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Emotional Correlates of the Celiac Disease: A Possible Link in the Gut-Brain Connection?

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Abstract: *The purpose was to examine the alexithymic characteristics of patients with celiac disease. In view of the evidence about higher scores of alexithymia in patients with different physical disorders in general and gastrointestinal ones in particular, we expected that celiac patients would score higher on alexithymia than healthy controls. The subjects were 40 celiac patients (mean age=28.37 yrs) and 39 healthy controls. The groups did not differ in age, gender distribution or education. The subjects were administered the Toronto Alexithymia Scale (TAS-20). The results showed that celiac patients scored significantly higher than the controls on alexithymia (the total score and the 3 subscales constituting the TAS-20). There were no significant differences between celiac patients with long and short disease duration, except for a tendency for long duration patients to score higher on one subscale. The findings indicate that celiac patients have alexithymic characteristics, and that this tendency is unrelated to disease duration, age of disease onset and diagnosis and strength of genetic background. The importance of the findings in regard to the gut-brain axis is discussed.*

Keywords: *Celiac disease, Alexithymia*

The study deals with alexithymia which is a particular syndrome of emotional tendencies, manifested in a reduced capacity to identify, describe and express one's own feelings, difficulty distinguishing between emotions and sensations, lack of imaginative thought and focusing on concrete external facts (Taylor, Bagby, & Parker, 1997). The purpose was to explore the relation between alexithymia and celiac disease (CD). Celiac is an autoimmune gastrointestinal disorder characterized by damage to the small intestine following the ingestion of foods with gluten. The study was inspired by the recent increase in information about the gut-brain connection and its impact on experiential and behavioral manifestations. Several studies suggest that the gut-brain axis constitutes a bidirectional route of communication, involving neural, hormonal and immunological connections (Cryan & Dinan, 2012; Mayer, 2011) and that dysfunction of this axis may result in pathological symptoms, such as autism, Parkinson's disease or schizophrenia (Buie, 2015; Petra et al., 2015; Schneiderhan, Master-Hunter, & Locke , 2016; Wang & Kasper, 2014). Further, there is evidence that the composition and function of the gut microbes are affected by stress and anxiety, thus modulating the activity and activation of the gut-brain axis (Dinan & Cryan, 2012; Rhee, Pothoulakis, & Mayer, 2009). The role of stress in this context is of particular importance because several studies showed that alexithymia is related to poor coping with stress (Funkenishi & Rahe, 1995; Kerr, Johnson, Gans, & Krumrine, 2004; Martin & Pihl, 1985; Singh, Arteche, & Holder, 2011; Martínez-Sánchez, Ortiz-Soria, & Ato-García, 2001).

A major reason for the choice of alexithymia as a focal construct in this study is the role it was shown to play in regard to different physical disorders. A large body of data testifies to the salience of alexithymia in patients with different psychosomatic disorders, as chronic pain (e.g., Kreitler, Gohar, Eldar, Ezer, & Niv, 1995; Sriram, Chaturverdi, Gopinath, & Shanmugan, 1987), temporomandibular joint disorders and orofacial pain (Sipilä et al., 2001), migraine headache (Federman & Mohns, 1984), fibromyalgia (Ghiggia et al., 2017), pain in cancer patients (Porcelli 2007). respiratory diseases (Kleiger & Jones, 1980), chronic obstructive pulmonary disease (Tselebis et al., 2010), cancer (Todarello, La Pesa, Zaka, Martino, & Lattanzio, 1989), myocardial disorders (Silva, Freitas, Moreira, Santos, & Almeida, 2016), multiple sclerosis (Chalah & Ayache, 2017), lupus erythematosus (Barbasio

et al., 2015), chronic kidney disease (Kojima, 2012), chronic hair disorders (Poot, 2004), chronic skin disorders (Giovannelli et al., 2016), chronic urticaria (Barbosa, Freitas, & Barbosa, 2011), Ankylosing Spondylitis (Solmaz, Binbay, Cidem, Sağir, & Karacan, 2014), inflammatory responses (Conti, Caraffa, Kritas, Ronconi, & Fulcheri, 2017) . Summarizing the results of 11 studies with a total of 1568 patients, Pedinielli (1992, p. 50) concluded that the percentage of alexithymic subjects in the different groups of patients ranged from 20% (for gastroenterologic patients) to 47% (for pneumology patients).

Also patients with different kinds of mental disorders were found to score higher on alexithymia than healthy controls, for example, conversion disorders (Farooq & Yousaf, 2016), eating disorders (Westwood, Kerr-Gaffney, Stahl, & Tchanturia, 2017), pathological gambling (Elmas, Cesur, & Oral, 2017), and even suicide risk (De Berardis et al., 2017).

Since CD is a gastrointestinal disorder it is of special importance in this context to examine studies of alexithymia in patients suffering from disorders in this domain. As compared with healthy controls alexithymia was found to be higher in patients with gastrointestinal symptoms (Acklin & Alexander, 1988), peptic or duodenal ulcer (Banerjee & Vyas, 1993; Heerlein, de la Parra, Aronson, & Lolas, 1984; Strauss, 1988), inflammatory bowel disease (Porcelli, Zaka, Leoci, Centonze, & Taylor, 1995), ulcerative colitis or Crohn's disease (Smith & van der Meer, 1994). Further, as compared with a mixed control group of subjects with gallstone disease, inguinal hernia or varicose veins, alexithymia is higher in a mixed group of patients with duodenal ulcer, ulcerative colitis and irritable colon syndrome (Keltikangas-Jaervinen, 1986). However, as compared with back pain patients alexithymia is lower in patients with gastrointestinal symptoms (Acklin & Alexander, 1988); and as compared with psychoneurotic patients it is lower in patients with irritable bowel syndrome, ulcerative colitis (Taylor, Doody & Newman, 1981), or Crohn's disease (Taylor & Doody, 1982). Notably, comparing different diagnoses of gastrointestinal disorders showed that while Crohn's disease and ulcerative colitis patients did not differ in alexithymia (Porcelli et al., 1995; Taylor & Doody, 1992), some other groups did differ in alexithymia: patients with duodenal ulcer scored higher on alexithymia than patients with erosive gastritis (Fukunishi, Kikuchi, Kaji, & Yamasaki, 1997) or irritable bowel syndrome (Heerlein et al., 1984).Patients with irritable bowel syndrome scored higher than those with ulcerative colitis or appendicitis (Fava & Pavan, 1976-7), though in Japan patients with ulcerative colitis scored higher than those with irritable bowel syndrome or peptic ulcer (Nakagawa, Sugita, Nakai & Ikemi, 1979); patients with chronic pancreatitis scored higher than those with peptic ulcer or irritable colon syndrome (Nakagawa et al., 1979); but no differences in alexithymia were found in the following four groups of gastroenterological disorders: chronic gastritis associated with helicobacterial infection, intestinal irritation syndrome**,** gastro-oesophageal reflux disease and chronic recurring duodenal ulcer (Sekoian & Grigorian, 2008). In patients with irritable bowel syndrome alexithymia scores were correlated with gastric specific anxiety (Porcelli, De Carne, & Leonardo, 2014). It is of interest to note that at least in patients with inflammatory bowel disease alexithymia did not change with the duration of the disease and - unlike depression or anxiety - was unrelated to changes in the level of disease activity over time (Porcelli et al., 1995; Porcelli, Leoci, Guerra, Taylor, & Bagby, 1996). In functional gastrointestinal disorders alexithymia may be indicative of a poor outcome (Porcelli et al., 2003). The reviewed studies show that alexithymia is a correlate of gastrointestinal disorders in general and of specific gastrointestinal disorders in particular. Further, it appears to be one of the potential risk factors for gastrointestinal disorders (Keltikangas-Jarvinen, 1987), especially in combination with other factors, such as poor social support (Fukunishi, Kaji, Hosaka, Berger, & Rahe, 1997).

In sum, empirical evidence shows that alexithymia is a psychological correlate of physical disorders, as well as of the specific disorders in the gastrointestinal domain. Alexithymia seems to be of particular importance relative to the different psychological factors that have been shown to be related to physical diseases. The reason is that on the psychological level it was found to be related particularly to stress (Fukunishi & Rahe, 1995) and to emotional dysregulation (Derks, Westerhof, & Bohlmeijer, 2017), both of which are general tendencies likely to be involved in a great many physical disorders. On the physical level, it was found to be related to specific physical indicators, mainly inflammatory cytokines (Conti et al., 2017),

impaired immunological functioning (Guilbaud, Corcos, Hjalmarsson, Loas, & Jeammet, 2003), and frontal EEG asymmetry (Flasbeck, Popkirov, & Brüne, 2017), which seem to be indicative of general physiologically-based tendencies. Hence, alexithymia is a construct with a unique potential to shed light on basic psychophysiological processes important for disease and health.

In the present study the construct of alexithymia is applied to the celiac disease (CD), which is a physical gastrointestinal disorder whose psychological correlates have hardly been studied up to now. CD is a disorder of the small bowel related to eating wheat gluten which results in malabsorption of nutrients and diarrhea (therefore it is also called gluten-sensitive enteropathy). Its major diagnostic criteria are small bowel mucosal atrophy and clinical remission on a gluten-free diet. The disease occurs all over the world, wherever wheat is eaten, especially in Europe. Although its precise incidence is not yet known, the prevalence of CD has been estimated to approximate 0.5%-1% in different parts of the world (Gujral, Freeman, & Thompson, 2012). The incidence of CD is age and gender dependent: it occurs most frequently in children 0 to 4 years old, with another peak in the fourth decade of life, and at all ages is slightly more frequent in women.

The etiology of CD involves interactions between environmental and physiological factors. The environmental factors are mainly dietary ingestion of wheat gluten and other alcohol soluble proteins (prolamins) found in rye, barley and oats, as well as possible infection by the adenovirus 12 (Kagnoss, 1992). Further, absence of breast feeding is a likely environmental risk factor (Auricchio et al., 1983). The physiological factors are mainly genetic and immunological. The evidence for genetic involvement shows that the risk for developing CD is about 10-20% in first-degree relatives and approaches 100% in monozygotic twins (Morris & Ciclitira, 1997), with a polygenic pattern of inheritance (human leukocyte antigen (HLA) and non-HLA genes) (Gujral et al., 2012), which however is assumed to accountonly for 30% of the genetic risk for CD. Immunological factors are involved through humoral and cell-mediated immunological responses that are directly responsible for the tissue damage (Rosenberg, Mantzaris, & Jewell, 1992).

Symptomatology is one of the most striking aspects of CD. Most notable is the great variation in the incidence of symptoms: some individuals with CD have no symptoms at all, others have slight symptoms and still others suffer from a great many symptoms, partly severe ones. Additionally, there is a great variety of symptoms of CD: apart from the gastrointestinal manifestations, there are pulmonary, cardiac, hepatic, nephrologic, neurologic, endocrinological and skin symptoms, with a frequent involvement of the ophtalmic, oral, dental, connective tissue and hematologic systems (Branski et al., 1992; Dinari, Branski, & Walker-Smith, 1992; Howdle, 1992). Of particular importance in this context are the neurologic manifestations (e.g., progressive cerebral syndrome, aphasia, spinocerebellar degeneration, epilepsy, Down's syndrome) and the psychiatric symptoms (e.g., anorexia nervosa, schizophrenia, autism and depression). In addition, there are symptoms that reflect long-term effects of CD (e.g., short stature in children, chronic anemia, bone diseases, infertility) and associated disorders, mainly cancer (of the small intestine, esophagus, pharynx, and T cell lymphoma) and dermatitis herpetiformis (Isaacson, 1992; Klaus, 1992).

The brief review of CD clarifies the kind of difficulties and stresses to which CD patients are exposed. First, the broad range of symptoms of CD that may encompass the whole body and most diverse types of functioning on the physical as well as psychological levels. Second, prolonged periods of ill health, continuous and episodic, often from early childhood, attended by failure to develop normally so that ill health comes often to be regarded as 'normal'. Third, being bound for life to medical surveillance and follow-up. Fourth, awareness that the disease is chronic and for life, with almost no potential for recovery. Fifth, long periods of suffering and long-term harmful effects of CD due to undiagnosed CD, which even nowadays is fairly common (Maki & Collin, 1997). Sixth, difficulties attendant upon complying with a gluten-free dietary regimen which is hard to maintain, distorts regular daily life (work, entertainment etc.), and often is not kept despite harmful effects (Dinari, Branski, & Walker-Smith, 1992). Seventh, awareness of the many uncertainties which still plague CD concerning diagnosis, inheritance, success of dietary control, and manifestations. Eighth, fear of serious even malignant complications that may develop.

The eight listed reasons clarify the psychological load carried by CD patients. Regardless of whether alexithymia is considered as a correlate or outcome of disease, it is possible to conclude that it could help patients cope with serious physical stresses by enhancing the experienced distance from the body and its ailments and by reducing the load of anxiety the disease is likely to evoke.

Accordingly, we expected CD patients to score higher on alexithymia than healthy controls, both because this would be in accord with the findings about the alexithymic tendencies of individuals suffering from physical ailments in general and of gastrointestinal disorders in particular, as well as because of the heavy psychological load likely to oppress CD patients.

There is very little information about the relation of CD with alexithymia. Two studies showed that there were no significant differences in alexitymia between CD patients without and with a gluten-free diet (Brottveit et al., 2012; Collin, Kaukinen, Mattila, & Jukamaa, 2008). The study about CD and alexithymia (Collin et al., 2008) reported that CD patients did not differ in alexithymia scores from those published "in the Finnish population". However, the Finnish population which served as control was not described in detail except for one reference to female subjects, while there was no mention of the gender distribution in the original sample of the study. Hence, it was expected that the present study would contribute to information about CD and alexithymia.

1. METHOD

1.1. Subjects

The subjects were 40 patients with diagnosed CD, 8 men and 32 women, whose mean age was 28.37 yrs (SD = 13.32) and 39 matched controls, 5 men and 34 women, whose mean age was 28.72 yrs (SD = 12.57). The two groups did not differ in their age or gender distribution.

1.2. Tools

For assessing alexithymia we used The Toronto Alexithymia Scale - 20 (TAS-R), translated and validated in Hebrew by A. Rabinowitz and A. Etzion. Each subject got a total score for the whole scale and three additional scores, one for each of the subscales of the TAS-R assessing: (a) Difficulty identifying feelings; (b) Difficulty describing feelings; and (c) Externally-oriented thinking. The first subscale focuses on labelling feelings, the second on distinguishing between feelings and the physical sensations of emotional arousal, and the third on a style of thinking emphasizing concreteness, sticking to external facts, and avoidance of fantasy.

1.3. Procedure

The CD patients were recruited by means of advertisements in clinics and stores in which CD patients show up as well as by means of the organization of CD patients. The healthy controls were recruited from workers of different levels at the university as those matching CD patients in age, gender and education.

Subjects of both groups were requested to complete the TAS-20 which was presented to them as a research task likely to contribute to a better understanding of psychological aspects of CD. The study was done after the approval of the university ethics committee.

2. RESULTS

The results were computed for all subjects together without considering gender differences because gender comparisons yielded no significant results in regard to the TAS-20 total scores: for celiac patients (Men: Mean=72.55, SD=10.95, n=8, Women: Mean=76.41, SD=12.62, n=32; t=0.404) and for healthy control (Men: Mean=48.30, SD=17.52, n=5, Women: Mean=49.52, SD=15.81, n=34; t=0.889).

Table 1 presents the major findings of the study. It shows that, as expected, patients with CD scored significantly higher than healthy controls on all alexithymia scores - the total score as well as the scores of the three subscales of the TAS-20. By the Bonferroni procedure, for attaining a significance level of p<.01 in the case of four comparisons, it is necessary to get p < .0025. The results in regard to all four scores fulfill this criterion.

Table 1: *Comparisons between Celiac Patients and Healthy Controls on TAS Scores*

	Celiac patients		Healthy controls		t-test
	(n = 40)		(n = 39)		(df = 77)
	Mean	StD	Mean	StD	
Difficulty identifying feelings	24.957	5.689	16.537	8.461	5.18***
Difficulty describing feelings	18.695	4.531	12.359	6.632	4.95***
Externally-oriented thinking	31.990	4.729	20.470	9.720	6.67***
Total TAS score	75.643	10.558	49.366	23.542	6.37***

*** P < .001

In order to learn about further aspects of the interrelation of CD with alexithymia we compared the alexithymia scores of patients with long and short duration of disease. We expected this comparison to shed light on the consistency of alexithymia scores and their possible dependence on disease duration. Long and short disease duration were defined in terms of the mean duration (M = 12.89 yrs), namely, above and below the mean, respectively. The number of patients with long duration was 22 and with short duration 18. Table 2 shows that the two groups did not differ significantly in the total alexithymia score and in two of the subscales (Difficulty identifying feelings, and Externally-oriented thinking). They differed on the p <.05 level on the subscale of Difficulty describing feelings, but this finding should be treated with caution since it does not pass the Bonferroni criterion for the p < .05 level with four comparisons (p < .0125).

Table 2: *Comparisons between Celiac Patients with Long (above mean) and Short (below mean) Disease Duration on TAS Scores*

	Long disease duration		**Short disease duration**		**t-test**
	(n = 22)		(n = 18)		(df = 38)
	Mean	StD	Mean	StD	
Difficulty identifying feelings	24.772	5.520	25.085	6.036	.17
Difficulty describing feelings	17.435	5.024	20.167	3.434	2.03*
Externally-oriented thinking	30.825	5.222	33.444	3.434	1.83
Total TAS score	73.131	10.877	78.712	9.562	1.70

* P < .05

Note: *Mean disease duration was 12.890 yrs.*

In order to be better able to appreciate the implications of these findings we compared the patients with long and short disease durations on a number of further variables. One variable was gender distribution: in the long duration group there were 5 men and 17 women, in the short duration 3 men and 15 women. The difference between the two groups was not significant (Chi square = .823, df=1, ns). Another variable was age: the mean age of long duration patients was 24.91 yrs (SD = 10.34) and of short duration patients 32.61 yrs (SD = 15.51). The age difference between the two groups was not significant (t = 1.80, df=38, p=.08). A third variable was age of patients at disease diagnosis: for the long duration patients the mean age at diagnosis was 6.15 yrs (SD = 11.11), for the short duration 26.89 (SD = 16.95). The difference was significant (t=4.46, df=38, p<.001). So also was the difference on the fourth variable - age of disease onset: mean age of the appearance of the first symptoms was 1.06 (SD = 1.46) for the long duration patients and 19.06 (SD = 17.53) for the short duration ones (t=4.10, df=38, p<.001).

Hence, long and short disease duration does not reflect an age difference or a delay in diagnosis but seems to reflect a difference in the age of disease onset. This conclusion led us to consider the family background of the two groups. We compared them for the number of blood relatives afflicted with CD. In the long duration group there were significantly more blood relatives with CD (13 or 59.1%) than in the short duration group (2 or 11.1%) (Chi square = 4.409, df=1, p<.05). Moreover, the blood relatives in the long duration group were closer kin (i.e., parents, siblings, uncle/aunt) than in the short duration group (i.e., one was a cousin, the other a more distant relative).

3. DISCUSSION

The major findings of the study were that alexithymia is a correlate of CD. This conclusion holds in regard to the total score as well as each of the three subscales constituting it. In this sense, CD appears to resemble other physical disorders and especially gastrointestinal ones which have been found to be characterized by alexithymia. Hence, our findings may be considered as a contribution to the ever-growing literature about alexithymic tendencies of individuals with physical disorders.

The findings also have a further contribution, which concerns the controversy about whether alexithymia is a predisposing factor for physical disorders or a correlate that develops with the disease, perhaps even as a means of coping with it psychologically (Lumley, Stettner, & Wehmer, 1996). If it is the latter, it would be expected to increase with disease duration. However, our findings show that it did not. The differences between scores of alexithymia for patients with long and short disease duration were not significant (except for a tendency in one subscale). Hence, alexithymia could be conceptualized rather as a personality tendency predisposing to physical disorders. One possible conceptualization of the impact of alexithymia

on celiac disease could be based on the assumption that alexithymia results in the failure to process and elaborate adequately emotional arousal, which may in turn be related to a failure to modulate or inhibit sites of visceromotor activation, leading to autonomic dysregulation and subsequent disorder (Lumley et al.1996).

The low awareness of emotional stimuli and reactions may contribute to the deficit of alexithymic patients to handle autonomic arousal on time and adequately. The result may be that stress is evoked or not prevented or controlled, as indicated by the findings that alexithymia is indicative of poor coping with stress (e.g., Funkenishi & Rahe, 1995). These conclusions may be relevant in regard to the gut-brain axis. The findings that stress affects the nature and functioning of the microbes in the gut (Dinan & Cryan, 2012) may shed light about how alexithymia is involved in the gut-brain axis, and why it appears as a correlate of so many different diseases. In terms of the patho-generative model, alexithymia would be considered as a risk factor that forms part of the background conditions that render the occurrence of the disease more likely when a pathogen is at work (Kreitler & Kreitler, 1991; Kreitler, in press).

Our explorations into the differences between patients with long and short disease durations revealed that at least in our case these two subgroups did not differ in age. Hence, disease duration was not an outcome of better diagnostic procedures or greater awareness of CD in more recent years. However, the two subgroups did differ significantly in age of disease diagnosis and age of disease onset (both were earlier for the long disease duration patients). It is of particular interest to note that our assumption that the patients with long disease duration will have more blood relatives with CD was confirmed. The additional observation that these blood relatives were closer kin in the patients with long than in those with short disease duration raises the further assumption that in the long duration subgroup the genetic basis was not only evident but also stronger and clearer. This conclusion is in line with the iceberg model of CD suggested by Maki and Collin (1997). This model assumes a continuum of genetic susceptibility for CD which is minimal in 'healthy individuals', increases in the next level called 'coeliac disease latency', and again in 'silent coeliac disease' and is most salient in 'clinical coeliac disease', which forms the tip of the visible iceberg. In parallel to the increase in genetic susceptibility there is an increase in jejunal morphology, which is normal in the first two levels, and with 'manifest mucosal lesion' in the last two levels. It seems justified to consider patients with short disease duration as situated in a lower level of the iceberg than those with long disease duration. Further, Maki and Collin (1997) assume a genetic basis already from the second level. In view of the assumption of polygeneticity in CD, we would suggest that lower levels have fewer genes promoting CD than later or higher levels of the iceberg. Be it as it may, our findings suggest that alexithymia in CD is unrelated to the strength of the genetic susceptibility for CD.

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