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Prevalence of Clinical phenotypes of celiac disease among school children (4 – 17 Years) in Sri Ganganagar District, Rajasthan, North India

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ABSTRACT

Celiac disease has several other names including coeliac (with oe ligature), celiac spure, nontropic-sprue, endemic sprue, and gluten enteropathy. The term celiac derived from the greek "koliakos" means abdominal and was introduced in the 19th century in a translation of what is generally regarded as an ancient greek description of the disease by Aretaeus of cappadocea[1].Celiac disease, as of today, of the world, although it is rare among people of purely African Caribbean, Japanese and Chinese background. Worldwide celaiac disease rates are estimated at about 1%, but the disease is thought to be uncommon in both India and Asia. Interestingly many of the susceptibility genes are shared with other auto immune disorder (eg. Type 1 diabetes) supporting the concept that other auto immune disorders may share common pathogenic pathways with celiac disease. This further supports the idea that understanding the immunological response in the gut of celiac patients may help elucidate general mechanisms involved auto immunity.

Result : This study was designed to evaluate the clinical phenotype of celiac disease in a small group of SriganganagarDistrict ,Northern India. Over a period of 2 years, a total of 1288 children (878 boys , 410 girls)with clinical suspicion of CD were evaluated. Their detailed clinical features, investigation, and follow-up up data were recorded.The onset of CD was symptomatic in1030 (80%) patients, whereas the remaining 258 (20%) . a subclinical phenotype. In the period 2012 – 13 the Classical, non –Classical and subclinical phenotype were respectively found in 48 %, 44.3 % and 9.7% of CD cases, whereas in the period 2013- 14 , the most frequent clinical phenotype was the non- classical (59 %), followed by the Subclinical (27. 5 %) and by the classic (13.3%).The most frequent gastrointestinal features were Abdominal pain, diarrhea, and bloating.

Key Words : CD (celiac disease) /coeliac disease, GIT disorders (gastrointestinal tract disorders), epidemiological, clinical, histological, diagnosis, hypertransaminasemia , diagnosis, immune – mediated disorder, phenotype, gluten – free diet (G FD)

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INTRODUCTION

Celiac disease has several other names including coeliac (with oe ligature), celiac spure, nontropic-sprue, endemic sprue, and gluten enteropathy. The term celiac derived from the greek "koliakos" means abdominal and was introduced in the 19th century in a translation of what is generally regarded as an ancient greek description of the disease by Aretaeus of cappadocea[1].

Celiac disease, as of today, of the world, although it is rare among people of purely African Caribbean, Japanese and Chinese background. Worldwide celaiac disease rates are estimated at about 1%, but the disease is thought to be uncommon in both India and Asia.

However, there has generally been a lack of study data on the actual prevalence of celiac disease in Asian nations. The disease has also been considered uncommon in India until recently. Hospital records revealed an increasing trend of the disease is predominantly wheat eating areas on North India[2].

Celiac disease, or glutten-induced enteropathy, is a T-cell mediated entity that results in lifelong intolerance to dietary gluten in genetically predisposed individuals. Morphological changes in the small bowel mucosa of such patients result in impaired intestinal function and a range of outcomes from no or few clinical symptoms to extensive malabsorption[3].

"The term prevalence of celiac disease usually refers to the estimated population of people who are managing celiac disease at any given time."

"The term incidence of celiac disease refers to the annual diagnosis rate or the number of new cases of celiac disease diagnosed each year."

Celiac disease is the most common genetic disease in Europe. In Italy about 1 in 250 people and in Ireland about 1 in 300 people have celiac disease. It is rarely diagnosed in African, Chinese and Japanese people. An estimated 1 in 4700 Americans have been diagnosed with celiac disease. Some researchers question how celiac disease could be so uncommon in the United States since it is hereditary and many Americans descend from European ethnic groups in whom the disease is common. A recent study in which random blood samples from the Red Cross were tested for celiac disease suggests that as many as 1 in every 250 Americans may have it. Celiac Disease affects children and adults. At least 1 in 1000 people and in some populations 1 in 200 people have celiac disease. Most often celiac disease first causes symptoms during childhood usually diarrhoea, growth failure and failure to thrive, but the disease can also first cause symptoms in adults.

Celiac disease is a complex multifactorial disorder arising from glutten ingestion in genetically susceptible individuals, who carry the HLA-DQ2 and/or HLA-DQ8 predisposing alleles. As with most multifactorial disorders, celiac disease is the result of the interplay between and genetic and environmental factors that co-operate to induce an immune-mediated response that results in the small intestinal damage (increased intraepithelial lymphocytes, crypt hyperplasia and villous atrophy) typically found in active celiac patients, and in the various systemic and auto immune features of the disease.

HLA alleles explain about 30% of the genetic susceptibility of celiac disease, while the remainder is due to numerous non-HLA genes. Recently, 13 new loci have been identified to be associated with celiac disease, bringing the number of known celiac associated susceptibility

loci to 40. In those regions, more than 115 non-HLA genesgenes have been found to be associated with celiac disease, although they contribute only modestly to the overall disease risk. Almost 30 genes are implicated in the immune response, and some of are involved in the inflammatory response against viruses, reinforcing the central role of immune disregulation in celiac disease pathogenesis and suggesting that immune response to viral infections may play a role in the development of the disease.

Interestingly many of the susceptibility genes are shared with other auto immune disorder (eg. Type 1 diabetes) supporting the concept that other auto immune disorders may share common pathogenic pathways with celiac disease. This further supports the idea that understanding the immunological response in the gut of celiac patients may help elucidate general mechanisms involved auto immunity[4].

The celiac iceberg:

Celiac disease is a multi system disorder whose primary target of the injury is the small intestine. The disease is triggered by glutten, the main storage protein found in certain grains specially in wheat, barley, rye etc. Glutten damages the small intestine so that it is unable to absorb the nutrients properly. As food malabsorption continuous and the disease progresses, the manifestations inevitably become more varied and complex.

Celiac disease is the most common and one of the most under diagnosed-hereditary auto immune conditions in the United States as well as in India today. It is common as hereditary high cholesterol.

Once considered a rare "diarrheal" disease of childhood, celiac disease is now recognised predominantly as a disease of adults and the majority of people are either asymptomatic or consult doctors for a variety of other complaints. While the disease is considered common in Europe, South America, Canada and Australia – a recent study of school children in Finland showed the incidence to be 1 per 99, in parts of England 1 per 100 – only recently have studies shown that celiac disease affects a approximately 1% in the US population (approximately 1 in every 100 people) and 90% of them are undiagnosed. In India also 97% of cases are undiagnosed. A very first study on celiac disease prevalence among school children in India showed disease frequency of 1 in 310 and is thought to be an under-assessment. It clearly shows that celiac disease is not rare in wheat eating areas of North India[5].

A delay in diagnosis also increases the chances of developing associated auto immune diseases. Most adults with celiac disease have bone loss, resulting in osteopenia and osteoporosis, anemia, malignancies, peripheral neuropathies, dental enamel defects, hyposplenism and infertility are also secondary conditions associated with the disease. Since patients with one auto immune disease are more likely to have or to develop another, patients with celiac disease are Sgogren's syndrome, type 1 diabetes, auto immune thyroid disease, dermatitis herpetiformis (an intensely itchy skin condition) or alopecia areata (a condition that causes hair loss).

In USA out of the 2.1 million people with type 1 diabetes, 8 to 10% also have celiac disease. In India no specific data are available. Often people are treated for an auto immune condition before being diagnosed with celiac disease.

Unfortunately, there is an increased mortality rate for people with celiac disease, exceedingly that of the general population, due mainly to malignancies. Current research shows a statistical risk that is 33 times greater for small intestinal edenocarcinoma, 11.6 times greater for esophageal cancer, 9.1 times greater for non-hodgkin's lymphoma, 5 times greater for melanoma and 23 times greater for papillary thyroid cancer.

Celiac disease is significant medical condition. It is far too often masked by or mistaken for a number of more commonly diagnosed conditions. This result is a huge population of patients suffering unnecessarily and at considerable risk for major complications. These patients may also be burdened by depression and complicated professional and family dynamics as a result of their long term undiagnosed illnesses. Celiac disease is a huge iceberg that is moving, not quite so silently, across many of our lives[6].

METHODOLOGY

Health Questionnaire:

Section 1:- Symptoms:

Check each of the symptoms that you have experienced at least once a week during the past 3 months:

- Bloating
- Gas and /or stomach cramping
- Diarrhoea or runny stools
- Constipation
- Joint pain
- Numbness or tingling in your extremities
- Itchy skin lesions
- Constant unexplained fatigue
- Frequent headaches or migraines

Section 2: Diagnosis:

Check if you have had or been diagnosed with any of the following:

- Irritable bowel syndrome
- Eczema or unexplained contact dermatitis
- Fibromyalgia
- Chronic fatigue syndrome
- Nervous stomach (non-ulcer dyspepsia)

Section 3:- Associated illnesses:

Check if you have any of the following:

- Lactose intolerance
- Osteopenia and/or osteoporosis
- Auto immune disorders:

a) Thyroid disease (hypo/hyper)
b) Diabetes Mellitus (type 1)

c) Sgogren's syndrome
d) Chronic liver disease
– An immediate family member with an auto immune condition
– Peripheral neuropathy
– Non-Hodgkin's lymphoma
– Small intestinal cancer
– Psychiatric disorders or depression
– Anemia (iron deficiency)
– Infertility

Scoring :

If you have checked one or more illnesses in either section 1 or 2 and have any of the illnesses in section 3 you should consider testing for celiac disease. If you have checks in all three sections, you and your doctor should definitely explore a diagnosis of celiac disease.

All of the symptoms in section 1, all of the diagnosis in section 2, and all of the associated illnesses in section 3 are intimately related to celiac disease, 1 in every 100 people in the United States in affected by celiac disease and 97% of them are undiagnosed. In India also 97% cases are undiagnosed. People don't have much awareness and also research work is also on ground level. Exact data regarding prevalence is not available.

Common Signs and Symptoms of Celiac Disease:

Signs:

1. Retarded height (<25th percentile)
2. Low body weight (<25th percentile)
3. Wasted muscles
4. Abdominal distension
5. Edema
6. Finger clubbing

Symptoms:

1. Failure to thrive
2. Diarrhoea
3. Irritability
4. Vomiting
5. Anorexia
6. Fowl stool
7. Abdominal pain
8. Excessive appetite
9. Rectal prolapsed

Classification of Celiac Disease:

1. Classic Celiac Disease
2. Non- Gastrointestinal Celiac Disease

3. Subclinical Celiac Disease
4. Latent Celiac Disease
5. Non – Celiac gluten sensitivity

Pathogenesis and Risk factors:

1. Autoimmunity
2. Genetic Factors
3. Feeding Practices in infancy and Early Childhood
4. Additional trigger factors

High Risk Groups:

1. Type 1 Diabetes Mellitus
2. Relatives of Patient with Celiac Disease
3. Down Syndrome
4. Selective IgA deficiency
5. Autoimmune Thyroiditis

Clinical Manifestations in Children:

1. Classical gastrointestinal symptoms
2. Non – gastrointestinal Manifestations
3. Iron deficiency Anaemia
4. Pot belly (Liver Disease)
5. Bone deformities (Metabolic bone disease)
6. Arthritis
7. Behavioral Disorders (Neurologic Disease)
8. Growth Retardation (Growth and development)
9. Subclinical disease and Risk of Malignancy

Review of literature:

February 2003, an article published in Arch Intern Med titled:"Prevalence of celiac disease at-risk and not-at-risk groups in the United States: A large multi centre study". The aim of the study was to determine the prevalence of celiac disease in at-risk and not-at-risk groups in the United States. According to authors celiac disease is an immune mediated enteropathic condition triggered in genetically susceptible individuals by the ingestion of gluten. Although common in Europe, celiac disease is thought be rare in the United States, where are no large epidemiologic studies of its prevalence. Their conclusion was that celiac disease occurs frequently not only in patients with gastrointestinal symptoms, but also in 1 and 2 degree relatives and patients with numerous common disorders even in the absence of gastrointestinal symptoms. The prevalence of celiac disease in symptomatic patients and not-at-risk subject was similar to that reported in Europe. Celiac disease appears to be a more common but neglected disorder than has generally been recognised in the United States[7].

While celiac disease is estimated to affect about 1% of the world's population, it is

thought to be uncommon not only in India but in Asia also. There is a lack of studies on the prevalence of celiac disease from Asian nations. May 26th 2011, an article titled: "Prevalence of celiac disease in the northern part of India: A community based study" was published in J Gastroenterol Hepatol. According to their findings they conclude that the prevalence of celiac disease in the north Indian community is 1 ion 96. Celiac disease is more common than is recognised in India[8].

October 21st 2006, possibly first research article on celiac disease published in J GastroenterolHepatol titled: "Prevalence of celiac disease among school children in Punjab, North India". According to their findings they conclude that celiac disease has been considered uncommon in India until recently. Hospital records have revealed and increasing trend of the disease in predominantly wheat eating areas of North India. Although this disease frequency of 1 in 300 is thought to be under assessment, is clearly shows that celiac disease is not rare in wheat eating areas of the North India[9].

February 26th 2011, another article published in J GastroenterolHepatol titled: "Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in North India". According to their findings they conclude that there is scanty data on the occurrence of celiac disease in patients with type 1 diabetes mellitus in South Asia. Their aim was to study the prevalence and clinical profile of celiac disease in patients with type 1 diabetes mellitus in a tertiary care referral centre in North India. Celiac disease is highly prevalent in patients with type 1 diabetes mellitus (11.1%) and majority of them (90.5%) were diagnosed on screening. Routine screening is required for early diagnosis and combat associated co-morbidities[10].

Celiac disease is a chronic GIT disorder and is estimated to affect approximately 0.5 to 1 % of the general population in many parts of the world (More than 1 million cases per year in India). In Europe, the united States and Australia, prevalence estimates range from 1:80 to 1:300 children (3 to 13 per 1000 children)[11].

And hyper transaminasemia (40 – 50 % of untreated patients), which can be ascribed to food and bacteria antigen translocation reaching the liver due to increased intestinal permeability [11].

A wide array of neurological symptoms can be detectable in CD patients. Notably, these Manifestations can be reversed when patients start a strict gluten- free diet (GFD), although fatigue and some neurological manifestation as well as functional gastrointestinal symptoms can persist for a long period in a subgroup of CD patients.

Females are affected approximately twice as often as males, although the ratio varies depending on the strategy used to find cases [12].

The number of "Silent celiacs" (Patients with non specific symptoms) is much higher than the number of patients with classic celiac disease. A study from Italy reported that asymptomatic cases outnumbered symptomatic cases by a ratio of 7:1 [13].

A large serological Screening study in the united states suggested a prevalence of 1: 133 Among patients with no risk factors or symptoms [14].

Celiac disease is one of the most common autoimmune disorders, with a reported prevalence of 0.5 to 1 % of the general population, with the exception of areas showing low frequency of CD – predisposing genes and low gluten consumption e. g., Sub –Saharan Africa and Japan [15].

Studies have shown that most CD cases remain undetected in the absence of serological screening due to heterogeneous symptoms and poor disease awareness. CD prevalence is increasing in western countries. CD prevalence increased 5 – fold in the US, for reasons that are currently unknown [16].

Natural history of Celiac disease autoimmunity in a USA cohort followed since 1974.

The prevalence of C D relatives (10 to 15 %) and in other at – risk groups, particularly patients with Down syndrome, Type diabetes, or IgA deficiency [17].

Studies have shown that By cause of Iron malabsorption or chronic Inflammation, Iron deficiency microcytic anemia, detectable in up to 40% of cases [18].

Or, more rarely, macrocytic anemia due to folic acid and /or vitamin B12 deficiency (more frequent in Europe than in the US).

Changes in bone mineral density (affecting about 70% of patients at diagnosis), are related to altered absorption of calcium and Vitamin D3 [19].

In children, growth retardation and short stature can raise the suspect of an underlying CD. Other signs include tooth enamel defects, aphthous stomatitis (identified in about 20% of undiagnosed CD patients[20] .

Background:

Celiac disease is an immune- mediated disorder with a multiform presentation and therefore a challenging diagnosis.

Objective :

My purpose is to identify the epidemiological, clinical, laboratory and histological characteristics of children with celiac disease at diagnosis and follow up.

RESULTS AND DISCUSSION

Clinical Findings:

This study was designed to evaluate the clinical phenotype of celiac disease in a small group of Sriganganagar District, Northern India. Over a period of 2 years, a total of 1288 children (878 boys, 410 girls) with clinical suspicion of CD were evaluated. Their detailed clinical features, investigation, and follow-up up data were recorded.

Table 1 : Distribution of Respondents on the basis of their clinical phenotype of celiac disease (n=1288)

Sr. No.	Groups	Percentage
1.	Boys	68%
2.	Girls	31%

Table 2: Distribution of Respondents on the basis of theirsymptomatic and subclinical phenotype of celiac disease (n= 1288)

Sr. No.	Groups	No. of Respondents	Percentage
1.	Symptomatic	1030	80%
2.	Subclinical	258	20%

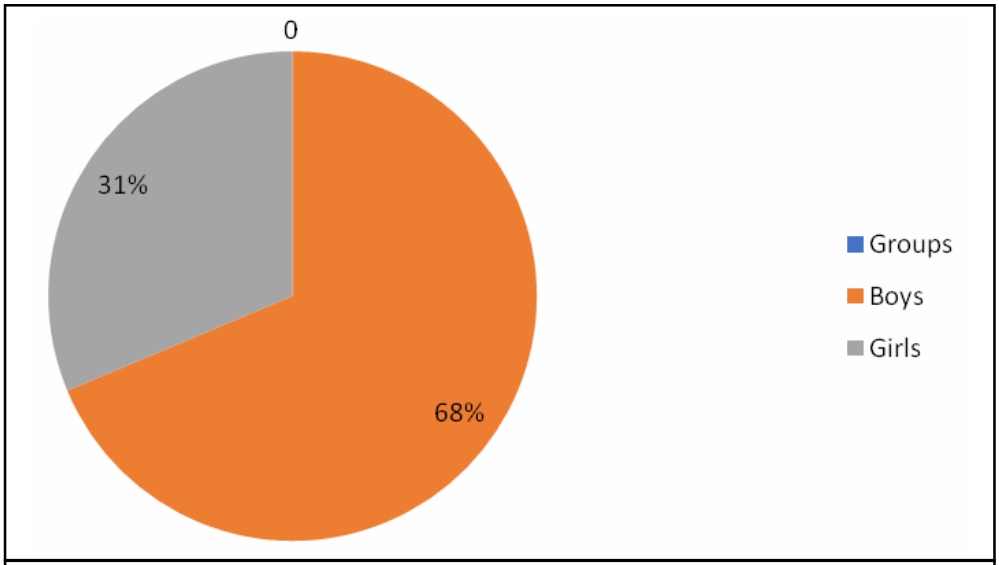

Fig. 1 : Distribution of Respondents on the basis to their clinical phenotype of celiac disease

The onset of CD was symptomatic in 1030 (80%) patients, whereas the remaining 258 (20%) a subclinical phenotype.

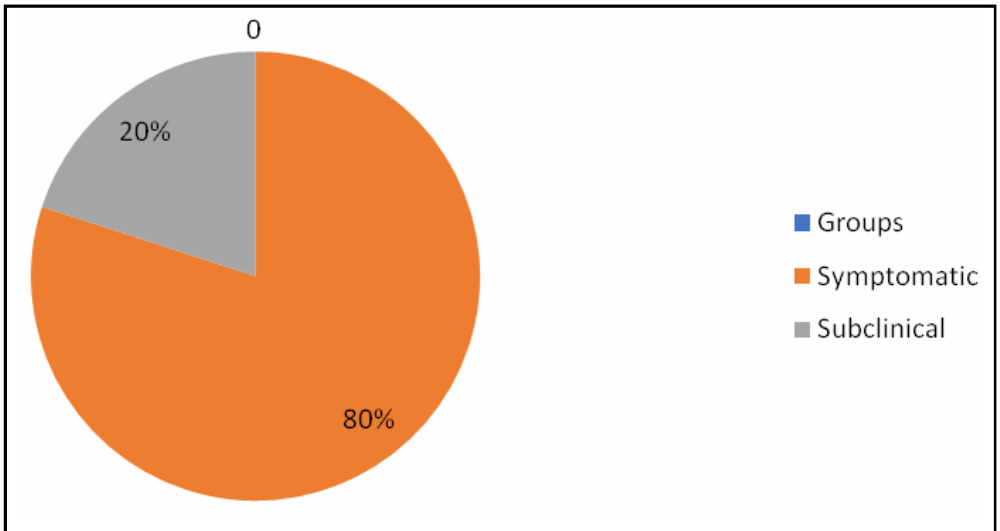

Fig. 2 : Distribution of respondents on the basis of their symptomatic and subclinical phenotype of celiac disease

Table 3: Distribution of Respondents on the basis of their Classical and Subclinical phenotype (n= 1288)

Sr. No.	Groups	No. of respondents	Percentage
1.	Classical	620	48%
2.	Non –Classical	570	44.3%

In the period 2012 – 13 the Classical, non –Classical and subclinical phenotype were respectively found in 48 %, 44.3 % and 9.7% of CD cases, whereas in the period 2013- 14, the most frequent clinical phenotype was the non- classical (59 %), followed by the Subclinical (27. 5 %) and by the classic (13.3%).

Table 4 : Distribution of Respondents on the basis of theirGastrointestinal Features were Abdominal pain, Diarrhoea, Bloating, Aphthous stomatitis, Constipation and Gastroesophageal Reflux Disease (GERD) (n= 1288)

Sr. No.	Groups	No. of respondents	Percentage
1.	Gastrointestinal Features	750	58%
2.	Diarrhoea	390	30%
3.	Bloating	220	17%
4.	Aphthous stomatitis	210	16%
5.	Alternating Bowel Habit	160	12%
6.	Constipation	150	11%
7.	Gastroesophageal Reflux Disease (GERD)	190	14%

The most frequent gastrointestinal features were Abdominal pain , diarrhoea, and bloating.

Taking into account all CD patients (n= 1288), more than half of them (58%) had gastrointestinal symptoms, *i.e.* Diarrhea (30 %), bloating (17%), Aphthous stomatitis (16 %), alternating bowel habit (12%), constipation (11%) and gastroesophageal reflux disease (GERD – 14%). Extra intestinal symptoms were common in children.

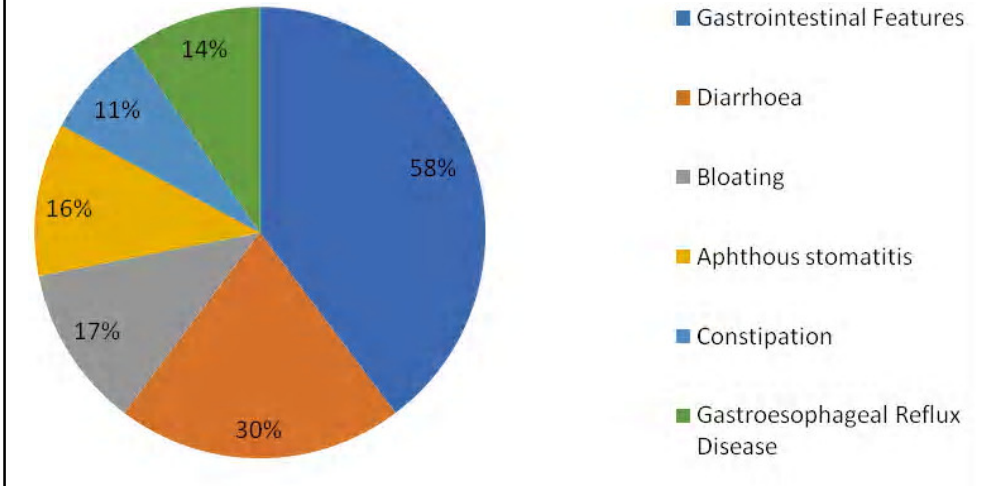

Fig. 3 : Distribution of Respondents on the basis of their Gastrointestinal Features were Abdominal pain, Diarrhoea, Bloating, Aphthous stomatitis, Constipation and Gastroesophageal Reflux Disease (GERD)

Frequent findings were Anaemia in 43 %, low ferritin in 65%, and moderate to severe deficiency of 25- OH Vitamin D3 in 62%. Iron deficiency with low level of ferritin was found in Patients with anaemia, which was also related to folic acid malabsorption.

Table 5 : Distribution of Respondents on the basis of theirAnaemia, Low Ferritin and Vitamin D3 (n= 1288)

Sr. No.	Groups	No. of respondents	Percentage
1.	Anaemia	560	43%
2.	Low Ferritin	840	65%
3.	Vitamin D3	800	62%

Conclusion:

Our findings outline the diverse clinical presentation of celiac disease among school children that should be considered irrespective of socio economic status and age. Increased clinician's awareness will enable an early diagnosis and treatment with subsequent symptom and nutritional status improvement.

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