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GLUTEN ALLERGY (CELIAC DISEASE) WITH MALNUTRITION IN CHILDREN BETWEEN 6 MONTHS TO 5 YEARS CENTRAL TEACHING HOSPITAL OF PEDIATRICS

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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 hundred 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 IgG antitissue transglutaminase antibody test(tTG). HLA typing was performed in patients with positive IgA and IgG-tTG serology. A comparison was made between celiac and non celiac 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 tTG IgG 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.

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INTRODUCTION

What is malnutrition?

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 under nutrition, while over nutrition is increasing. On the community level, economic status seems to influence the dual burden's extent, 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].

Pathophysiology of malnutrition

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life. This process is called reductive adaptation. Fat stores are mobilized to provide energy. Later protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs and by reducing inflammatory and immune responses [18].

These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.
- Heat production is less, making the child more vulnerable to hypothermia.
- The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.
- The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.
- Sodium builds up inside cells due to leaky cell membranes and reduced activity of the sodium/potassium pump, leading to excess body sodium, fluid retention, and edema.
- Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.
- Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.
- The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
- Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
- Immune function is impaired, especially cell-mediated immunity. T he usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection [18].

Clinical manifestation of malnutrition

History: Low intake of calories or an inability to absorb calories is the key factor in the development of kwashiorkor. A variety of syndromes can be associated with kwashiorkor. [19] This can include a rice milk diet used to treat atopic dermatitis. [20] In children, the findings of poor weight gain or weight loss; slowing of linear growth; and behavioral changes, such as irritability, apathy, decreased social responsiveness, anxiety, and attention deficit may indicate protein-energy malnutrition. In particular, the child is apathetic when undisturbed but irritable when picked up. Kwashiorkor characteristically affects children who are being weaned. Signs include diarrhea and psychomotor changes. Kwashiorkor was reported in an infant presenting with diarrhea and dermatitis, due to infantile Crohn disease. [21] The diarrhea and dermatitis improved in 2 weeks with treatment. "Cupping" (placing suction cups on the body to cure disease) on the abdomen in patients with diseases resulting in abdominal swelling (eg, kwashiorkor) can give interesting clinical presentations. [22]

Physical: In marasmus, the child appears emaciated with marked loss of subcutaneous fat and muscle wasting. The skin is xerotic, wrinkled, and loose. Monkey facies secondary to a loss of buccal fat pads is characteristic of this disorder. Marasmus may have no clinical dermatosis. However, inconsistent cutaneous findings include fine, brittle hair; alopecia; impaired growth; and fissuring of the nails. In protein-energy malnutrition, more hairs are in the telogen (resting) phase than in the anagen (active) phase, a reverse of normal. Occasionally, as in anorexia nervosa, marked growth of lanugo hair is noted. Kwashiorkor typically presents with a failure to thrive, edema, moon facies, a swollen abdomen

(potbelly), and a fatty liver. When present, skin changes are characteristic and progress over a few days. The skin becomes dark, dry, and then splits open when stretched, revealing pale areas between the cracks (ie, crazy pavement dermatosis, enamel paint skin). This feature is seen especially over pressure areas. In contrast to pellagra, these changes seldom occur on sun-exposed skin. Depigmentation of hair causes it to be reddish yellow to white. Curly hair becomes straightened. If periods of poor nutrition are interspersed with good nutrition, alternating bands of pale and dark hair, respectively, called the flag sign, may occur. Also, hairs become dry, lusterless, sparse, and brittle; they can be pulled out easily. Temporal recession and hair loss from the back of the head occur, likely secondary to pressure when the child lies down. In some cases, loss of hair can be extreme. Hair can also become softer and finer and appear unruly. The eyelashes can undergo the same change, having a so-called broomstick appearance. Nail plates are thin and soft and may be fissured or ridged. Atrophy of the papillae on the tongue, angular stomatitis, xerophthalmia, and cheilosis can occur .Inflammatory bowel diseases, such as Crohn disease and ulcerative colitis, may also produce skin manifestations secondary to malnutrition. [23].

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):

1. Moderate wasting – weight/height Z-score <-2 to -3
2. Severe wasting – weight/height Z-score <-3

Stunting (indicates chronic malnutrition):

1. Moderate stunting – height or length Z-score <-2 to -3
2. Severe stunting – height or length Z-score <-3

Malnutrition:

1. Moderate malnutrition – moderate wasting or stunting
2. Severe malnutrition – severe wasting, severe stunting, OR edematous malnutrition[24].

Risk factors

Risk factors for under nutrition range from distal broad national scale determinants to proximal individual specific and factors which effect at various age and periods of life. National socioeconomic and political determinants have a bigger impact and include political stability, economics, food security, poverty, and literacy, among others. Natural disasters including famine, floods, and other emergencies have detrimental effect, maternal education is associated with improved child-care practices related to health and nutrition, and reduced odds of stunting, and better ability to access and benefit from existing facilities. Worrisome food insecurity is obviously critical, but a factor that is potentially even more important (especially for children with marginal intake) is the inability to absorb what they do take in because of repeated or persistent intestinal infections. Severe infectious diseases in early childhood, such as measles, diarrhea, pneumonia, meningitis, and malaria, can cause acute wasting and have long-term effects on linear growth. But the most important of these infections is diarrhea; hence, the need for understanding the impact and mechanisms of malnutrition and diarrhea, which forms a vicious cycle of enteric infections worsening and being worsened by malnutrition. Several recognized processes by which enteric infections cause malnutrition, range from well-recognized anorexia and increased catabolic or caloric demands to direct protein and nutrient loss or impaired absorptive function [25]. Modifiable risk factors for childhood obesity include maternal gestational diabetes; high levels of television viewing; low levels of physical activity; parents' inactivity; and high consumption of dietary fat, carbohydrate, and sweetened drinks, yet few interventions have been rigorously tested [26].

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 [27].

Epidemiology of celiac disease

Prevalence of celiac disease is approximately 0.6 to 1.0% worldwide, with wide regional differences [28]. A recent multinational study in Europe found a big differences in CD prevalence with the lowest prevalence (0.3%) in Germany and the highest in Finland (2.4%) [29]. 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% [30]. CD is prevalent in the first-degree relatives of patients with CD and it has been found to be 4.8% [31].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) [32]. Children with HLA haplotype DR3-DQ2 homozygote are at higher risk for celiac disease especially early in childhood by the age of 5 years [33]. 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 [34] this indicate that the HLA-DQ genotype is necessary but not solely responsible for the development of the disease.

Genetic and pathogenesis of celiac disease

A genetic predisposition is suggested by the family aggregation and the concordance in monozygotic twins, which approaches 100%. The strongest association is with human leukocyte antigen (HLA) DQ2.5 (1 or 2 copies encoded by DQA1 *05 [for the chain] and DQB1*0 genes [for the chain]). Such a DQ molecule has been found to be present in more than 90% of celiac patients. The highly homologous DQ2.2 molecule confers a much lesser risk, while the data available on DQ2negative celiac disease patients indicate that they almost invariably are HLADQ8– positive (DQA1*0301/ DQB1*0302). A gene dosage effect has been suggested, and a

molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLADQ2 molecules on gluten peptide presentation to T cells. Other non HLA genes confer susceptibility to celiac disease. Genome wide association studies have shown risk variants in genes controlling T-cell activation and recruitment, some being shared with type 1 diabetes and other autoimmune diseases. Celiac disease is a T-cell–mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability and activation of innate immunity mechanisms precede the activation of the adaptive immune response Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favor the immunostimulatory and toxic effects of these sequences. Some gliadin peptides (p3143) are able to activate innate immunity, in particular they induce interleukin (IL)15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T- cell activation by other peptides presented in the context of HLADQ2 or HLADQ8 molecules. Gliadin specific Tcell responses are enhanced by the action of TG2; the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLADQ2 or HLADQ8. The pattern of cytokines produced following gliadin activation is clearly dominated by interferon γ (Thelper type 1 skewed); IL21 is also upregulated. Downstream T cell activation, a complex remodeling of the mucosa takes place, involving increased levels of metalloprotein ases and growth factors, which leads to the classical flat mucosa. A severe impairment of intraepitheleal lymphocytes (IELs) homeostasis is present in celiac disease. IL15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. Potential‖ celiac disease, in which TG2 antibodies can be detected in situ without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding of IgA deposits on extracellular TG2 in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut derived autoantibodies. [35]

Clinical Presentations of celiac disease

GI manifestations are understandably present and in many cases prominent, CD goes well beyond the GI tract, so that basically all systems and organs can be involved. GI signs and symptoms due to malabsorption, such as diarrhea and abdominal pain, are very common and easily lead to evaluation for CD, but they are by no means universally present. In fact, there is evidence [36] that CD presentation in children and teenagers has substantially changed over time, moving from a malabsorptive disorder causing GI symptoms and malnutrition to a more subtle condition causing a variety of extraintestinal manifestations. Thus, it is understandable that the term typical, reserved for the GI manifestations of CD, is quickly becoming obsolete, as the extraintestinal manifestations are now so prevalent they are no longer to be referred to as atypical [37]. It is indeed this variety of presentations, and the fact that CD may also be entirely asymptomatic, that is responsible for the dismal rate of diagnoses around the globe. reports the main clinical presentations of CD, with their prevalent age distribution. As it can be seen, the clinical manifestations can be protean, thus making the diagnosis not obvious in most cases. When CD has its onset in infancy and very early childhood, the GI manifestations prevail and can be quite aggressive, resulting in a clinical picture of malnutrition and failure to thrive, often associated with a protein-losing enteropathy. Subsequently, however, the onset may be more subtle, and more extraintestinal manifestations become common. GI Manifestations Abdominal pain and distention is probably the most common symptom of patients diagnosed with CD worldwide; in Canadian children, it has been reported in as many as 90 % [38]. Chronic or intermitted diarrhea, characterized by bulky, foul-smelling, greasy stool, is a very common symptom in children with CD. Its occurrence, however, is progressively becoming less frequent than in the past. Counter intuitively, long-standing and occasionally severe constipation can be the presenting manifestation in a significant amount of patients, children, as well as adults [39]. Other presenting symptoms related to the GI tract are vomiting (especially in infants and toddlers), weight loss, or failure to thrive leading particularly in cases of delayed diagnosis—to severe malnutrition and cachexia. More rarely, other disorders such as acute electrolyte disturbances, hypotension, and lethargy can accompany the clinical picture [40].

Extra intestinal Manifestations

Anemia in celiac children can be the end result of several different, and sometimes combined, causes; however, the single most common type of anemia is due to iron deficiency. IDA has in fact been reported in between 12 and 69 % of newly diagnosed celiac cases [41]. Even when asymptomatic, CD can lead to IDA; in a large series of patients with subclinical CD. The pathogenesis of iron deficiency in celiac seems to be straightforward; in fact, iron is absorbed in the duodenum and proximal jejunum, areas that are typically most affected in florid CD. Thus, most cases result from an impaired absorption of iron. While children with CD, once on a GFD, seem to be able to improve their bone mineral density more fastly [42]. Thus, there is a risk for suboptimal peak bone mass acquisition and a retarded growth in CD children, as the bone density increases until the end of puberty, when it reaches its peak value: if normal peak bone mass is not achieved, the individual is at a higher risk for developing osteoporosis [43]. Children with CD have a slightly increased frequency of neurological symptoms compared to controls. These include peripheral neuropathy and seizures and shortstature, arthritis and arthralgia, cardiomyopathy, isolated hypertransaminasemia, dental enamel hypoplasia, aphthous stomatitis, and alopecia [44].

Disease Associations

A series of recent large-scale epidemiological investigations, mostly, but not solely, conducted in Sweden, have also revealed a growing number of associated conditions that can occur with CD, although in most cases the reasons for such associations and the clinical relevance of them remain unclear. Among the conditions with increased prevalence in CD, in most cases related to adult patients, are: chronic obstructive pulmonary disease [45], eosinophilic esophagitis and gastroesophageal reflux disease [46], pancreatitis [47], hemochromatosis [48], idiopathic dilated cardiomyopathy [49], nephrolithiasis [50] adrenal insufficiency [44],Other

associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes [44].

Autoimmune Conditions

A strong association has also been shown between CD and autoimmune disorders, thought to be mostly due to a shared genetic component in the HLA region. The best described association is with type 1 diabetes mellitus (T1DM), where a prevalence of approximately 10 % of CD is found [51], autoimmune thyroid disease, Addison disease, Sjogren syndrome, autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis. [35].

Diagnosis of celiac disease

The diagnosis of celiac disease is based on a combination of symptoms, antibodies, HLA, and duodenal histology .The initial approach to symptomatic patients is to test for antiTG2 IgA antibodies and in addition for total IgA in serum to exclude IgA deficiency. As an alternative for total IgA in serum direct testing for IgG anti–deamidated forms of gliadin peptides antibodies can be performed. If IgA antiTG2 antibodies are negative and serum total IgA is normal for age (or IgG anti–deamidated forms of gliadin peptides antibodies are negative), celiac disease is unlikely to be the cause of the symptoms. If antiTG2 antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels. Patients with positive antiTG2 antibody levels <10 × upper limits of normal should undergo upper endoscopy with multiple biopsies. In patients with positive antiTG2 antibody levels at or >10 × upper limits of normal, blood should be drawn for HLA and EMA testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of celiac disease is confirmed, a gluten free diet is started and the patient is followed for improvement of symptoms and decline of antibodies. In the rare case of negative results for HLA and/or antiEMA in a child with TG2 antibody titers ≥10 × upper limits of normal, the different possibilities for false positive and false negative test results need to be considered. In these circumstances, the diagnostic workup should be extended, including repeated testing and duodenal biopsies. In totally asymptomatic persons belonging to high risk groups, celiac disease should always be diagnosed using duodenal biopsies. [35]**.** When biopsies are indicated at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten free diet. Gluten challenge and repetitive biopsies will only be necessary in selected cases in which diagnostic uncertainty remains [35]**.**

Table Sensitivity and specificity of celiac serologic tests [52].

Specificity	Sensitivity	Antibody
82–95%	79–90%	Anti-gliadin
97–100%	85–98%	Anti-endomysial
94–95%	95–98%	Anti-tissue transglutaminase(IgA)
94–98%	95–98%	Anti-deamidated gliadin (IgG/IgA)

HLA typing

Because more than 98% of people with celiac disease share the major histocompatibility complex II class HLA-DQ2 or HLA-DQ8 haplotype, the inclusion of HLA typing for these haplotypes is useful, especially in patients with equivocal biopsy results or negative serological tests, or for patients already on a gluten-free diet. People who do not have HLADQ2 or HLA-DQ8 haplotypes are unlikely to have celiac disease[53].Antibody testing and HLA testing have similar accuracies [54]. Only less than 1 % of patients who fulfill clinical criteriafor CD do not carry the DQ2 (including half heterodimer)nor the DQ8 alleles.Thus, in the clinical practice CDcan be virtually excluded in individuals lacking HLA-DQ2or -DQ8 [55].

Treatment of Celiac Disease

Treatment of CD involves a gluten free diet (i.e., a diet with no wheat, rye, or barley proteins) for lifelong. Although no gluten consumption is the ideal treatment for CD, a minimal degree of gluten contamination is difficult to avoid. The term ―gluten free‖ indicates a diet that contains gluten at such a low level as to be considered harmless [28] .the diet requires continuous education of patients and their families by both doctors and dieticians. A GFD will result in resolution of symptoms and repair of the intestinal damage over time in most people with CD, there is some evidence that people with untreated CD are more frequently deficient in a number of micronutrients compared to those without CD. Micronutrient deficiencies identified include iron, folic acid, and vitamin B12 and B6, copper, zinc and carnitine [56]. Low bone mineral density in people with untreated CD is believed to be partly due to vitamin D deficiency [57]

New Advances in Celiac Disease Treatment

Newer Strategies include developing agents to degrade or alter dietary gluten, prevent gluten peptides from crossing the epithelial barrier, inhibit tTG-induced potentiation of gliadin peptides or block gliadin binding to HLA-DQ2. Immune-based strategies involve preventing T-cell activation or innate and adaptive immune responses [58]. However only 2 agents are in late phase 2 clinical trials. ALV003 (2 recombinant, orally administered, gluten-specific proteases) is given orally, reduce the small intestinal mucosal injury caused by 6 weeks of gluten challenge [59]. Larazotide acetate, an oral peptide that modulates intestinal tight junctions, reduce symptoms in patients who are symptomatic despite a GFD [60]. Additional studies are underway to determine if these agents are safe and effective for patients with persistent symptoms and mucosal injury despite a continued GFD. These or other effective therapies could reduce the burden of GFD by decreasing the effects of inadvertent gluten exposure. CD is a lifelong inflammatory condition that affects multiple organ systems, so patients should be followed up routinely. Serologic testing should be done every 3-6 months until normal and then every 1-2 years. Nutritional evaluation for iron, vitamin B12, folate etc. should be done every 3-6 months until it becomes normal. Low bone mineral density is one of the more common extraintestinal manifestations of celiac disease, thyroid functions monitoring should be done first at diagnosis and then in every 1-2 years [61]. The optimal timing of the follow-up biopsy is unclear as all celiac disease patients do not reach mucosal recovery in 1 year time despite strict gluten-free diet. In patients with high dietary adherence, incomplete villous recovery after 1 year does not affect the clinical response or long-term prognosis so personalized approach is required to decide the optimal timing of the follow-up biopsy [62].

Non responsive celiac disease (NRCD)

NRCD may be defined as persistent symptoms, signs or laboratory abnormalities typical of CD despite 6-12 months of dietary gluten avoidance. NRCD is common, affecting from 7 to 30% of patients treated with a GFD for CD, there are many distinct etiologies including inadvertent gluten ingestion (the most common cause), other food intolerances (including lactose and fructose intolerance), small-intestinal bacterial overgrowth, microscopic colitis, pancreatic insufficiency, irritable bowel syndrome and refractory CD [63]. Thus careful evaluation is needed to identify and treat the specific source in any given patient. the first step in evaluation is to re-confirm the initial diagnosis of CD by review of small-intestinal histology and serology obtained at the time of diagnosis [64].

Refractory Celiac Disease (RCD)

It may be defined as persistent or recurrent symptoms and signs of malabsorption with small-intestinal villous atrophy despite a strict GFD for more than 12 months and in the absence of other disorders including overt lymphoma. RCD is uncommon, affecting 1-2% of patients with CD [65]. Refractory celiac disease can be classified as type 1 (normal intraepithelial lymphocytes) or type 2 (abnormal intraepithelial lymphocytes; clonal intra epithelial lymphocytes lacking surface markers CD3, CD8, and T-cell receptors; or both). Type 2 RCD is associated with a higher risk of ulcerative jejunoileitis and lymphoma than type 1 and associated with a significantly less favourable prognosis as compared to Type I RCD [66]. Management of Type I RCD includes strict gluten free diet, nutritional support and in severe cases steroid therapy is required [67]. in patients with an incomplete response to steroid treatment immunosuppressive agents such as azathioprine may be beneficial but should be used with caution, since they may promote the progression to lymphoma [68]. Management of Type II RCD is difficult because they are less likely respond to therapy. Treatment options include systemic corticosteroids, enteric-coated budesonide, azathioprine, alemtuzumab (anti-CD52 monoclonal antibody) infliximab or cladribine (2-chlorodeoxyadenosine) [69].

Aims of study

1. To determine the frequency of positive serology of CD in malnutrition children in Child's Central Teaching Hospital.
2. To assessing of HLA typing in patients who have positive serology of celiac disease.

PATIENTS AND 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)[24]. 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 Microsoft excel.
- Mean, 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 p-value less than 0.05 was considered as significant.

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, as shown in Table 1:

Table1. Frequency distribution of the variables within the sample (n 100)

Variable			Frequency	%
Gender	Male		52	52
	Female		48	48
Residence	Urban		50	50
	Rural		50	50
Degree of malnutrition	-	2SD	33	33
	-	3SD	45	45
	-	4SD	25	25
Chief complaint	Weight loss		60	60
	Diarrhea		29	29
	Vomiting		11	11
Signs and symptoms	Muscle wasting		67	67
	Abdominal distension		21	21
	Edema		9	9
	Skin lesion		3	3
Age of complementary feeding	≤ 4 months		62	62
	> 4 months		38	38
Type of feeding	Breast		13	13
	Bottle		59	59
	Mixed		28	28

Among these 100 patients patients (11%) were celiac as shown in Figure 1.

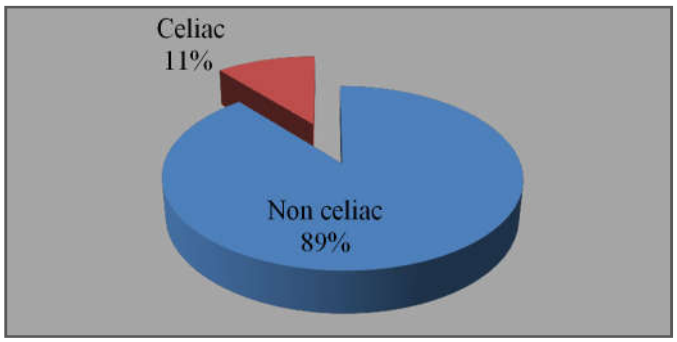

Figure 1. Proportion of the celiac disease cases within the sample (n 100)

In our study, there was no statistical difference between celiac and non celiac according to gender but there was highly statistically significant difference between the ages of celiac and non celiac, 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. as shown in table2 and Figure 2. 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 tTG IgG 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 as shown in Table 3:

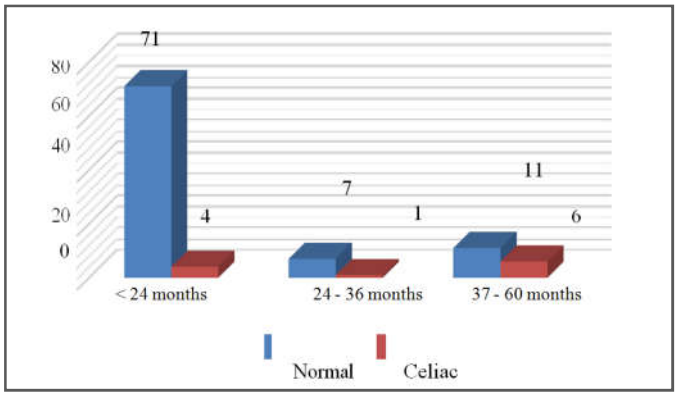

Figure 1. Distribution of celiac disease according to age group

Table 2. Distribution of celiac and non celiac according to gender and age groups (n 100)

		Non celiac (no 89)		Celiac (no 11)		p value
		No	%	No	%	
Gender	Male	44	49.4	8	72.7	0.145(NS)
	Female	45	50.5	3	27.2	
Age (months)	< 24 months	71	79.8	4	36.4	0.001(*)
	24 - 36 months	7	7.7	1	9.1	
	37 - 60 months	11	12.3	6	54.5	

(*) statistically significant of less than 0.05
(NS) not significant

Table 3. Characteristic laboratory finding of serology and HLA gene typing in celiac patients

No	Age	Sex	tTG IgA,I Gg	HLA type
1	48	Male	Ve Both+	DQ2,DQ8
2	10	Male	Ve Both+	DQ2
3	16	female	Ve IgA +	DQ2
4	33	Male	Ve IgG+	DQ2
5	23	Male	Ve IgA+	DQ8
6	53	Female	Ve Both+	DQ2
7	52	Male	Ve Both +	DQ2
8	22	Male	IgA+ ve	DQ2
9	43	Female	Both+ve	DQ2,DQ8
10	60	Male	Both+ve	DQ2
11	48	Male	IgA+ Ve	DQ2

Table 4. t distribution of the of Hb level within the sample (n 100)

	Celiac disease (n 11)		Non celiac (n 89)		p value
	Mean	±SD	Mean	±SD	
Hb (g/dl)	10.26	1.54	10.64	1.59	0.461(NS)

- Independent sample t test used to compare between means
- (NS) not significant

As shown in the Table (5) there was male sex predominant in celiac patient 8/11 (72.7%) and female sex predominant in non celiac 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 statistical 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

Table 5. Comparison of celiac and non celiac according to the following variables

		Non celiac (n = 89)		Celiac disease (n = 11)		p value
		No	%	No	%	
Gender	Male	44	49.4	8	72.7	0.145(NS)
	Female	45	50.5	3	27.2	
Residence	urban	46	51.7	4	36.4	0.338(NS)
	rural	43	48.3	7	63.4	
Degree of malnutrition	-2SD	29	32.6	4	36.4	0.517(NS)
	-3SD	39	43.8	3	27.3	
	-4SD	21	23.6	4	36.4	
Chief complaint	W/T LOSS	57	64	3	27.3	0.025(*)
	Diarrhea	22	24.7	7	63.6	
	Vomiting	10	11.2	1	9.1	
Signs and symptoms	Muscle wasting	63	70.8	4	36.4	0.000(*)
	Abdominal distension	12	13.5	9	81.9	
	Edema	9	10.1	0	0	
	Skin lesion	2	2.25	1	9.1	
Age of complementary feeding	< 4 months	52	58.4	10	90.9	0.036(*)
	>4 months	37	41.6	1	9.1	
Type of feeding	Breast	13	14.6	0	0	0.078(NS)
	Bottle	54	60.	5	45.4	
	Mixed	22	24.7	6	54.5	

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. [70]. 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 [71], 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 [70]. 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.* [70]. In serology, anti tTGA was positive in 11 (100%) cases of celiac disease is similar to Indian study reported by Rana *et al.* [70]., also in other studies published in nelson textbook of pediatrics the sensitivity is 100% [36].

In 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) [72]. 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 [73]. 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[74]. 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%)[75]. 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.* [70]. 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) [76], 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 [77]. 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) [78], had a higher prevalence of CD even at 5 years of age. Similarly, in the multicentre European trial, [79], 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) [80], found an increased risk for both early and late gluten introduction while Strødal *et al.* (2013) [81], 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 Aaronson *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 [82] and also Italian study done by Lionetti *et al.* (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 [83].

Conclusion

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. Celiac disease can be virtually excluded in individual lacking HLA DQ2, DQ8 or both.

Recommendations

1. BECAUSE of the high prevalence of CD in malnutrition patients, and we suggest that all children with malnutrition be screened for CD.
2. Advice the mother not introduce gluten diet early before 4 months to reduce risk of development of celiac disease
3. Encourage mother for breast feeding because it has a protective effect on development of CD.
4. We suggest to compete the study by using endoscopical biopsy and comparing with HLA genotypes to confirm the diagnosis of celiac disease.

List of abbreviations

CD	Celiac disease
EMA	Endomysium Antibody
GFD	Gluten free diet
GI	Gastrointestinal
HLA	Human Leukocyte Antigen
IDA	Iron deficiency anemia
IELs	Intra Epithelial Lymphocytes
IL	Interleukin
IgA, IgG	Immunoglobulin class A and G
MUAC	Mid-upper arm circumference
NRCD	Non responsive celiac disease
RCD	Refractory Celiac Disease
ReSoMal	Rehydration solution of malnutrition
RCD	Refractory Celiac Disease
SAM	Severe acute malnutrition
T1DM	Type 1 diabetes mellitus
tTG	Tissue Transglutaminase
WHO	World Health Organization
W/L	Weight loss
WHZ	Weight-for-height index

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