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TEACHING FILES (GRAND ROUNDS)

A 5 YEARS OLD GIRL WITH SUSPECTED CELIAC DISEASE

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Clinical Problem:
A 5 ½ years old girl presented with recurrent diarrhea since 1 year of age. Her stool was watery and the frequency was about 4-5 times/day. She was treated symptomatically with multivitamin and multimineral suspensions along with probiotics but had no response. On examination, her weight was 15.3 kg (<3rd centile as per Indian Academy of Pediatrics (IAP) growth charts) and height was 110 cms (between 25th and 50th centile as per IAP growth charts). Systemic and general examination were normal. Investigations showed hemoglobin of 10.8 gm/dl, white cell count of 7900 cells/cumm (66% polymorphs, 30% lymphocytes), platelets 437000 cells/cumm, ESR 28 mm and stool examination was normal. Her red cell indices was suggestive of microcytic hypochromic anemia with mean corpuscular hemoglobin (MCH) 23.1 pg (Normal 27-33 pg) and mean corpuscular hemoglobin concentration (MCHC) 30.1 g/dl (Normal 33.4-35.5 g/dl), mean corpuscular volume (MCV) 74 fl (Normal - 80-96 fl) and red cell distribution width (RDW) of 19.7% (Normal 12-15%). Stool routine was normal and stool culture did not grow any organism except normal gastrointestinal flora. She was suspected to have celiac disease in view of anemia and recurrent diarrhea. Anti endomysial IgA was positive (1:10) with simultaneous IgA (total) of 214 mg/dl (normal). Anti-tissue transglutaminase (tTG) IgA report was not available initially but on subsequent testing on gluten diet was 120U/ml (Normal <15 U/ml). HIV ELISA was negative. She did not undergo upper gastrointestinal biopsy or any genetic test as parents were not willing for the same. She was started on gluten free diet and treated with anti-helminthics. On follow up, after 6 months her TTG IgA and anti-endomysial IgA became negative and her HLA DQ2 and DQ8 were tested of which HLA DQ2 was positive confirming the diagnosis of celiac disease. She continues to be on gluten free diet.

How to diagnose celiac disease and how should these patients be monitored?

Discussion:
A child with recurrent diarrhea, with growth faltering,iron deficiency anemia, positive anti tissue transglutaminase 2 (tTG) IgA, with positive anti endomysial (EMA) - IgA creates a suspicion of Celiac Disease (CD) which is a disorder of the small intestine caused by autoimmune reactions brought on by dietary gluten exposure in people with a genetic predisposition.[1] Due to heterogenous presentation of clinical signs and symptoms, CD is underdiagnosed. Celiac disease can have gastrointestinal and/or extraintestinal manifestations which include chronic or intermittent diarrhea/ constipation/ abdominal pain, recurrent nausea and/or vomiting, weight loss/ failure to thrivce, delayed puberty, amenorrhea, irritability, chronic fatigue, neuropathy, arthritis/ arthralgia, chronic iron deficiency anaemia, osteopenia/ osteoporosis, repetitive fractures, recurrent aphthous stomatitis, dermatitis herpetiformis type rash, dental enamel defects, abormal liver biochemistry.[2] In children with suspected CD, total IgA and tTG IgA is tested after ensuring consumption of normal quantities of gluten by the child. If serum Ig A levels are normal, tTG IgA should be used regardless of age and if total IgA levels are low for age an IgG based test (Deaminated Gliadin Peptide (DGP), EMA or tTG) should be performed as second step. All patients who are IgA deficient and who are positive for an IgG based serological test should be biopsied.[2] As per ESPGHAN guidelines, children with positive tTG-IgA but low titers (less than 10 times the upper limit of normal) should have an intestinal biopsy which needs to be taken when the child is on a gluten-containing diet. Endoscopic biopsies are taken from distal duodenum (=4 biopsies) and =1 biopsy from the bulb of duodenum. Children with tTG-IgA values =10 times the upper limit of normal, should have a no biopsy approach and positive endomysial antibodies (EMA-IgA) should be shown in a second serum sample. In asymptomatic children, CD can be diagnosed using same criteria as in patients with symptoms.[2] On endoscopic duodenal biopsy, most pathologists currently evaluate the intestinal lesions of CD patients for diagnosis and to determine whether the lesions have improved after a gluten-free diet using the Marsh classification of intestinal celiac lesions, as modified by Oberhuber et al which is based on characteristics like villous atrophy, intraepithelial lymphocytes and crypt depth.[3]

In patients with positive tTG-IgA and EMA and no or minor small bowel histological changes are diagnosed as having potential CD. This may be due to low gluten intake prior to biopsy, sampling error or incorrect

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orientation of the biopsies. On confirmation as potential CD, clinical, serological surveillance is required along with further biopsies to monitor evolving villous atrophy.[2]

EMA-IgA test has a sensitivity of about 95% and specificity of 99% which is lesser for children under 2 years.[4] Testing for other antibodies like anti-tissue transglutaminase IgA (tTG -IgA) is recommended for initial screening test for celiac disease in all age groups as both the sensitivity and specificity of tTG -IgA test is about 98%.[4,5] HLA testing and presence of symptoms are not obligatory criteria for serology based diagnosis without biopsies.[2] A negative HLA-DQ2 and/or -DQ8 test result indicates a very low risk of CD, whereas a positive result does not confirm the diagnosis. Hence HLA testing has a high negative predictive value. It might be used in children who have a family history of the disease to avoid non-essential serological tests.[6] Patients with celiac disease are three to ten times more likely to develop another autoimmune disease. The most common accompanying disease is Type 1 diabetes mellitus (DM). As a result, it has been recommended that screening for celiac disease should be done in patients at the time of diagnosis of Type 1 DM and follow-up testing every 2 yearly, Ig A deficiency have also been shown to have an association with celiac disease.[7] Children having first degree relatives with CD, with the following conditions should be screened for celiac disease: Autoimmune thyroid disease, autoimmune liver disease, Down syndrome, Turner syndrome and Williams syndrome, Ig A deficiency.[2] The mainstay treatment in these patients is switching to a gluten free diet(GFD). A GFD can significantly helpful in reduction of symptoms, normalisation of biochemical parameters and an improvement in quality of life, but this does not always translate into the best possible management.[8] Adherence to the primary treatment is inextricably linked to follow-up. The follow-up focuses not only on energy, growth and vitamin deficiencies, but also on overall development and coping strategies.[8] The follow-up should be problem-oriented and based on symptoms and signs like in children and adolescents a satisfactory increase in the weight and height are essential markers for success of GFD. The use of serology for follow up still remains uncertain.[8]

Persistent positive antibodies are usually indicative of ongoing intestinal damage and gluten exposure. Serological testing should be performed within 6 and 12 months of diagnosis and then once a year thereafter. The tTG-IgA test is believed to be the best follow-up test. It has been demonstrated that the average time to return to normal levels of the tTG test in gluten-free patients is one year.[7] Though GFD is safe and effective in most patients, the limitations imposed by dietary restriction and gluten contamination in gluten free products highlight the need for new CD therapies. One of the most advanced drug, larazotide acetate has shown a reduction in symptoms as well as anti-tTG antibody titers. The use of glutenases as food pre-processors is amongst the most researched treatment. In addition, many intriguing drugs are in the early stages of development, including tTG inhibitors, HLA blockers and probiotics. While several trials for CD are ongoing or in progress, there is no agreement on outcome measures in CD patient trials.[9]

Compliance with ethical standards

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