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Prevalence of celiac disease among children with malnutrition between 6-60 months of age in Childs central teaching hospital in Baghdad

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Abstract
Background: Celiac disease (CD), considered as a common chronic and genetic disease that caused by hypersensitivity to gluten. Failure to thrive (FTT), is one of three major clinical features of CD during childhood.
Objectives: The current study aimed to determine the frequency of celiac disease in children with malnutrition. To assess and compare the HLA geno typing of those has positive serology for celiac disease with other studies.
Patients and Methods: one hundered malnourished children (52 males, 48 females), age ranged between 6-60 months with the diagnosis of malnutrition according to WHO criteria who were currently attending the Rehabilitation Unit of Malnutrition at a Child's Central Teaching Hospital in Baghdad city during 13 months and from begging of September 2016 to end of September 2017, All patients were screened for CD using the IgA and IgGantitissuetransglutaminase antibody test(tTG).
HLA typing was performed in patients with positive IgA and IgG-tTG serology. A comparison was made between celiac and nonceliac according to age, gender, chief complain, clinical feature, residence, onset of complementary feeding and type of feeding.
Results: eleven of 100 malnourished patients (11%) had positive tTG antibodies, 8
(72.7%) patients were males and 3 (27.2%) were females, Among these 11 patients,(4) were only tTG IgA positive, one only tTGIgG positive and 6 positive for both (IgA, IgG) with male to female ratio 2.6:1, 90.9% of celiac patients carry DQ2, (27.3%) carry DQ8 and (18.1%) carry both DQ2 and DQ8. It was found that celiac disease were significantly higher at age group (37-60 months) and in those who had started early complementary feeding, abdominal distention and diarrhea were higher in celiac patients
Conclusion: At current study, the prevalence of CD in children with malnutrition was 11%.HLA typing was comparable to that of other studies. Since CD is an important cause of malnutrition in children, tTG and HLA typing is available tool that can be used for screening celiac disease at an earlier age.

Keywords: celiac, disease, failure to thrive

Introduction

Malnutrition or malnourishment is a condition associated with either consuming a diet without enough (under nutrition) or too much nutrients (over nutrition) resulting in different types of health problems [1]. However, in less developed countries, food malnutrition is often used specifically to refer to under nutrition [2]. Under nutrition can be due to lack of protein or deficiency in other dietary nutrients [3]. Moreover, the protein energy malnutrition can manifest as either marasmus, which is lack of proteins and other dietary nutrients whereas kwashiorkor, is just protein deficiency [4]. Several studies have indicated that under nutrition during pregnancy or before the first two years of life impacts negatively on both physical and mental development of children [5]. The main driver of malnutrition in developing countries is poverty leading to food insecurity while in developed countries it is the abundance of food leading to malnutrition associated with obesity [6]. However, recent studies indicate that even in developing countries there is double burden of malnutrition where children are presenting with both under nutrition and over nutrition [7]

It has been demonstrated that malnourished children have lowered resistance to infection; therefore, they are more likely to die from common childhood ailments such as diarrhoea l diseases and respiratory infections [2]. In addition, malnourished children that survive are likely to suffer from frequent illness, which adversely affects their nutritional status and locks them into a vicious cycle of recurring sickness, faltering growth and diminished learning ability [2, 4]. In developing countries, malnutrition is a major health problem [8]. Frequent and chronic attacks of malnutrition in early childhood have a potential negative impact on the physical and mental growth of children [9]. Moreover, malnutrition is associated with stunting (low height-for-age) which can cause chronic restriction of a child's potential growth [10]. In addition, malnutrition can result in severe acute malnutrition (SAM) defined by WHO and UNICEF by a weight-for-height index (WHZ) less than -3 z-score or a mid-upper arm circumference (MUAC) less than 115 mm, or presence of edema in children age below 5 years [6].

Significantly, the causal factors for stunting in children less than 5 years old, varies with age and are ecologically linked with each other [2].

This includes environmental factors in households such as household food security and healthy household environment that are important in long term in preventing stunting in children [2, 11].

In addition, the other household environment related to child

nutrition includes the knowledge and perception of caregivers, care givers age and food insecurity [12], child health and food selection [13], and household socio-economic status [14], infestations with ecto-parasites [2]. Studies have also shown that gender of the child is a determinant of malnutrition with females being more likely to suffer from malnutrition relative to males [2]. These intrahousehold environmental factors contribute to the neglect of children's needs, especially their nutritional status from birth to preschool [13].

Prevalence of malnutrition

Global trends indicate a decrease in diseases of undernutrition, while over nutrition is increasing. On the community level, economic status seems to influence the dual burden'sextent, with obesity increasingly affecting the already malnourished poor [15]. Significant worldwide challenges are posed by the various forms of under nutrition (stunting, wasting, micronutrient deficiencies) in children under five, pregnant women and the elderly. In 2010, an estimated 171 million children under five years of age were stunted, with almost all occurring in developing countries [16]. Although, the global prevalence of stunting has declined from 39.7% in 1990 to 26.7% in 2010, this trend has not been consistent in all regions of the world. Stunting in Africa has remained relatively unchanged around approximately 40%, Projections for 2020 indicate that the situation in Africa will not improve much, whereas prevalence in Asia and Latin America will continue to improve [15]. Also, micro-nutrient deficiencies in children under five years of age continue to be problematic, 47% are reported to be anemic and 33% are vitamin A deficient [17].

WHO classification of degree malnutrition

The World Health Organization (WHO) has developed criteria for the classification of moderate or severe malnutrition in children. These criteria are based upon the degree of wasting, stunting, and the presence of edema. The child's weight for his or her height, and the height for his or her age are expressed as Z-scores. Wasting and stunting are defined by the following (these diagnoses are not mutually exclusive):

Wasting (indicates acute malnutrition):

- Moderate wasting – weight/height Z-score <-2 to -3
- Severe wasting – weight/height Z-score <-3
- Stunting (indicates chronic malnutrition):
- Moderate stunting – height or length Z-score <-2 to -3
- Severe stunting – height or length Z-score <-3
- Malnutrition:
- Moderate malnutrition – moderate wasting or stunting
- Severe malnutrition–severe wasting, severe stunting, OR edematous malnutrition [18].

Celiac disease

Celiac disease (CD) is a systemic, immune-mediated disorder that primarily affect small intestine and triggered by dietary gluten in genetically susceptible individuals. Gluten is a water insoluble protein complex which is found in wheat, rye and barley. A significant finding of celiac disease is villous atrophy of small intestine which leads to nutrient malabsorption and broad range of clinical manifestations [19]

Epidemiology of celiac disease

Prevalence of celiac disease is approximately 0.6 to 1.0% worldwide, with wide regional differences [20]. A recent multinational study in Europe found a big difference in CD prevalence with the lowest prevalence (0.3%) in Germany and the highest in Finland (2.4%) [21]. The frequency of celiac disease is increasing in many developing countries also. India has CD predominance in northern part of country where the prevalence is around 1.04% [22]. CD is prevalent in the first-degree relatives of patients with CD and it has been found to be 4.8% [23]. Genetic background plays a key role in the predisposition to the disease. Majority (90%) of celiac disease patients express HLA-DQ2 haplotype (DQA1 0501/DQB1 0201). Another 5% of patients express HLA-DQ8 haplotype (DQA1 0301/DQB1 0302) [24]. Children with HLA haplotype DR3-DQ2 homozygote are at higher risk for celiac disease especially early in childhood by the age of 5 years [25].

Most patients are carriers of the HLA-DQ2/DQ8 genes but these genes are also present in about 40% of the general population, and only a small percentage (2-5%) develops CD [26] this indicate that the HLA-DQ genotype is necessary but not solely responsible for the development of the disease [27].

Patients & Methods

Study design and period

prospective study design was employed
from September 2016 to September 2017.

Study area

The study was conducted in Rehabilitation Unit for Malnutrition at a Child's Central Teaching Hospital in Baghdad.

Sampling and data collection procedures

100 patients was collected (52 males and 48 females), for each patient enquiry sheet was filled including the following variables: age, sex, residency, chief complain, degree of malnutrition and other signs and symptoms: Diarrhea, vomiting, abdominal distention, edema, wasted muscle, and skin lesion.

Anthropometric measurements were also taken for all children aged 6-60 months to assess their nutritional status; Length of the child aged 6-23 months was measured in a recumbent position using a board with an upright wooden base and a movable headpiece. Height of children (24-60 months of age) was measured in a standing-up position using vertical board with a detachable sliding headpiece, and weight measure by beam balance scale for infant and digital scale for older children, their height and weight were measured and plotted on the growth chart of WHO (weight for height\ length)and assessing degree of malnutrition according to WHO program (mild -2SD, moderate -3SD, severe -4SD) [18].

Each patient has been sent for complete blood picture and blood serology for tissue transglutaminase antibodies (tTG) IgA and IgG outside our hospital in different laboratory because not available at that time. Patients with a positive serology screen were recommended for HLA typing gene done by PCR in Alkarama Teaching Hospital.

The diagnosis of celiac disease was based on serology and HLA DQ2, DQ8 in association with clinical signs and symptoms according to the criteria proposed (53, 54, 36, 69). All serum samples have been collected at the time of diagnosis when the patients were receiving normal diet without any restrictions.

Inclusion and exclusion criteria

Inclusion criteria

All children age 6-60 months old who were malnutritioned patients.

Exclusion criteria:

1. Children below 6 months of age
2. Children with chronic disease (cerebral palsy, renal failure, heart disease, endocrine disease).

Statistical analysis

- Data entry and analysis were performed using SPSS (statistical package for Social Sciences) version 24 and microsft excel.
- Means, stander deviation and frequencies were calculated.
- The data presented as frequency and percentage tables and pie and bar charts were used also.
- t Test of significance of association was performed to assess relations between categorical variables.
- A level of less than 0.05 was considered as significance.

Results

Results: A total of 100 malnutritioned patients were attended the rehabilitation unit of malnutrition in the a Child's Central Teaching Hospital during period from September 2016 to September 2017. The mean age of our cases was 19.69±14.33 months (range 6–60 months), male to female was 2.6:1, there was 52% of patients males and 48% of patients females, 50% of patients from urban and 50% from rural area,33% of patients with -2SD,45% with -3SD and 25% with -4SD,60% of patient complain from weight loss, 29% from diarrhea and 11% from vomiting, 67% of patients with muscle wasting, 21% with abdominal distention, 9% with edema and 3% with skin lesion, 62% of patients started complementary feeding before 4 months and 38% started after 4 months, 13% of patient takes exclusive breast feeding,59% bottle feeding and 28% takes mixed feeding. Among these 100 patients patients (11%) were celiac. In our study, there was no statistical difference between celiac and nonceliac according to gender but there was highly statistically significant difference between the ages of celiac and nonceliac, 4 /11 (36.4%) celiac children and 71/89(79.8%) non celiac children were in the age group of less than 24 months, 1/11(9.1%) celiac children and 7/89(7.7%) non-celiac were between 24-36 months, 6/11(54.5%) celiac children and 11/89(12.3%) non celiac children between 37-60 months. The sero-prevelance tissue transglutaminase (tTG) was positive > 10 upper limit of normal found to be (11%). 8 patients were males and 3 were females, Among these 11 patients, (4) were only tTG IgA positive, one only tTGIgG positive and 6 positive for both (IgA, IgG).10/11(90.9%) of patients carry HLA genotype DQ2 which encoded by (DQA1*05/DQB1*02) alleles, 1/11(10%) not carry DQ2, 2/11 (18.1%) carry both (DQ2,DQ8),3/11(27.3%) carry DQ8 which encoded by (DQA1*0301/DQB1*0302) alleles. there was male sex predominant in celiac patient 8/11 (72.7%) and female sex predominant in nonceliac 44/89(49.4%) but without statistical significance (p-value = 0.145). There was no statistically significant association with child residence (51.7%) of non-celiac and (36.4%) of celiac from urban area, (48.3%) of non-celiac and (63.4%) of celiac from rural area (p-value =0.338), the degree of malnutrition 32.6 % of non-celiac patients and 36.4 % of celiac patients with -2SD, 43.8% of non-celiac and 27.3% of celiac with -3SD, 23.6% of non-celiac and 36.4% of celiac patients with -4SD without statistical significant (p-value =0.517). there was statistically significant association with the chief complain and signs and symptoms 64% of non-celiac and 27.3% of celiac complaining from weight loss, then diarrhea. 63.6% of celiac and 24.7% of non-celiac complaining from diarrhea, 11.2% of non-celiac and 9.1% of celiac complaining from vomiting which is higher in non-celiac than celiac p-value =0.025, muscle wasting were noted in 63 (70.8%) of non-celiac and 4 (36.4%) of celiac patients. abdominal distension were noted in 12 (13.5%) of non-celiac and 9 (81.9%) in celiac patients, edema were noted in 10 % of non-celiac and no celiac patients have edema, skin lesion was found in 2.25% of non-celiac and 9.1 % in celiac patient p- value =0.000. Also there was significant association with the age of complementary feeding 10 (90.9%) celiac children and 52(58.4%) started before 4 months of age and 1 (9.1%) celiac and 37 (41.6) non celiac started after 4 months p-value = 0.036.and there was no significant association with the type of feeding 13(14.6%) of non-celiac and no one of celiac patients was taken exclusive breast feeding, 54(60.7%) of non-celiac and 5(45.4%) of celiac was taken bottle feeding, 22(24.7%) of non-celiac and 6 (54.4%) of celiac was taken mixed feeding p-value =0.078.

Discussion

Early and correct diagnosis of CD is critical. Early diagnosis is essential to avoid complications like local malignancies, other autoimmune disorders, strictures and ulceration. Correct diagnosis is important because of strict lifelong adherence to gluten free diet. Children

Presenting with atypical form of CD are usually missed. Strong suspicion and screening is essential [28].

The prevalence of CD in children with malnutrition in rehabilitation unit of malnutrition in the a Child's Central Teaching Hospital during period from September 2016 to September 2017 was 11% (at least one out of 9). In a study in Iran, reported by Taheri *et al* (2017), the CD prevalence was 8.8% in children with unexplained FTT is close to our study [29], and the prevalence is lower than that a study in India, done by Rana *et al* (2010) which was 24% from one to twelve years in children with unexplained FTT [28]. the mean age of our cases was 19.69 ± 14.33 months and mean age at diagnosis of celiac disease was 37.09± 17.01 months, while the mean age of diagnosis in Iran study done by Taheri was less than 24 months, It may be explained on the basis of late diagnosis of celiac disease.

Present study showed the male predominance (8 boys & 3 girls) without significance. This could be due to better care and attention given to males in our country who are brought earlier to the hospital. Late detection is due to poor suspicion, atypical presentations and non-availability of diagnostic tools. our study is similar to study in India reported by Rana *et al* [28]. In serology, anti tTGA was positive in 11 (100%) cases of celiac disease is similar to Indian study reported by Rana *et al* [28], also in other studies published in nelson textbook of pediatrics the sensitivity is 100% [27]. this study all positive serology carry DQ2 and or DQ8,90.9% of celiac patients carry DQ2gene which encoded by (DQA1*05/DQB1*02) alleles and 27.3% of celiac patients carry DQ8 which encoded by (DQA1*0301/DQB1*0302) is comparable to other Iraqi study 95% of Iraqi celiac patients have DQ2 and/or DQ8 and 5% have no DQ2 or DQ8 alleles,

reported by Hameed *et al* (2016) [30]. the results of this study are close to the results that obtained by Mostafa *et al* (2012)when they studded the signature of HLA class II genes in celiac Sudanese patients and found that frequency of HLADQB1* 0201 allele (HLA-DQ2) was found in 81.4% of Sudanese celiac patients, while, HLA-DQB1*0302 allele (HLA-DQ8) was seen in 17.14% of those patients [31]. and also similar to Iranian study reported by Rafeey et at (2014), found HLA-DQ2 was identified in 92.3% patients, and HLA-DQ8 was identified in 11.53% patients [32]. The common clinical presentation observed in celiac patients were failure to thrive (100%) then gastrointestinal symptoms such as abdominal distension (81.9%), diarrhea (63.6%), vomiting (9.1%) this result was close to Rana *et al* [70]. diarrhea found (56%) and vomiting (25%) and similar to other Indian study done by pooni *et al* (2006) which found failure to thrive (90%) [33]. Most of celiac patients from rural region in our country, it may be explained on base the early begging of complementary feeding. Anemia was present in (63%) of celiac patients, it is similar to Rana *et al* [28]. Breast feeding had a protective role in preventing development of celiac disease, in our study suggest that breast feeding may offer protection against the development of CD, is comparable with a study reported by Akobeng *et al* (2006) [34], which reported protection against CD with longer duration of breast feeding, and study done by Radlovic *et al* (2010) found Longer breast feeding and continuation of breast feeding after gluten introduction delay the onset of classic celiac disease. On the other hand, neither breast feeding nor the timing of gluten introduction affects the severity of celiac disease [35].

The early introducing of gluten increase risk of celiac disease, in our study (90.9%) of celiac patients start early complementary feeding before 4month and (9.1%) of patients started later after 4months,

It is noteworthy that, in the Italian multicentre study, the group of baby girls (but not boys) at high genetic risk of CD, who were introduced to gluten earlier (at 6 months) [36], had a higher prevalence of CD even at 5 years of age. Similarly, in the multicentre European trial [37], the girls (and again, not the boys) in the group where gluten was introduced early (at 4 months) had a higher prevalence of CD (21%) at 5 years of age than those who were first exposed to gluten at 6 months (8.5%).

Similarly, in the multicentre European trial [37], the girls (and again, not the boys) in the group where gluten was introduced early (at 4 months) had a higher prevalence of CD (21%) at 5 years of age than those who were first exposed to gluten at 6 months (8.5%).

in this study, there was relationship between celiac disease and early introduction of gluten, most of our patients started before 4 months, two study found a correlation between the time of gluten introduction and development of CD.

Norris *et al* (2005) [38], found an increased risk for both early and late gluten introduction while Strødal *et al* (2013) [39], reported an increased risk for CD when gluten is introduced after 6 months of age and a higher risk in children breastfed after 12 months age.

The result of study done by aronsson *et al*. (2015), neither the early (<17 weeks). nor the delayed introduction of gluten-containing cereals (>26 weeks) is a risk factor for the later development of CD [40] and also Italian study done by lionetti et at. (2014) found neither 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 [41].

Conclusion

1. 1.There is a high prevalence of Celiac disease in malnutrition. Screening for Celiac disease should be an essential part of work-up in all children with malnutrition.
2. The early introduction of gluten before 4 months is increase the risk of development of celiac disease.
3. Breast feeding may offer protection against the development of CD. Breast feeding associated with reduced risk of developing CD
4. 4.celiac disease can be virtually excluded in individual lacking HLA DQ2, DQ8 or both.

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