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The Burden of Depressive and Bipolar Disorders in Celiac Disease

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Abstract: *Introduction*: Aims: to measure the association between Celiac Disease (CD) and affective disorders, particularly Bipolar Disorder (BD), since it has not been studied yet, and to measure how much the quality of life (QoL) of a person with CD is affected by comorbidity with these disorders. *Methods*: Design: Case-control study. Cases: 60 consecutive patients with CD. Controls: 240 subjects without CD, randomly selected after sex- and age-matching from a database of an epidemiological study. Psychiatric diagnoses according to DSM-IV carried out by physicians using structured interview tools (ANTAS-SCID). QoL was measured by means of SF-12. *Results*: The lifetime prevalence of Major Depressive Disorder (MDD) was higher in CD than in controls (30.0% *vs* 8.3%, P<0.0001) as well as Panic Disorder (PD) (18.3% *vs* 5.4%, P<0.001) and BD (4.3% *vs* 0.4%, *P<0.005*). Patients with CD show a lower mean score than controls on SF12 (35.8±5.7 *vs*. 38.2±6.4; p=0.010), but those without comorbidity with MDD, PD and BD do not. The attributable burden of CD in worsening QoL - when comorbid with these disorders - was found comparable to that of serious chronic diseases like Wilson's Disease, and lower than Multiple Sclerosis only. *Conclusion*: MDD, PD and BD are strictly associated with CD. The comorbidity with these disorders is the key determinant of impaired quality of life in CD. Thus a preventive action on mood and anxiety disorders in patients suffering from CD is required. Moreover a screening for CD in people with affective disorders and showing key symptoms or family history of CD is recommended.

Keywords: Attributable burden, bipolar disorder, case control study, celiac disease, depressive disorder, quality of life.

INTRODUCTION

A previous case control survey carried out by our group showed significant risks for the patients with celiac disease, of mood disorders such as major depressive disorders (MDD) (OR = 2.7), and of anxiety disorders such as panic disorders (PD) (OR = 7.3) [1]. Several studies have confirmed this association in the past years, even if none of the new researches adopted both a case control design and a psychiatric diagnosis made by a clinical structured interview, unlike our previous research [2].

According to other authors the association was interpreted as being caused by malabsorption of tryptophan leading, in turn, to a decreased central serotonin synthesis [3]. Other mechanisms related to the autoimmune pathogenesis of celiac disease need to be taken into account as well: cytokines may exert an effect on the brain circuits related to mood regulation; pathogenetic links between autoimmune disease and affective disorders were recently underlined [4, 5]. The association with celiac disease - especially in the case of panic disorders - was found strictly linked to thyroid autoimmunity [1].

It should be noted that a close association with autoimmune diseases, and especially with thyroid disease that is so common in celiac disease, was recently found in bipolar disorder as well [6].

Our previous research did not allow to identify bipolar disorder (BD): given the requirement to apply a consistent diagnostic method to cases and controls, the psychiatric diagnosis was made with the Italian version of the CIDI simplified interview [7], a tool adopted in a community survey in Sardinia, and the databank of which was used to draw controls [8]. This short version did not identify BD. It is, however, interesting to underline that a subsequent paper produced by the same research found an even stronger association between recurrent brief depression and celiac disease (OR = 7.6) than the association found with MDD. This disorder is believed to fall in the Spectrum of Bipolar Disorders [9].

More recently an epidemiological study was conducted in Italy with the specific objective to identify bipolar disorder and a consequent diagnostic methodology [10].

Today the database of this research allows to conduct a case-control study on celiac disease similar to the previous study, but with the possibility to clarify the association between celiac disease and BD. Thus the aim of this study is to measure the association between Celiac Disease and affective disorders, particularly with BP, which has not been studied yet.

The new community survey has also been conducted with the aim of measuring the health-related quality of life in

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the community. The quality of life is a relevant concept introduced as a measure of general well being [11], but also of outcome in chronic diseases inducing disability [12]. This allows the new case-control study to verify the impairment of health-related quality of life in celiac disease compared to a community control sample, and to measure how much the comorbidity with a mood disorder can affect the quality of life of a person with celiac disease.

METHODS

Study Design

Case-Control Study

Sample. The sample of cases was recruited at the Gastroenterology Unit of the University Hospital of the University of Cagliari. Participation to the study was proposed to all patients admitted consecutively to the Unit with a diagnosis of celiac disease from July 2014 to March 2015.

The inclusion criteria were: age ≥18 years; a diagnosis of celiac disease. Subjects with cognitive deficits making assessment impossible were excluded.

The selected sample was compared with a control sample extracted with a computerized randomization technique after sex and age (± 1 year) matching from the database of a population study, the main results of which were already published [13]. For each case, a cell was built containing all the possible same-age and -sex controls. Within each cell, four controls were randomly extracted. The extracted controls were then excluded from the extraction pool.

Psychiatric Evaluation. Patients and controls underwent a clinical evaluation through:

1. The semi-structured computerized interview ANTAS (Advanced Tools and Neuropsychiatric Assessment Schedule) [13], derived in part from the SCID [14], to assess the presence of psychiatric disorders. Diagnosis was made according to DSM – IV-TR [15]. A preliminary study found a good reliability between ANTAS and SCID (13).
2. Mood Disorder Questionnaire (MDQ) [16], Italian version [17] to assess bipolar-spectrum disorders.
3. Health Survey Short Form (SF - 12) [18] for the evaluation of quality of life. The SF-12 includes dimensions concerning: physical functioning, role and activities linked to physical health, emotional state, physical pain, self-assessment of general health, vitality, social activity and mental health. The tool refers to the month preceding the interview.

Diagnosis of Celiac Disease in Cases

The diagnosis of Celiac Disease (CD) relies on the concordance of clinical, serological, pathological and genetic features [19]. Gastrointestinal mucosal inflammation results in malabsorption, diarrhea, iron-deficiency anemia and ostheoporosis; while other several secondary symptoms, like dermatitis herpetiforme, arthritis and neurological disorders are linked to innate immune responses that act in concert with the adaptive immunity. Serology is based on the detection of class IgA or IgG anti-tissue transglutaminase (anti-tTG) and antiendomysial antibodies [20]. However the diagnosis of CD still rests on evidence of changes in the histology of the small intestinal mucosa, following duodenum biopsy. The classic celiac lesions occur in the proximal small intestine with villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytosis [21]. Well identified haplotypes in the human leukocyte antigen (HLA) class II region (either DQ2 –DQA 0501-DQB 0201 or DQ8 -DQA 0301- DQB 0302) confer a large part of the genetic susceptibility to CD [22].

Diagnosis of Celiac Disease in Controls

Each control was interviewed about general wellbeing, the current presence of any disease and any illness suffered during the subject's life; consultation with physicians; and medical tests made either routinely (*e.g.*, work or driver license eligibility tests), or to help diagnose or monitor medical issues. Diagnosis of physical illness was reported using a structured form.

Statistical Analysis. The analysis of variance (one-way ANOVA) was adopted for the comparison of parametric variables, while the χ^2 test was adopted for nonparametric variables. Odds ratios and confidence intervals (95%) were calculated through Miettinen's simplified method. The "Attributable Burden" of celiac disease in deteriorating quality of life was measured by subtracting the score at the SF-12 of the sample with celiac disease from the average score achieved at the SF-12 by the standardized sample without celiac disease.

This value was compared to the score calculated for other conditions and on the basis of studies conducted with a similar case-control design, where cases were consecutive patients selected at the same University Hospital of Cagliari and control groups had been extracted with the same matching technique after stratification by sex and age from the same database [23-27].

Ethical Aspects

Subjects (Cases and Controls) gave their informed consent for the use of anonymous data for an aggregate study. The epidemiological study (from which data bank controls had been drawn) was approved by the ethics committee of the Italian National Health Institute (Rome), and the approved project anticipated and planned the conduction of a series of case–control studies like this one. This project was additionally approved by the independent ethics committee of the Azienda Mista Ospedaliero Universitaria di Cagliari. Data were not nominal at the source, and each subject was identified by a code number.

RESULTS

The sample of this research consists of 60 patients with celiac disease: 10 men (16.7%) and 50 female (83.3%). The control group consists of 240 subjects without diagnosis of celiac disease; thanks to the block-randomization technique after matching, the sample of controls is perfectly homogeneous with that of cases concerning such variables as gender and age. The demographic characteristics of the sample are summarized in Table **1**.

Table 1. Demographic characteristics of the sample.

	Cases (46)	Controls (240)
Age (mean ± sd)	40.95± 12.88	40.79±12.34
Gender		
m **f**	10 (16.7 %) 50 (83.3%)	40 (16.7%) 200 (83.3%)

Patients with celiac disease (cases) show a lifetime prevalence of manic / hypomanic episodes, identified as positives at the screening test (MDQ ≥7), similar to controls (Table **2**) (6.7% *vs* 3.75%, χ^2=0.98, P=0.321, OR=1.83, CI 95% 0.46 -6.84). The lifetime prevalence of major depressive disorder, according to DSM-IV TR criteria, is higher than in controls at a statistically significant level (30.0%*vs* 8.3%, χ^2=20.37, P<0.0001, OR=4.71, CI 95% 2.17 -10.25) as is the lifetime prevalence of Panic Disorder (18.3% *vs* 5.4%, χ^2=10.88, P<0.001, OR=3.92, CI 95% 1.53 -10.250). Regarding the prevalence of DSM-IV-TR Bipolar Disorder (BP 1/2 BP), the difference of frequencies between cases and controls reaches statistical significance, with higher frequencies in celiac disease (4.3% *vs* 0.4%, χ^2=7.94 (with Yates correction, P<0.005, OR=17.1, CI 95% 1.75 -409.17). Patients with celiac disease (cases) show a significantly lower mean score on SF12 than healthy controls: 35.83 ± 5.72 *vs.* 38.21 ± 6.47; (df 1, 288, 289, F=6.789, p=0.010).

Table **3** analyzes in detail whether the difference in the impairment of quality of life highlighted in celiac disease as against healthy controls can be related to comorbidity with Major Depressive Disorder, Panic Disorder and Bipolar Disorder. Statistical analysis showed a sharp deterioration of the SF-12 score in patients with celiac disease having at least one diagnosis of the following: Major Depressive Disorder, Panic Disorder, or Bipolar Disorder. The level of quality of life perceived by the sample of patients with celiac disease and by those without this type of diagnosis does not differ from the control sample without celiac disease.

Table **4** shows that the "Attributable Burden" due to celiac disease in deteriorating quality of life is estimated at 2.38±1.0 SF-12 points on average. The table highlights how the condition involves an attributable burden lower than severe diseases such as Wilson's disease, Major Depressive Disorder; Eating Disorder; Severe Carotid Atherosclerosis or Multiple Sclerosis, but also lower than less severe illnesses such as Panic Disorder.

However, when comparing the attributable burden of celiac disease comorbid with mood or anxiety disorders (major depressive disorder, bipolar disorder and panic disorder) a "weight" comparable to that of the serious diseases considered in this paper is found, this weight being lighter only than that of multiple sclerosis, and higher than the weight attributable to Panic Disorder in patients without celiac disease.

DISCUSSION

The study has found that 30% of the sample of patients with celiac disease has a lifetime diagnosis of Major Depressive Disorder, or a risk almost 5 times higher than the reference sample without celiac disease. Panic disorder has a frequency of 18% and a 4-fold risk in celiac disease than in the control sample. The figures about Major Depressive Disorder and Panic Disorder confirm a previous study of our group (1) conducted with a similar case-control design in which lifetime MDD was found in 41.7% of a celiac sample (OR=2.7%) and Panic Disorder in 13.9% (OR=7.3). In that study the psychiatric interviews were conducted through a short and highly structured instrument, the CIDIS Italian version [7], that did not allow the diagnosis and screening of Bipolar Disorder.

Regarding Bipolar Disorder, it had a frequency in approximately 4% of patients, therefore lower than that of Major Depressive Disorder; however, since the frequency of Bipolar Disorder in the sample drawn from the general population is low, the risk in our sample, as compared to the general population, exceeds 17 times and is even higher than the risk of MDD or Panic Disorder.

The risk of bipolar disorder in patients with celiac disease had never been highlighted before this study. The study of Ludviqsson *et al*. [28] conducted in a community sample of Sweden did not find any association between bipolar disorder and celiac disease, but in this survey both diagnoses were carried out with screening tools, which might have caused bias considering the well-known difficulty of diagnosing bipolar disorders with screening tools [29]. The study of Dickerson *et al*. [30] showed high levels of IgG anti-gliadin in patients with acute mania, but no other markers of celiac disease. One Irish study found the presence of bipolar disorder in 4% of a clinical sample of patients with celiac disease

Table 2. Lifetime prevalence of mood and anxiety disorders in cases and controls.

Lifetime prevalence disorder	Cases (60)	Controls (240)	χ2 (1df)	P	OR	CI 95%
MDQ+	4 (6.7%)	9 (3.75%)	0.98	P=0.321	1.83	0.46 -6.84
MDD	18 (30.0%)	20 (8.3%)	20.37	P<0.0001	4.71	2.17-10.25
BD (BP1-BP2)	4 (4.3%);	1 (0.4%)	7.94 (Yates)	P=0.005	17.1	1.75-409.17
Panic Disorder	11 (18.3%)	13 (5.4%)	10.88	P<0.001	3.92	1.53-10.2

Table 3. Quality of life in celiac disease with or without affective disorders and in controls.

	Quality of life in cases (N=60)	Quality of life in cases with comobid DSM-IV TR, MDD; BD and Panic Disorder (N=26)	Quality of life in cases without comorbid DSM-IV TR, MDD; BD and Panic Disorder (N=26) (N=34)	Quality of Life in controls (N=240)
SF-12 Score	35.83 ± 5.72	33.9±5.23	37.3±6.1	38.21± 6.47
Differences between cases and controls	F=6.789, p=0.010 (df 1, 288, 289)	F=8.975, p=0.004 (1,84,85)	F=4.447, p=0.505	----------

Table 4. "Attributable Burden" due to Celiac Disease in worsening quality of life: comparison with other conditions on the basis of case-control studies where cases were consecutive patients selected at the same University Hospital of Cagliari, and control groups were extracted with equal matching technique after stratification by sex and age from the same database (Carta *et al.* 2012; Carta *et al.* 2014a; Carta *et al.* 2014b; Carta *et al.* 2015).

Disorder	SF-12 (Mean±sd)	Attributable burden in worsening QoL	Comparison with Celiac disease (df)	Comparison with celiac disease and comorbidity (df)
Major Depressive Disorder	33.8±9.2	**5.6±3.6 (N=287)**	F=40.38, P<0.0001 (1,345,346)	F=2.48, P=0.116, (1,311,312)
Multiple Sclerosis	29.5±7.3	**7.0±3.5 (N=201)**	F=101.8, P<0.0001 (1,259,260)	F=15.1, P<0.0001 (1,255,226)
Wilson's Disease	33.8±9.0	**4.4±1.7 (N=23)**	F=44.8; P<0.0001 (1,81,82)	F=0.05; P=0.828 (1,47,48)
Eating Disorders	34.9±6.2	4.4±6.6 (N=60)	F=5.49; P<0.021 (1,118,119)	F=0.01; P=939 (1,84,85)
Panic Disorder	35.5±4.6	2.9±0.9 (N=123)	F=12.5; P=0.001 (1,181,182)	F=39.87; P<0.0001 (1,147,148)
Carotid Atheriosclerosis	30.6±8.1	6.2±5.0 (N=46)	F=33.3; P<0.0001 (1,104,105)	F=3.55; P<0.064 (1,70,72)
Celiac Disease	35.83±5.72	2.4±1.0 (N=60)		
Celiac Disease with comorbidity (DDM+DB+DP)	33.9±5.23	4.3±1.5 (N=26)		

addressed to a specialized center [31]. The hypothesis of an association between bipolar disorder and celiac disease is, moreover, consistent with the fact that celiac disease increases immune activation, which is hypothesized to act as an important factor in the pathogenesis of bipolar disorder [32].

An apparently contradictory characteristic of our sample is that we found an association with celiac disease and Bipolar Disorder diagnosed by a clinical interview, and not between celiac disease and "cases" screened with the MDQ. Positivity at this questionnaire should include "subthreshold" forms that do not reach the diagnostic criteria but fall in the "spectrum" of bipolar disorders [33]. This feature differentiates celiac disease from other disorders that have revealed an association with bipolar disorder, such as multiple sclerosis [34] or Wilson's disease [3], notwithstanding the risk of resulting positive to the MDQ hen using a similar methodology was highlighted.

The discrepancy may be explained by two hypotheses:

1) In the specificity of such bipolar disorders' being associated with celiac disease, the screener MDQ may be less accurate than in other conditions. This hypothesis acquires a different profile of bipolar disorder symptoms in the course of celiac disease, for example a greater preponderance of dysphoric-irritable symptoms, also in subthreshold form, which are hardly highlighted with the MDQ. On the other hand, when measuring the sensitivity of the instrument in this sample by means of the clinical diagnosis of Bipolar Disorder as made with the Gold Standard interview, such sensitivity results acceptable (0.75) and even more accurate than in other samples.
2) The hypothesis is that the association could not be based on a common genetic background between the two disorders; rather, if a person is vulnerable to bipolar disorder (independently from celiac disease), then there is a risk that celiac disease triggers the bipolar disorder.

Future studies will clarify these findings. The role of autoimmunity will also be evaluated in a pathogenetic framework.

Our research shows that celiac disease causes a statistically significant impairment in the quality of life of the affected subjects, as compared to the control sample without the disorder. Results point out that this worsening of quality

of life does not reach the burden of chronic and disabling diseases such as multiple sclerosis, cerebral vascular disease or Wilson's disease, or of severe psychiatric disorders such as major depression or eating disorders, and it does not even reach the burden of less serious disorders like panic disorder.

However, given the close association of celiac disease with other disorders, which are in themselves capable of disabling and impairing the quality of life, the question was whether comorbidity could play a role in the impairment of quality of life.

The results show, surprisingly, that in the absence of psychiatric illness people with celiac disease do not have an impaired quality of life compared to the people who do not suffer from celiac disease. But when measuring the burden suffered by people with celiac disease comorbid with mood disorders and anxiety, the "dual diagnosis" (celiac disease plus at least one diagnosis of MDD, panic disorder, or bipolar disorder) lowers the quality of life in the same manner as serious chronic diseases (Wilson, cerebrovascular vascular disease), well above panic disorder, and second only to multiple sclerosis.

This result provides important insights: in celiac disease affective disorders must be not only treated promptly but above all, prevented.

An adequate method should be applied to more extensive samples allowing multivariate statistical analysis, to understand whether the deterioration of the quality of life is completely dependent upon psychiatric disorders or whether it is, at least in part, a result of the conditions frequently found in celiac disease and associated with mood disorders, such as autoimmune diseases.

Past research found a high frequency of mood disorders and anxiety disorders in celiac disease: considering our two research works conducted almost fifteen years apart, and considering only the three most important diagnoses of anxiety and mood disorders, almost a person with celiac disease out of two presented such comorbidities; while considering the fact that celiac disease itself shows a significant frequency in the general population - around 1-2% [35] - our results suggest it advisable to perform an adequate screening for celiac disease on all the people with affective disorders that show some key symptoms, or have a family history of celiac disease.

LIMITS

An obvious limitation of our study is that while the sample of cases had received a diagnosis of celiac disease according to clinical and laboratory standard criteria, in the control sample the diagnosis was based solely on medical history and previous investigations. It might be possible, then, due to the high frequency of celiac disease, that a portion of the subjects checked as healthy is actually undiagnosed cases of celiac disease.

But this does not detract any importance of our findings because, if this were true and conspicuous, it would only decrease the measure of odd ratios and the measure of risk between cases and controls.

The celiac disease cases were recruited at a rheumatologic unit. A Berkson's bias may have occurred even if the study sample consists of patients for long time in charge with the same unit, thus most of them were stabilized and in clinical remission.

Little has been documented in the present study about any potential additional determinant, which may have affected the quality of life. With a special emphasis towards some potential medical comorbidities found to be associated to celiac disease. A future research with a more large sample allowing a multivariate analysis can clarify these hypotheses.

CONCLUSION

Our study found that major depression, bipolar disorder and panic disorder are strictly associated with celiac disease.

The comorbidity with these three diagnoses is the key determinant of impaired quality of life in celiac disease. Therefore it is extremely important to conduct a preventive action of mood and anxiety disorder in patients suffering from celiac disease.

By contrast, given the high frequency of mood disorders and anxiety disorders in celiac disease and the fact that celiac disease itself has a significant frequency in the general population, a screening of celiac disease is recommended to all the people with affective disorders showing some key symptoms or family history of celiac disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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