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False-negative IgA Anti-tissue Transglutaminase

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Abstract The expanding knowledge about gluten-related autoimmunity led to a serology-based step-wised approach to diagnose celiac disease that might be misleading due to laboratory techniques. We present a rare case associating initial false-negative anti-transglutaminase IgA antibodies while CD was confirmed by IgG anti-transglutaminase and subsequent duodenal biopsy.

Keywords: *celiac disease, autoimmunity, immunoglobulin A, tissue transglutaminase*

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1. Introduction

Celiac disease (CD) is an autoimmune disease occurring on specific genetic (i.e. Human Leukocytes Antigens HLA DQ2/DQ8) backgrounds [1,2]; its prevalence is increasing over the last decades and recent estimates in Europe and the United States range from 1:80 to 1: 300 children to 13 per 1000 children) [1] and CD is reported at a very high frequency in North Africa: a prevalence as high as 5.6% was found in the Sahrawi population [3,4], and the world's highest frequency (= 16%) of CD in diabetic children was retrieved in Algeria [5].

In addition, the diagnosis of this clinical chameleon is made at any age and st short stature may be associated or even indicative of celiac disease, specially in such high-frequency areas.

Through a retrospective study of short stature screening in algerian primary schools, we depict a peculiar case of a child diagnosed as CD: initial negative IgA anti-transglutaminase antibodies were confusing until CD was confirmed by IgG anti-transglutaminase and subsequent duodenal biopsy.

2. Case Presentation

A cross-sectional descriptive anthropometric study was conducted in a sample of preschool and primary school pupils in the town of Setif (Algeria) from october to december 2014.

Out of 2493 pupils, 47 short children < - 2 standard deviation (SD) in height were detected.

Short stature pupils benefited of a celiac serological screen with IgA and IgG anti-tissue transglutaminase II, along with total serum IgA.

Five children of this investigated group had a positive celiac serology.

This panel of celiac patients encompassed:

- 04 children already diagnosed as celiac patients
- an asymptomatic boy, newly detected by this screening.

The last patient, aged 9 years and 9 months without any personal nor familial history, had a statural deficiency at (- 2.04) SD.

His celiac serology was confusing as he had an initial negative IgA anti-transglutaminase < 5 IU / ml. He did not exhibit any total Ig A deficiency; while IgG anti-transglutaminase levels were as high as 90.73 IU / ml.

Subsequent duodenal-jejunal biopsy confirmed the diagnosis of celiac disease (Marsh type 3, according to the Marsh Classification of Histologic Findings in CD).

When checking the laboratory work-up of celiac serology (Samples were centrifuged at 4000 rpm for 10 min), we deduced that long-lasting blood samples and consequent hemolysis are the most probable source of this diverting result.

3. Discussion

Only one, non-symptomatic, boy was detected de novo in this screening: such silent forms are more reported in boys; while girls carry more frequently the HLA DQ2 genes haplotype which is associated with early digestive complaints [6].

Similar cases with IgA negative /IgG positive anti-transglutaminase (with normal total IgA and 9 fold upper-limit IgG anti-transglutaminase) are sparse but were diversely reported worldwide. [7,8].

Even if IgA anti-tissue transglutaminase represent a cheap, reliable biomarker of celiac disease, hemolysis may be a crucial pre-analytical factor [9].

In fact, tissue transglutaminase is an ubiquitous enzyme and is particularly plentiful in erythrocytes.

Thus, hemolysis during immunoassay release the enzyme that may bind IgA anti-tissue transglutaminase to the coated enzyme and induce a false negative test. [10].

An interesting study recently conducted in Denmark clearly showed how hemolysis may affect IgA anti-transglutaminase detection, and authord suggested to enhance test reliability with other tests such as deamidated gliadin peptide-antibodies and anti-endomysial antibodies. [11].

4. Conclusion

The modern, serology-based screening and diagnosis of celiac disease should be warranted through a robust laboratory management (i.e. without hemolysis)

False-negative results in such cases, specially in asymptomatic patients, may drive a long odyssey before a correct diagnosis can be definitely assessed.

Check twice before saying tests are nice!

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