Transient Glutenopathy and Abdominal Tuberculosis; a cause or effect? Preliminary Report

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Abstract:

Introduction: Tuberculosis remains an important disease worldwide. It is difficult to estimate its incidence in children. The association between intestinal tuberculosis and glutenopathy was not reported before.

Methodology: Three hundred patients who presented with chronic diarrhea to Gaafar Ibn Auf Specialized Children Hospital, Khartoum Sudan were investigated for intestinal tuberculosis and gutenopathy. The children were divided into two groups both were put on treatment for tuberculosis. However, one group was put on gluten free diet as well. The serological markers and intestinal biopsies were taken initially, six months after commencement of treatment and six months later. Also their clinical response to treatment was encountered.

Result: Out of the 300 children who presented with chronic diarrhea, 30 were diagnosed to have intestinal tuberculosis. Their ages ranged between 2-10years. At commencement of the study all the patients [30] had positive IgA and IgG antigliadin antibodies and anti tTG (table 1). The group which was put on gluten free diet showed rapid clinical, biochemical and histological response.

Conclusion: Despite the limitation of this preliminary study; we can conclude that ITB can cause transient glutenopathy and gluten free diet may facilitate clinical recovery in patients with ITB.

Key words: chronic diarrhea, Celiac disease, endomysial antibody, antigliden, villous atrophy

Introduction:

Tuberculosis in children is gaining relatively less interest worldwide probably because around 95% of infected children are sputum negative and so are less infectious. However, it has significant impact on health and economy of developing countries as it affects around 1.3 million children annually[1, 2].

TB can affect multiple systems simultaneously. Intestinal tuberculosis [ITB] has protean manifestations; one of these is chronic diarrhea. While investigating children with chronic diarrhea we noticed that almost all those who turned eventually to have ITB had positive serology for some markers of celiac disease.

We put a hypothesis that ITB may cause transient gluenopathy and we designed this prospective study to prove or disprove this hypothesis.

Methodology:

In the period January 2005- January 2007 we had 300 patients with chronic diarrhea in the gastrointestinal unit at Gaafar Ibn Auf Specialized Children Hospital, Khartoum Sudan.

History, clinical examination and investigations including ESR, serum albumin, and hemoglobin were performed for all children. Children who were suspected on clinical grounds to have ITB had mantoux test and ultrasonographic examination of abdomen. These children had immunological testing for evidence of celiac disease as well (IgA and IgG antigliadin antibodies and anti tissue transglutaminase (tTG)) and were subjected to upper gastrointestinal endoscopy and proximal small intestinal biopsy using Olympus video upper gastrointestinal endoscope [Olympus GIFP3 with diameter 8.5mm]. Histopathology after proper staining was done. The children were divided into two equal groups each composed of 15 children. Group [A] including those with tuberculosis and total villous atrophy with half [five] of those with subtotal atrophy. Group [B] included those with tuberculosis and minimal change atrophy and the remaining half of children with subtotal atrophy.

All the children were put on appropriate doses of anti-tuberculosis treatment (Streptomycin injections + Rifampicin +INH+ Pyrazinamide for two months and Rifampicin + INH for another 10months). Children in group A were put on gluten free diet as well.

Series of serological testing for celiac disease and intestinal biopsies were taken initially, six months after the start of treatment and further six months later

Out of the 300 children who presented with chronic diarrhea, 30 were diagnosed on clinical grounds (fever, malaise, ill health, chronic diarrhea, failure to thrive, and doughy abdomen) to have intestinal tuberculosis. This was further supported by the ultrasonographic findings (enlarged lymph nodes and thickened bowel with

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or without hepatomegally), positive mantoux test and raised ESR. Their ages ranged between 2-10years.

At commencement of the study all the patients [30] had positive IgA and IgG antigliadin antibodies and anti tTG (table 1). Out of these ten children had biopsy evidence of total villous atrophy (TVA), eight had subtotal villous atrophy (STVA) and 12 had minimal mucosal changes(MMC)(table 2).

Table (1) serology of cases at diagnosis (N=30)

	Group A		Group B	
Test	positive	negative	positive	negative
Ani tTG	15	0	15	0
IgA antigl	15	0	15	0
IgG antigl	15	0	15	0

Table (2) mucosal biopsy at diagnosis (N=30)

	Group A	Group B
TVA	10	0
STVA	5	3
MMC	0	12
Normal mucosa	0	0

STV =Total villous atrophy
STVA = Subtotal villous atrophy
MMC = Minimal mucosal changes
Group A on gluten-free diet
Group B on normal diet

Clinical course

In group A, the abdominal pain, diarrhea and malaise disappeared and the children stared to gain weight within the first week of treatment. They were kept in hospital for one to two weeks and there were no readmissions, while in group B diarrhea and malaise took up to two weeks to disappear, and the children started to gain weight after 10 days, stayed in hospital for up to three weeks and few of them were re admitted 2 – 3 times in the following six months.

After six months of treatment two patients from group A were dropped from the study because they were found to be HIV positive. All the children in both groups remained positive for IgG antigliadin. However, all the patients in group A and five in group B became negative for tTG (table 3).

Table (3) serology at 6 months (n=28)

	Group A		Group B	
Test	positive	negative	positive	negative
Ani tTG	0	13	10	5
IgA antigl	3	10	8	7
IgG antigl	13	0	15	0

After six months of re challenging with gluten rich diet the result was as follows: The 13 patients in group A remained negative for anti tTG and IgA antigliadin and 10 became also negative for IgG antigliadin antibodies, while seven patients in group B remained positive for IgG but all of them became negative for tTG and IgA antigliadin antibodies (table 4).

Table (4) serology at one year (N=28)

	Group		Group B	
Test	positive	negative	positive	negative
Ani tTG	0	13	0	15
IgA antigl	0	13	0	15
IgG antigl	3	10	7	8

Mucosal biopsy

After six months of treatment the intestinal mucosa of eight children in group A became normal, five continue to have MMC, while the mucosa of six out of the 15 children in group B became normal and nine continued to have MMC.(table 5)

Because of some difficulties, only two biopsies could be obtained from children in group A one year after treatment and it were found to be normal.

Table (5) mucosal biopsy after 6 month of treatment (N=9)

	Group A	Group B
TVA	0	0
STVA	0	0
MMC	5	9
Normal mucosa	8	6

STV =Total villous atrophy
STVA = Subtotal villous atrophy
MMC = Minimal mucosal changes
Group A on gluten-free diet
Group B on normal diet

Discussion

Although identifying mycobateria tuberculosis in small bowel biopsy is the gold standard finding for the diagnosis of ITB, this is not always feasible. Hence the clinical presentation in the appropriate setting when supported by some other investigations is an acceptable substitute to diagnose the condition[3]. Despite the non-availability of IgA endomysial antibody testing in our unit, the other tests can give reasonably reliable diagnosis of glutenopathy in our patients. This was further augmented with the histopathological picture and the good response to gluten free diet. IgA antiendomysial, IgA tTG and IgA antigliden antibodies fall with treatment and hence they were good non invasive monitors for the patients' response to treatment [4]. All our patients were initially positive for IgA anti tTG, IgA and IgG antigliadin. When the treatment was started; patients on gluten free diet showed remarkable and quick clinical recovery and after six month of treatment 100% and 76.9% of them turned negative for IgA anti tTG an IgA anti gliadin respectively compared to only 33.3% and 46.7% in group B. This indicates an excellent response to gluten free diet therapy. A paralleled histopathological recovery was observed. After six months of treatment with anti TB drugs none of the patients in both groups had persistent subtotal villous atrophy. Eight [61.5 %] patients in group A compared to six [40 %] in group B had normal intestinal mucosa and the rest of the patients had only minimal changes pointing to a good response to treatment. The absence of clinical, histopathological and immunological relapse after resumption of gluten rich diet in group A and the other indices in group B with the continuation of anti tuberculosis treatment indicate that the initial glutenopathy was a transient one and was probably related to the intestinal tuberculosis which was treated simultaneously. The exact mechanism behind this association is not clear. We could not come across clear direct association or causal relationship between intestinal tuberculosis and celiac disease in the literature. However, mucosal damage by intestinal infections was postulated before[5]. Intestinal TB may cause disturbance of the normal flora of the bowel and facilitate mucosal damage. Whether mycobacteria tuberculosis initiates direct local immunonological response involving T-cells and leading to this mucosal damage has to be further investigated. Also the possibility of more susceptibility of "celiac mucosa" to tuberculosis has to be studied. The remarkable clinical recovery in the patients who were put on gluten free diet highlights the importance of rapid resumption of the nutritional state in these patients. The role of gluten free diet in altering the intestinal bacteria flora in such patients and hence facilitating the clinical recovery reserves more focus. This study besides suggesting a causal relationship between ITB and glutenopathy in children is putting some questions: is there a similar relation in the adult diseases? Shall we look routinely for each disease when the other is present? Shall all such patients be put temporarily on gluten free diet? Have these patients got latent celiac? Is celiac disease an independent risk factor for acquiring ITB? Can genetic studies help in such a dilemma?

Conclusion

Despite the limitation of this preliminary study; [small number of children, inability to perform full serological test for celiac disease (e. g. anti endomyselial antibodies and anti reticulin antibodies) , isolate the mycobacteria tuberculosis in tissue or perform genetic studies] we can conclude that ITB can cause transient glutenopathy and gluten free diet may facilitate clinical recovery in patients with ITB . This finding is interesting and may have considerable impact on the diagnosis and management of both diseases if this is supported by other larger studies.

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