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Short Communication

Big differences in primary care celiac disease serological markers request in Spain

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On behalf of the Pilot Group of the Appropriate Utilization of Laboratory Tests

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Abstract

Introduction: Celiac disease (CD) prevalence is increasing but the disorder remains undiagnosed. The study compares CD serology markers requested by General Practitioners (GPs) over time and geographical areas. The aim of the current research is to assess the inter-practice and temporal variability in the request of CD serology markers by GPs in Spain, and the differences between regions.

Materials and methods: A cross-sectional study was conducted enrolling Spanish clinical laboratories. Primary care CD serology markers request in 2010, 2012 and 2014 from 15 autonomous communities (AACC), with more participants was reported. Test-utilization rates were calculated (tissue transglutaminase IgA antibodies (tTG-IgA) and deaminated peptide gliadine IgA antibodies (DGP-IgA) per 1000 inhabitants), and also the ratio of both tests request (DGP-IgA /tTG-IgA).

Results: The request of tTG-IgA per 1000 inhabitants increased significantly along years (from 3.99 to 5.90 ($P < 0.001$)). The demand of DGP-IgA *per* 1000 inhabitants was maintained in 2010 and 2012 (0.68 and 0.6), and decreased in 2014 (0.35) ($P = 0.927$). DGP-IgA /tTG-IgA diminished over time (from 0.16 to 0.06 ($P = 0.548$)), and in the 2014 edition, there was a significant regional difference, ranging from 0.01 to 0.57 ($P < 0.001$).

Conclusions: The variability in the request in CD serology markers emphasizes the need of inter-regional cooperation to develop strategies to optimize the use of laboratory tests.

Key words: celiac disease; quality indicators; clinical laboratory services; benchmarking

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Introduction

Celiac disease (CD) is an immune-mediated small intestinal enteropathy that is activated by exposure to dietary gluten in genetically predisposed individuals. Originally CD was considered a rare malabsorption syndrome affecting mainly children, but nowadays it has been recognized as a common condition that may be diagnosed at any age (1). CD is characterized by the presence of a variety of gluten-dependent clinical manifestations, specific antibodies of CD, haplotypes HLA-DQ2 and/or HLA-DQ8 and enteropathy.

Traditionally patients presented with malabsorption but over time the proportion of newly diagnosed patients with malabsorptive symptoms have decreased and even asymptomatic or patients with variable non-gastrointestinal findings have increased (2). Patients with CD can present with a wide range of symptoms and signs, and are classically diagnosed through a positive serology and ulterior duodenal biopsy while consuming a gluten-containing diet. Due to the diversity of the clinical symptoms, presentation at any age and the increasing prevalence, CD is more often diag-

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nosed in primary care by the General Practitioners (GPs) who serve as the patients' first point of contact (3).

The disease prevalence varies considerably, is increasing worldwide and many patients with CD still remain undiagnosed (4). In fact it is estimated that in 2020 there will be 5 million cases of CD cases just in the Mediterranean area (5).

Specific antibodies of CD are tissue transglutaminase IgA antibodies (tTG-IgA), endomysial IgA antibodies (EmA), and the deamidated gliadin peptide IgA antibodies (DGP-IgA).

Since publication of the European Society of Paediatric Gastroenterology and Nutrition (ESPGHAN) guidelines in year 2012, tTG-IgA antibody is the preferred single test for detection of CD (6). Tests that measure DGP-IgA may be used as additional tests in patients who are negative for other CD-specific antibodies but in whom clinical symptoms raise a strong suspicion of CD, especially if they are younger than 2 years. In subjects with humoral IgA deficiency, at least 1 additional test measuring IgG class CD-specific antibodies should be done (6).

The diversity of clinical symptoms and the increasing prevalence emphasize the need for strategies for the optimal detection of patients. A first step would be to study how appropriately CD serology is requested in primary care. A previous study has shown a higher variability in the rarely requested tests in primary care, in a population covering around 38% of the Spanish population (7).

We hypothesized that there is a high variability in the use of serological markers of CD in Primary Care. Thus, the aim of this study is to assess the inter-practice and temporal variability in the requests of serological markers of CD from primary care as well as to assess the differences between regions in Spain.

Materials and methods

Study Design

A cross-sectional study was conducted at the national level, enrolling clinical laboratories belonging to the Autonomous Communities (AACC) of Spain, all of which operate under the Spanish National Health Service, which is responsible for the majority of the national population. All applicable residents have free access to their primary care physician and to the hospital.

The study was designed and conducted at the University Hospital of San Juan de Alicante, where a questionnaire (Supplementary material) was developed and used to collect different variables from Spanish laboratories: number of tests performed from the Laboratory Information Systems Patient's databases and organizational data in three different years. In 2010 a call for data was posted on the Redconlab website, and also via email in the Redconlab 2012 study. In the edition of 2014, the dissemination of the questionnaire was also addressed through a LinkedIn (https://www.linkedin.com/in/redconlab-grupo-a5663bb7) group. In the three different years, or editions, participation in the REDCONLAB study was voluntary. In all, 37, 76 and 110 laboratories, on a voluntary basis, participated in the 2010, 2012 and 2014 editions.

Methods

Numbers of tTG-IgA and DGP-IgA, requested by all the GPs for the years 2010, 2012 and 2014 from laboratories at different health departments (HD) across Spain were reported in the three studies.

Test-utilization rates were calculated. Rates were expressed as tests (tTG-IgA and DGP-IgA) *per* 1000 inhabitants, and also through the ratio of both tests requests (DGP-IgA /tTG-IgA). The three editions results were compared.

In the 2014 edition, laboratories were grouped in the different AACC, when more than 4 participants, and a group joining the results of the rest. AACC were codified by numbers due to confidentiality, and DGP-IgA/tTG-IgA ratio was calculated.

Statistical analysis

The analysis of the distribution of the indicators was conducted by Kolmogorov-Smirnov test. The numerical data (tTG-IgA and DGP-IgA *per* 1000 inhabitants, and the ratio of both tests requests

(DGP-IgA /tTG-IgA), are presented as median (interquartile range). The differences in the indicators between years and AACC were calculated using the Kruskal-Wallis test analysis. A two-sided $P \leq 0.001$ rule was utilized as the criterion for rejecting the null hypothesis of no difference. All statistical analyses were carried out with SPSS version 22.0 (SPSS, Chicago, IL, USA).

Results

Table 1 shows the data of all participants and also the descriptive analysis of the three indicators in the three editions.

The request of tTG-IgA expressed *per* 1000 inhabitants increased along years from 3.99 to 5.90 ($P < 0.001$). On the other hand, the demand of DGP-IgA was maintained in the first two editions, and decreased in the third, although this difference was not statistically significant. The DGP-IgA/tTG-IgA ratio mildly diminished over time.

The 2014 edition joined 10 AACCS with more than 4 participants (in alphabetical order: Andalucía, Canarias, Castilla La Mancha, Castilla Leon, Extremadura, Galicia, Madrid, Murcia, País Vasco and Valencia). An eleventh group was created with those AACC that did not reach the 4 participants (in alphabetical order: Aragon, Asturias, Baleares, Cantabria and Cataluña).

Figure 1 shows graphically the DGP-IgA/tTG-IgA indicator results for year 2014 in the different AACC; there was a significant difference between regions, ranging from 0.01 to 0.57 ($P < 0.001$).

Discussion

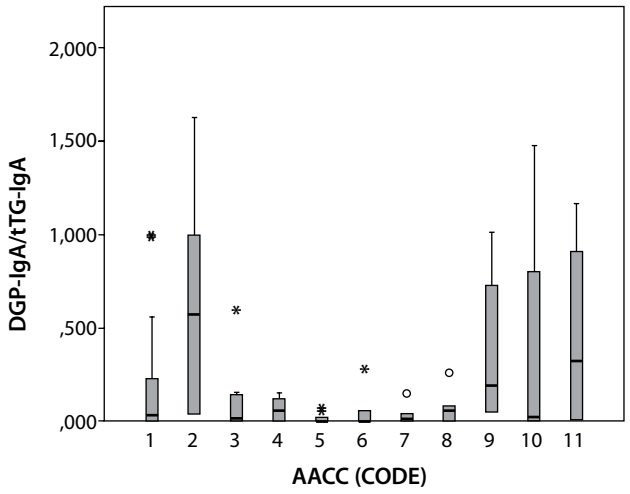
As expected, the primary care anti-tTG request increased along years and the ratio DGP-IgA/tTG-IgA decreased. No decrease was observed in the request of DGP-IgA in the first two editions, despite its request should have been limited to patients less than two years of age. There were big regional differences in the DGP-IgA/anti-tTG-IgA indicator result.

Although participants did not state if they implemented guidelines or not, the increment in tTG-IgA request along years was according to the guidelines for the diagnosis of CD. It took, however, more time to observe a subsequent decreased in the requests in DGP-IgA. It is true that the illness is more frequently detected in children, but the rates of DGP-IgA request seemed excessive at least in the first two editions, taking into account that only 2.85% of the Spanish population is younger than 2 years (8). Conversely, 6 AACCs showed very low results in that indicator, suggesting an earlier adoption of the new guidelines. However, the differences between regions of DGP-IgA/anti-tTG-

Table 1. Data and descriptive analysis of indicators in the three REDCONLAB editions

	REDCONLAB EDITION			
	2010	**2012**	**2014**	
Centers, N	37	76	110	
AACC, N	8	13	15	**P value**
Inhabitants attended, N	8,130,334	17,679,195	27,434,262	
Total DGP-IgA, N	8530	34,371	38,178	
Total tTG-IgA, N	34,996	86,962	169,097	
DGP-IgA/1000 inhabitants	0.68 (2.08)	0.60 (2.51)	0.35 (2.03)	0.927
tTg-IgA/1000 inhabitants	3.99 (3.20)	4.37 (3.45)	5.90 (4.30)	< 0.001
DGP-IgA/tTG-IgA ratio	0.16 (0.76)	0.12 (0.76)	0.06 (0.46)	0.548

AACC - Autonomous communities. tTG-IgA - tissue transglutaminase IgA antibodies. DGP-IgA - deamidated gliadin peptide IgA antibodies. Results are presented as median (interquartile range). The differences in the indicators between years were calculated using the Kruskal-Wallis test analysis. $P \leq 0.001$ was considered statistically significant.



	AACC code											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**P value**
Centers (N)	20	16	10	11	12	5	5	6	6	5	14	
Median	0.05	0.57	0.01	0.05	0.00	0.00	0.01	0.06	0.19	0.02	0.32	< 0.001
IQR	0.56	0.96	0.15	0.12	0.01	0.05	0.04	0.08	0.68	0.78	0.9	

IQR – interquartile range. AACC - Autonomous communities. The differences in the indicator between years was calculated using the Kruskal-Wallis test analysis. P ≤ 0.001 was considered statistically significant.

Figure 1. Bloxpot of ratio of tests requests (DGP-IgA /tTG-IgA) in different AACC.
tTG-IgA - tissue transglutaminase IgA antibodies. DGP-IgA - deamidated gliadin peptide IgA antibodies. AACC - Autonomous communities. º - outlier. * - extreme value.

IgA indicator results suggest that is probably due to different requesting customs in the different AACCs, or maybe different timing in the implementation of new clinical guidelines.

Our research is the first to study how CD serological tests are used over time in CD, a disorder prone to active case-finding strategy in primary care, to effectively improve its diagnostic rate (9).

Our results show that there is a need for a faster dissemination of scientific evidence, especially when it deals with a common and relevant disorder such as CD. In fact, an early diagnosis is clinically relevant, as possible evolution of undiagnosed cases include non-Hodgkin's Lymphoma, carcinomas or refractory CD. Our study also shows that the establishment of strategies is crucial to reach a homogeneous, appropriate and efficient request of diagnostic tests. There are interventions, that once designed through the application of scientific evidence and consensus with GPs, could be maintained over time, such as computer-aided algorithms that could substitute inappropriate tests for meaningful ones, as, in this case DGP-IgA for tTG-IgA when the patient is older than 2 years (10).

The main limitation of the study is that the differences in test requesting patterns, could be explained by case mix variations or groups of patients requiring similar tests, procedures, and resources, and also the number of children and adults among habitants attended in the different HD or AACC.

The variability in the request in CD serology markers, the delay in the demand of appropriate tests and the significant difference between AACC emphasize the need to improve communication and to establish interventions to enhance the appropriate use of laboratory tests to diagnose CD. Inter-

departmental and inter-regional cooperation would be crucial to develop strategies in order to optimize the use of laboratory tests.

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Potential conflict of interest

None declared.

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