخيص . وأغلب المرضى في هذه الدراسة كان الإسهال وقصر القامة هما العرضيين الأساسيين للمرض (30% و 25% على التوالي).

الكلمات المفتاحية: السيليك, الرضاعة الطبيعية المطلقة, مناعة ذاتية, جلوتين .

1. Introduction:

Celiac disease is a chronic small intestinal immune-mediated enteropathy triggered by exposure to dietary gluten in genetically susceptible individuals (Ludvigsson et al., 2001) The main storage protein found in wheat, rye and barley which belong to the same tribe called triticeae that diverged from oats belonging to the aveneae tribe (Kupfer and Jabri, 2012). Although some studies reported that oats is safe, a few celiac patients have oats prolamine–reactive mucosal T cells that can cause mucosal inflammation (Arentz-Hansen et al., 2004) . The disease represents a lifelong disorder that requires individuals to completely avoid ingestion of gluten (. Hill, 2005 and Greenand Jabri, 2003).

Traditionally; celiac disease has been thought to be a rare disorder in some western societies. In the US, for instances, it is reported that the disease affecting only 1 in every 2,000 to 5,000

Child (Book, 2002), consequently there are few data concerning its clinical presentation. However, serologic screening in the United States has revealed a surprisingly high prevalence which suggests that many American children with celiac disease are going undiagnosed (Fasano et al., 2003 and Hoffenberg et al., 2003)

On the other hand, European studies have reported that the disease represents a common health burden. Furthermore, its prevalence is strikingly increasing recently hence, prevalence rates of 1 % have been described in some studies (Bingley et al., 2004). Whereas, there is no recent published data regarding the prevalence of celiac disease in the east of Libya, the area from which the study sample has been collected. However, there are some unpublished work in 2007 suggesting that its prevalence is about 1 : 1329.

The typical form of celiac disease presents with GI symptoms that characteristically appear at age 9-24 months. Symptoms begin at various times after the introduction of foods that contain gluten. Infants and young children typically present with chronic diarrhea, anorexia, abdominal distension, abdominal pain, poor weight gain or weight loss, and vomiting. Severe malnutrition can occur if the diagnosis is delayed. (Kaukinen et al., 2010).

Behavioral changes are common and include irritability and an introverted attitude. Rarely, severely affected infants present with a celiac crisis, which is characterized by explosive watery diarrhea, marked abdominal distension, dehydration, hypotension, and lethargy, often with profound electrolyte abnormalities, including severe hypokalemia. An increasing number of patients are being diagnosed without typical GI manifestations at older ages. A reasonable assumption is that approximately 70% of patients with newly diagnosed celiac disease do not present with the typical major GI symptoms (Kaukinen et al., 2010).

In infants and toddlers, GI symptoms and failure to thrive predominate, whereas, during childhood, minor GI symptoms, inadequate rate of weight and height gain, and delayed puberty tend to be more common. In teenagers and young adults, anemia is the most common form of presentation. In adults and in the elderly, GI symptoms are more prevalent, although they are often minor (Kaukinen et al., 2010).

The main Extra intestinal manifestations of celiac disease

Dermatitis herpetiformis, Dental enamel hypoplasia, Iron-deficiency anemia (IDA), Short stature and delayed puberty, Chronic hepatitis and hyper-transaminasemia, Arthritis and arthralgia, Osteopenia and osteoporosis, Neurological problems, Psychiatric disorders, Subfertility or infertility (Kaukinen et al., 2010).

It is claimed that prolonged breastfeeding is associated with a reduction in the incidence of symptomatic disease or alteration of its classical presentation (D'Amico et al., 2005). So that the objectives of this study are: (1) Investigate the effect of EBF on the age of symptoms, age of diagnosis and mode of presentation of celiac disease in term of typical or atypical form. (2) Explore the socio-demographic characteristics of biopsy proven celiac disease patients. (3) Find the relationship between socio-demographic characteristics and clinical picture of celiac disease patients. with the aim to develop recommendations that could be a valuable resource for health practitioners who are in charge of providing health care to celiac disease individuals and their parents.

To accomplish this, a case series approach has been proposed. This allows the researcher to study the effect of exclusive breast feeding on the presentation of the disease. Information from the participants or their parents who agreed to take part in this study were collected through modified form of a questoinnire (appendix 1) , in which participants were given the opportunity to answer the questions related to their illness and other related characteristics. Following this the researchers analyzed the data using SPSS. The study will offer recommendations to potential health care practitioners aligned to celiac disease diagnosis and management that could help reduce the problem of late diagnosis and its consequences for both patients and their families. Hereafter reducing the cost of complications treatment and the duration of staying at hospital.

2. Patient and Methods:

Study design and settings

Case series study design was adopted to achieve the aims of this study, the sample was collected from Gastroentrology clinic of Benghazi Pediatric Hospital, this design has the advantages of ease in assembling the study population and collecting data, with reduced logistic efforts and thus the cost, the characteristics of several patients with celiac disease are

described but are not compared with those of a reference population, although it is a weak evidence design, it can be a base for analytic studies in the future.

Type of sample

Convenient sample was recruited in this study from 1st November 2011 up to April 2012.

Inclusion criteria

1-Intestinal biopsy is the gold standard of diagnosis; therefore only cases with confirmed biopsy were included in the sample for further analysis.

2- Age limit up to 18 years.

3- Libyan nationality was exclusively incorporated.

Data collection tool

The data was collected using a questionnaire (appendix 1) extracted from a study conducted in the USA to investigate the same question of the current study (D'Amico et al., 2005). The questionnaires were completed through an in depth interview in addition to phone call for any further clarification when needed.

Statistical test

The data were entered into a computer database using SPSS version 21 for analysis, descriptive statistics were extracted according to variable types so that, continuous data such as age, duration of breast feeding were displayed as mean, standard deviation and range, while categorical data such as sex, residence and type of formula were displayed as frequencies, percentage and plotted as bar or pie charts for clarification.Then some inferential statistics were calculated to find the correlation between the main effect (EBF) and the possible outcomes (age of CD presentation, type of presentation), a significance level (P value) of less than 5% was considered as cutoff point.

Ethical issue:

A verbal consent was obtained from all participants and their families prior to data collection, in addition this study contain no risk or exposure for the patients and the date kept anonymous to maintain the privacy of the patients and their personal information.

3. Results:

1. Descriptive analysis results:

According to the data collected from the sample of 100 Celiac disease cases, the mean age is 10.5 years (SD±4.45years), it follows normal distribution curve , 29% male and 71 % female (figure 1, 2). More than half of the sample (53%) are from Benghazi, the remaining are from cities and villages at the east and central region of Libya, 37% of the respondents have positive family history of celiac disease. Although 22% have positive family history of other autoimmune diseases, only 6% of the participants have other illness mainly diabetes mellitus, one case has vitiligo, age of symptoms appearance extends from 4 months to 15 years with mean age of around 3.3 years, the period between symptoms onset and confirmed diagnosis extend from one month up to 11 years (mean =29 months) as shown in table 1.

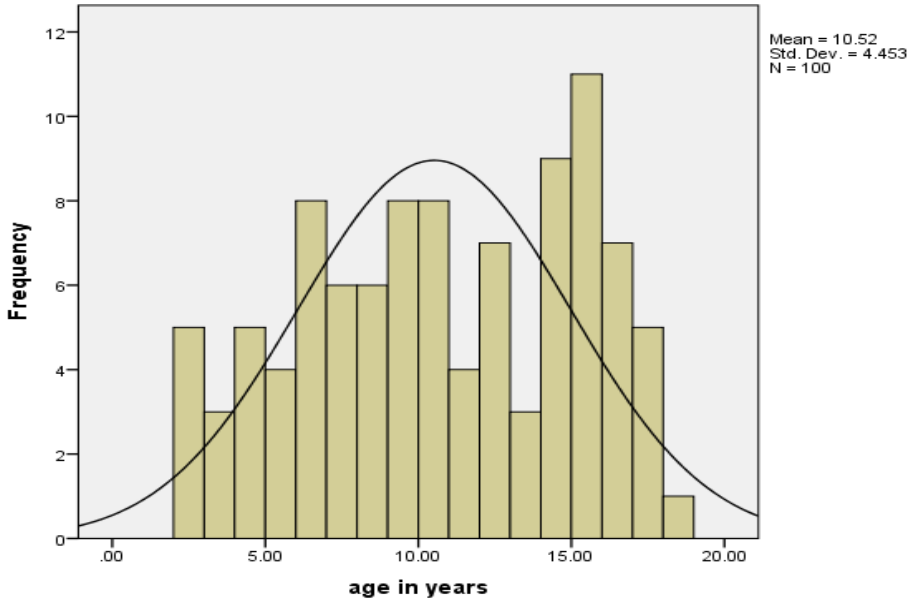


Figure (1): Age Distribution

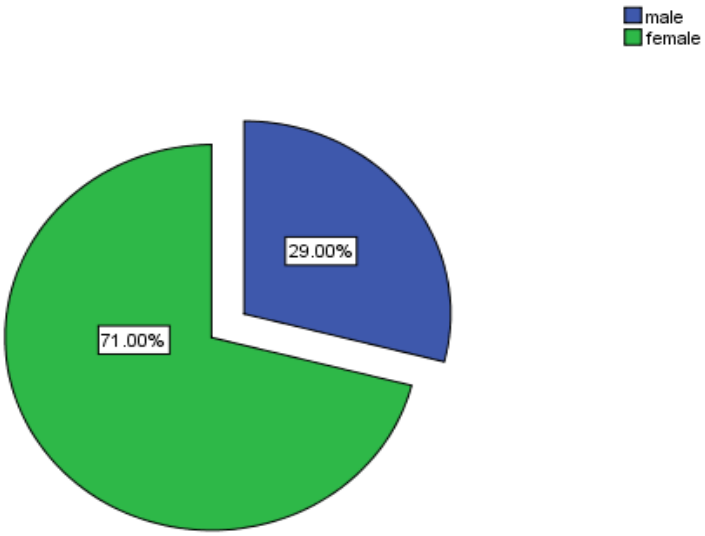


Figure (2): Gender Distribution

Table (1): Characteristics of Biopsy-Proven Celiacs (n=100)

Patient Characteristics	
Male to female ratio	**1:2.4**
Residence in Benghazi	**53%**
Mean age of onset of symptoms	**35.6 months**
Mean duration of symptoms before diagnosis	**29 months**
Mean period between symptoms onset and confirmed diagnosi	**36 months**
Family history of celiac disease	**37%**
Family history of other auto immune diseases	**22 %**
History of other illness	**6%**

Maximum duration of all breast feeding (exclusive and any) was 30 months (mean 7.8 months, (SD ±7.3), percentage of any breastfeeding 80% , while the duration of exclusive breast feeding varies between few days to 18 months with mean of 4 months (table 2), 28% breastfed for 5-6 months and the remaining 14 % were breastfed for more than 6 months.

Earlier age of starting of gluten containing diet was 2 months and maximum age was 2 years (mean = 7.2 months), 75% of the sample has been formula fed. Among them, 73 child was fed with fortified cow milk based formula, the remaining are other specific types of formulas namely soya milk or lactose free formula, Moreover 20% of the sample has been exclusively formula fed (not received breast milk at all).

Common symptoms and presenting complaint at diagnosis

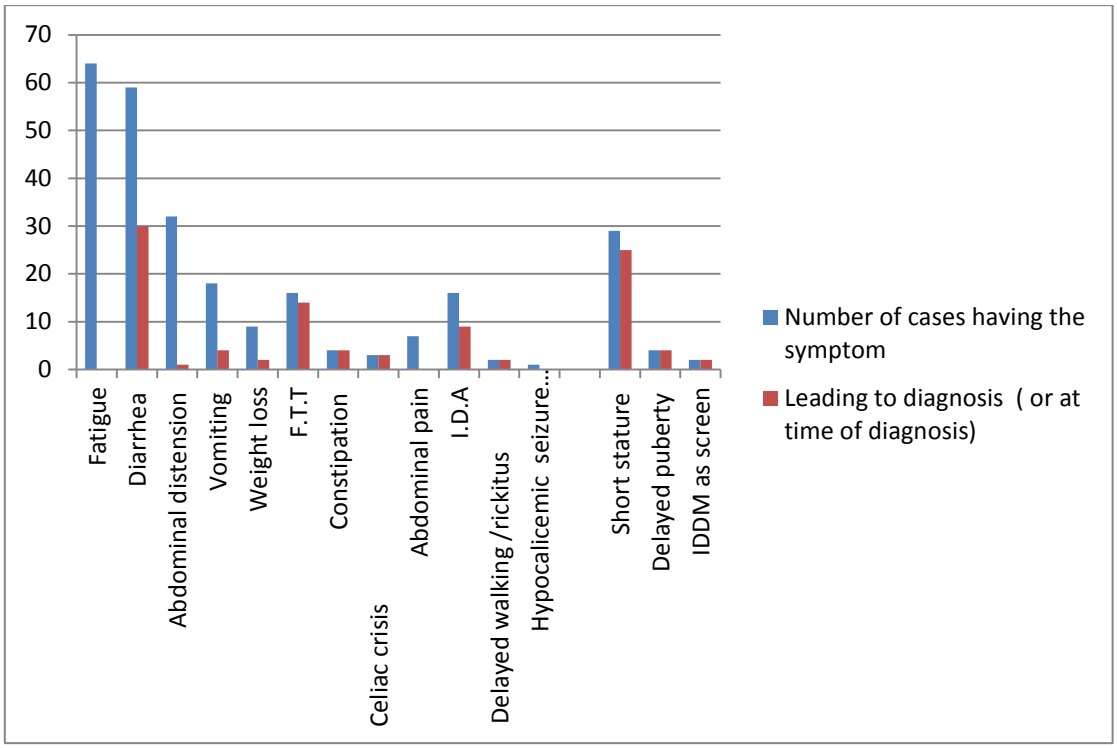
The sample of celiac disease reported a wide range of symptoms (figure 3), some of them non-specific symptoms such as fatigue which is reported by 64% of the cases and weight loss in 9% ,or symptoms related to gastro-intestinal tract such as diarrhea (59% of the cases), abdominal distension (32%), vomiting (18%), abdominal pain (7%) and constipation (4%), some symptoms related to growth and development for example short stature (29%), failure to thrive (16%), delayed puberty (4%) and delayed walking (2%).

At time of diagnosis the most frequent symptoms were diarrhea 30% followed by short stature in 25% of the cases. In general, less than half of the cases (48%) presented as typical picture of celiac disease, 27% of cases were atypical presentation. The remaining 25% presented by mixture of typical and atypical feature of celiac disease (figure 4).

Table (2) Feeding Practice of Biopsy-Proven Celiacs (n=100)

Feeding practice profile	
Mean duration of exclusive breast feeding	4 month*
Mean age at gluten introduction	7.2 months **
Formula feeding	75%
Fortified cow milk formula	73%
Compliance on gluten free diet	75

* SD ± 3.8 **SD ± 4 months



FTT : Failure To Thrive IDA : Iron Deficiency Anemia

Figure (3) The Most Common Symptoms and The Symptoms at Time of Diagnosis of CD in The Study Sample

Mode of CD presentation in both breastfed and formula fed respondents

The sample of this study shows that out of 100 participants 42 child received exclusive breast milk at least 5 month, of them 22 child had classical symptomes,14 non classical and 6 children presented with mixed picture of CD.

Contrary, in the 58 formula fed infants, 26 presented with classical mode of CD,13 non classical and the rest (19 child) presented with mixed features table (3). The mean age of symptoms emergence is 39 month in exclusive breastfed children versus 35.7 month in formula fed.

Diagnosis age and feeding

The mean age of CD diagnosis according to early feeding practice is 4 years in breast fed children compared to 5.5 years in formula fed individuals, this variation is statistically not significant in correlation assessment.

Table (3): Distribution of CD Cases According to Type of Feeding and Mode of Presentation (n =100)

Presentation of 100 respondents	Breast feeding	Formula feeding
Classical	22	26
Non classical	14	13
Mixed	6	19
Total	42	58

2. Correlation assessment

EBF is the main effect in this study. Therefore, it was engaged in bivariate correlation against child age of time of disease diagnosis, symptoms, and type of disease presentation. The analysis did not show any significant correlation between any of the three mentioned possible outcomes. However, a significant positive high correlation coefficient between EBF and age at gluten introduction was seen (r = 0.7, p value = 0.00), EBF duration is also significantly and highly correlates with formula feeding (r = 0.62, p value =0.00).

Disease diagnosis by biopsy and serology is significantly associated with positive family history of celiac disease, moreover age of diagnosis by biopsy and serology has significant correlation with positive history of other illness, while mode of presentation at diagnosis and age at resenting symptom just approaches the significance (r=0.053). Gender and residence of the patients are not associated with any significant differences in relation to the exposure or the outcome

4. Discussion:

Although Celiac disease is a well-known disease worldwide and affects the quality of life of children, there is a relatively little research addressing the size of this health problem in Libya, therefore this study was conducted to obtain information on children diagnosed with celiac disease attending the Pediatric hospital of Benghazi. A survey was used to collect the data with main aim is to know the impact of EBF on presentation of celiac disease.

According to the current study EBF do not have any significant effects neither on time or clinical presentation of celiac disease nor on the mode of disease presentation. Age at diagnosis of CD is earlier in breastfed infants compared to formula fed infants, this difference has no statistical significance in correlation assessment, which might be an add to the evidence found by Jansen and others who concluded that the appearance of CD symptoms depends on immune response of each child, i.e. it is subjected to individual variation after exposure to antigen (Jansen et al., 2014).

Significant positive high correlation coefficient between EBF and age of gluten introduction was seen, this could be attributed to another unmeasured variable like socio-economic status (SES) which could links the two unrelated factors together (figure 6). Therefore in the current survey the direct effect of EBF on CD might be confounded and masked by SES. Thus, it could not be accurately measured. Socioeconomic status is a complex variable which includes income, education and employment (Winkleby et al., 1992). a study conducted in Tanzania that emphasis on the influence of socio-economic status on breastfeeding practice found that employed mothers tend to exclusively breastfed their children more compared to other unemployed mothers (Maonga et al., 2016).

EBF duration is also significantly and highly correlates with formula feeding, this supports the assumption of the effect of financial status of the family (part of SES) on breastfeeding and the introduction of expensive formulas and biscuits.

Disease diagnosis by biopsy or serology and age of diagnosis are significantly associated with positive family history of celiac disease, moreover many cases were missed and diagnosed very late by searching the cause of delayed puberty, short stature or failure to thrive

These results suggest lack of doctor knowledge and awareness regarding the disease, which is compatible with many studies such as a study done in Central Italy which concluded that although CD is well known common chronic childhood disorder, its diagnosis is still lagging behind and the average interval between symptom onset and diagnosis remains long (14.2 months). Furthermore, one third of their sample reported previous incorrect diagnoses. (Altobell et al., 2013) The present study demonstrated that gender and residence of the child did not significantly influence the duration of EBF, this result is consistent with the Tanzanian study which confirmed that infants' characteristics like sex were not associated with EBF. (Maonga et al., 2016).

The most common symptom at time of diagnosis of CD in the sample of this survey is diarrhea followed by short stature. This finding contradicts with the Italian study in which diarrhea comes in the 7th order of clinical symptoms at CD presentation preceded by bloating gases and abdominal pain. Diarrhea is a very common childhood complaint occurs with variety of diseases and called paraentral diarrhea if the pathology is systemic (non-GIT disease like otitis media, tonsillitis…etc) (Altobell et al., 2013). This makes suspecting a celiac disease whenever the baby is having diarrhea is unpractical as many non – GIT diseases are presented with diarrhea, and could be one of the possible explanations for late diagnosis of CD. (Alberto et al., 2000).

5. Conclusion

The results suggest that EBF does not modify CD neither its presentation, age of symptoms nor the age of diagnosis. In addition, the sample of this study presented more frequently with diarrhea and short stature, as diarrhea is a very common childhood complaint this makes CD one of the diseases that diagnosed with a long gap between the symptoms and diagnosis, therefore poor quality of life and extended suffering is very frequent among children with CD.

Positive family history is associated with earlier diagnosis of the disease this point can be referred to limited doctors knowledge which leads to delay diagnosis in children with negative family history who are presented repeatedly with the symptoms and misdiagnosed each time.

6. Recommendations

1. Further analytical studies are recommended with a bigger sample to address this issue with considering all possible confounders perhaps the socio-economic status.
2. Addressing the true prevalence of CD in Benghazi and Libya is strongly recommended to support the studies and health care provision.
3. Raising the pediatrician awareness of the burden of late diagnosis of CD to avoid an inappropriate management is of paramount importance

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Appendix 1

OUTLINE OF QUESTIONNAIRE1{modified}

- Demographic and personal data
- Gender, date of birth
- Geographic origin,
- Feeding history—breast vs formula
- Duration of exclusive breast feeding
- Duration of any breast feeding
- Type of formula feeding
- Age at introduction of wheat and/or other gluten contain diet
- Family history of celiac disease
- Family history autoimmune diseases
- Pre -diagnosis data
- Symptoms……..
- Presence of associated diseases in patient…….
- Age at presentation of symptoms
- Duration of symptoms before diagnosis
- Main symptoms lead to diagnosis
- Diagnosis data:
- Age at diagnosis
- Method of diagnosis—biopsy vs. serology /or both
- Follow-up management
- Were family members screened for celiac disease?
- Gluten-free diet (GFD)
- Adherence to the diet
- Regular follow up in clinic