

The prevalence of celiac disease and the appropriateness of the diagnosis in family medicine setting could be lower than expected

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Abstract. – **OBJECTIVE:** To assess the prevalence of celiac disease (CD) and the appropriateness of this diagnosis in the family medicine setting in Italy.

PATIENTS AND METHODS: The electronic databases of 16 general practitioners working in Rome (Italy) were analyzed. The prevalence of CD according to the Italian pathology identification code issued by the Italian National Health System was assessed. In addition, patients registered as having celiac disease without being assigned a pathology identification code were interviewed.

RESULTS: Overall, a population of 22,064 patients was analyzed. 91 patients had a diagnosis of CD (0.41%), 60 of whom had a pathology identification code (0.27%), and 31 did not (0.14%).

29 of these patients were interviewed, 16 (17.58% of the CD recorded patients) of whom reported being on a gluten-free or gluten restricted diet, with reported improvement in their clinical symptoms. Half of them further stated that they would not agree to resume a restriction free diet in order to make a definitive CD diagnosis, due to the risk of symptom recurrence.

CONCLUSIONS: In a family medicine setting, the prevalence of CD seems to be lower than expected, and one third of patients diagnosed with CD do not fulfill all diagnostic criteria. Any effort to improve the diagnostic work-up for CD should also be made in this setting.

Key Words:

Celiac disease, Diagnosis, Family medicine, Gluten-free diet, Prevalence.

Introduction

Celiac disease (CD) is a chronic small intestinal immune-mediated enteropathy triggered by dietary gluten in genetically predisposed people¹. Gluten is a protein present in cereals such as wheat, barley, rye and, probably, in some types of oats². The ingestion of gluten causes damage to the mucosa of the small intestine, which hinders correct nutrient uptake, and which causes several directly and indirectly related intestinal and extraintestinal diseases³. Currently, the only known treatment for CD is to follow a strict life-long gluten-free diet (GFD). Although CD is one of the most common chronic intestinal diseases⁴, its prevalence depends on the frequency distribution among the different populations of the HLA-DQ2 and HLA-DQ8 haplotypes⁵. It was estimated that the prevalence values for CD were 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania, with a higher prevalence in females and children⁶. However, these figures were drawn from referral centers, and generally, a lower prevalence is estimated in primary care⁷. A minority of people show the classic signs of CD, while the majority are asymptomatic. Thus, CD is difficult to diagnose in a definitive manner, explaining the significant underdiagnosis. Up to 90% of CD cases are being missed⁸.

In Italy, the prevalence of CD has increased in recent years. In 2019, the Italian National Health System (SSN) reported 225,418 CD cases, an increase of over 11,000 diagnoses compared to the previous year^{9,10}. Since the prevalence of CD is estimated to be 1% in Italy, this could mean that more than 350,000 cases did not get a correct diagnosis of CD. On the other hand, we know that GFD is currently advised in managing several functional disorders, with a concrete risk of over-diagnosis¹¹. Consequently, the role of general medicine becomes fundamental in making the correct diagnosis.

There are 6 million inhabitants in the Lazio region of central Italy, which is the second-largest Italian region in terms of the number of CD cases (more than 21,000)^{9,10}. We performed a study in a family medicine setting to assess the overall prevalence of CD and the appropriateness of this diagnosis.

Patients and Methods

We performed an observational study involving gastroenterologists and general practitioners (GPs) in family medicine to assess the prevalence of CD and the appropriateness of this diagnosis. The study was conducted in the Local Health Company “Azienda Sanitaria Locale (ASL) Roma 2”, (Rome, Italy), southeast of Rome, in the Lazio region, with around 1,300,000 inhabitants.

Firstly, an assessment of the prevalence of CD in primary care was undertaken, involving 16 GPs living and working in the ASL institution. Using either one or both their databases (Millewin/Medico 2000), we searched the International Classification of Diseases-Ninth Edition Revision-Clinical Modification (ICD-9-CM) for CD (code 579.0)¹². We interrogated the database for patients with a CD diagnosis who had the Italian exemption code for people with celiac disease (codes RI0060 or 059). This code indicates that a gastroenterologist expert in CD evaluated the patient, and that the diagnosis was made following the correct procedure required by the Italian National Health System^{9,10}.

The second step was to assess the appropriateness of this diagnosis. We identified patients with a recorded CD diagnosis but who did not have the exemption code for CD. All patients were contacted, and informed consent was obtained prior to their participation in a telephone interview. Participants were asked which symptoms they had experienced following gluten consumption and

which diagnostic evaluations had been performed according to their symptoms. Interviewed participants answered anonymously a list of 9 questions, some of which being multiple choice questions and others free text answers.

The study was conducted according to the World Medical Association Declaration of Helsinki of 1975 and adheres to the Belmont Report principles. It was reviewed and approved by the Ethics Committee of the “Sapienza” University, Rome, Italy (protocol 456/12).

Statistical Analysis

Data were analyzed using MedCalc® Release 14.8.1 (Mariakerke, Belgium).

Results

Of the 22,064 patients who were analyzed, 91 (0.41%) had a diagnosis of CD recorded as code ICD-9 CM 579.0. However, only 60 of them (65.9%, 0.27% of the overall investigated population) had the correct exemption code for CD, while 31 (34.1%, 0.14% of the overall investigated population) did not have the exemption code for CD.

29 of these subjects underwent a telephone interview, while two patients could not be traced. The interview results concluded that 9 subjects did not fulfill CD diagnostic criteria but were probably registered as having CD due to an error in the system. They currently consume gluten without any trouble. Four subjects who followed a GFD were confirmed as having CD and reported that they had forgotten to provide their exemption code to their family physician. 16 subjects followed a partial or total GFD to control their symptoms (Table I). Significantly, no gastroenterologist expert in CD suggested GFD in those patients. GFD was recommended by a nutritionist in four subjects and a homeopath in another two cases. However, in most cases, the patients decided to start a GFD independently. All patients found significant benefit from following a GFD and were concerned about returning to an unrestricted diet. When asked whether they would agree to stop their GFD and switch back to a free diet to start a correct diagnostic approach for CD, half of them (8 subjects) declined this opportunity despite the benefits of an accurate disease diagnosis. Their refusal was based on the significant benefits derived from the GFD and they did not want to risk renewed trouble with gluten ingestion. In

Table I. Patients under GFD without an established diagnosis of celiac disease.

Patient	Main symptom	EGD scopy with biopsy	Serological biomarkers (EmA/t-TGA)	Other significant diagnosis	Who did CD diagnosis	Symptomatic response to GFD	Do you agree to switch back to free diet in order to start a correct diagnostic approach for CD?
1	Abdominal pain	Not done	EmA - /t-TGA+	Suspected CD in childhood, never confirmed	Him/herself	Yes	Yes
2	Headache	Not done	EmA -/ t-TGA -	Lactose malabsorption	Him/herself	Yes	No
3	Abdominal pain	Not done	EmA -/ t-TGA -	Nickel allergy, Depression	Nutritionist	Yes	No
4	Dermatitis	Not done	Not done	/	Him/herself	Yes	Yes
5	Diarrhea	Not done	EmA -/ t-TGA -	/	Him/herself	Yes	Yes
6	Diarrhea	Not done	EmA -/ t-TGA -	CD family history	Him/herself	Yes	No
7	Abdominal pain	Not done	EmA -/ t-TGA -	/	Him/herself	Yes	Yes
8	Weight loss	Not done	EmA -/ t-TGA -	Infertility	Homeopath	Yes	No
9	Anemia	Not done	EmA -/ t-TGA -	CD family history	Homeopath	Yes	No
10	Asthenia	Not done	EmA -/ t-TGA -	/	Nutritionist	Yes	Yes
11	Asthenia	Not done	EmA -/ t-TGA -	/	Nutritionist	Yes	Yes
12	Oral ulcers	Not done	EmA -/ t-TGA -	Chrome allergy	Nutritionist	Yes	Yes
13	Flatulence	Not done	EmA -/ t-TGA -	/	Him/herself	Yes	Yes
14	Abdominal pain	Not done	t-TGA+	/	Him/herself	Yes	No
15	Constipation	Not done	Not done	CD family history	Him/herself	Yes	No
16	Diarrhea	Not done	Not done	Food allergy	Him/herself	Yes	No

CD: Celiac disease; EGD scopy: Esophago-Gastro-Duodenoscopy; EmA: anti-endomysium antibodies; t-TGA: anti-tissue transglutaminase antibodies; GFD: Gluten-Free Diet.

particular, the correct diagnostic approach was rejected by two patients with a history of anti-transglutaminase antibodies positivity but without an intestinal biopsy.

Discussion

Since gluten exposure in CD can lead to severe complications¹³, it is essential to obtain the correct diagnosis as soon as possible. Even considering the clinical pattern of the disease, which increasingly appears with subclinical or absent symptoms³, the prevalence in primary care seems to be lower than the 1% expected, a prevalence that only seems to be reached in the pediatric population^{14,15}. This study was designed to assess the real-life diagnosis of CD in primary care, leading to the main findings which deserve commenting.

Firstly, we found the actual prevalence of CD to be 0.41% in primary care. Although this prevalence was higher than that reported by a study conducted in the Aragón Spanish region⁷, it was significantly lower than the estimated 1%. This low prevalence could mean that the part hidden below the waterline of the “celiac iceberg” is much larger than estimated, at least in primary care¹⁵. The clinical manifestations of CD could likely justify this underdiagnosis. For example, most patients are still considered to be suffering from Irritable Bowel Syndrome (IBS) without any actual effort to identify other causes of the symptoms, despite the relationship between IBS and CD being well known¹⁶, and the investigation for CD in IBS patients being strongly advised¹. Therefore, primary care specialists are called upon to make further efforts to early identify suspicious symptoms which will require further investigation¹⁷.

Secondly, there are too many false diagnoses of CD in primary care which do not fit into the official criteria for CD diagnosis. As reported, 16 patients were registered as having CD and following a partial or total GFD without ever having searched for antibodies or having undergone an intestinal biopsy. These diagnoses are often performed by professional figures other than gastroenterologists and are often a consequence of non-validated tests for CD, such as the cytotoxic test, the sublingual or subcutaneous provocation/neutralization test. As a result, public healthcare spending is being unnecessarily burdened in several countries (including Italy) by the growing number of prescriptions for gluten-free diets¹⁷.

Moreover, it is often the patients themselves who decide to start a GFD, with several reasons

justifying this approach such as having a family history of CD, and therefore a fear of having CD¹⁸, or the possible association between CD and nickel allergy¹⁹, the hypothesized benefit of GFD on IBS symptoms that can mimic a response to CD²⁰ or even the possibility of suffering from Non-Celiac Gluten Sensitivity (NCGS)²¹. In fact, we cannot exclude that some patients may either have CD²² or may suffer from NCGS. Still, the most disturbing fact is that patients refuse to follow a clear and common path to reach a proper diagnosis of CD, preferring to rely on an unconventional approach. In this respect, mass media have had a negative impact when describing the “miraculous” properties of the GFD. The story of a famous tennis player saved by the gluten-free diet proposed by his nutritionist is well known²³, and many other celebrities have claimed to have had significant benefits on their health after starting GFD²⁴. Pity that all these celebrities forget the serious effects that the GFD can cause in non-CD or non-NCGS people²⁵.

Conclusions

In conclusion, this large study in primary care revealed that the prevalence of CD is lower than expected and that many CD diagnoses do not meet the official diagnostic criteria. Therefore, family medicine is called upon to make an effort on improving the CD diagnosis in patients with suspicious symptoms and also to discourage patients from following a GFD without a proper medical diagnosis.

Authors' Contributions

Conception and design of the study: A.T. Acquisition of data, or analysis and interpretation of data: G.M.G., I.D.V., F.F., A.C., G.N., R.C., A.F., A.S., C.B., A.T. Drafted the article or revised it critically for important intellectual content: W.E. and A.T. final approval of the version to be submitted: G.M.G., I.D.V., F.F., A.C., G.N., R.C., A.F., A.S., C.B., W.E. and A.T.

Conflict of Interest

All the authors have no conflict of interest to declare.

Ethics Approval

The study was reviewed and approved by the Ethics Committee of the “Sapienza” University, Rome, Italy (protocol 456/12).

Funding

No financial support was obtained for this study.

Informed Consent

Informed consent was obtained prior to their participation in a telephone interview.

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