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**Celiac crisis, rare occurrence in adult celiac disease: A systematic review**

Balaban DV *et al*. Celiac crisis in adults

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**Abstract**

***BACKGROUND***

Celiac crisis (CC), a potentially life-threatening condition, is one of the rare clinical presentations of celiac disease (CD). Several cases have been documented in the literature, mostly in children.

***AIM***

To perform a review of CC cases reported in adult CD patients.

***Methods***

A systematic search of the literature was conducted in two databases, PubMed/MEDLINE and EMBASE, using the term “celiac crisis" and its variant "coeliac crisis", from January 1970 onwards. Altogether 29 articles reporting 42 biopsy-proven cases were found on the search. We summarized here the demographic, clinical characteristics, laboratory and diagnostic work-up, and therapeutic management in these patients.

***Results***

Among the 42 CD cases, median age was 50 years (range 23-83), with a 2:1 female to male ratio. The majority of patients (88.1%) of patients developed CC prior to CD diagnosis, while the remaining were previously diagnosed CD cases reporting low adherence to gluten-free diet (GFD). Clinically, patients presented with severe diarrhea (all cases), weight loss (about two thirds) and in particular situations with neurologic (6 cases) or cardiovascular (1 case) manifestations or bleeding diathesis (4 cases). One in four patients had a precipitating factor that could have triggered the CC (*e.g.* trauma, surgery, infections). Laboratory workup of patients revealed a severe malabsorptive state with metabolic acidosis, dehydration, hypoalbuminemia, and anemia. Evolution on GFD was favorable in all cases except one in whom death was reported due to refeeding syndrome.

***Conclusion***

Celiac crisis is a rare but severe and potentially fatal clinical feature of CD. A high index of suspicion is needed to recognize this clinical entity and to deliver proper therapy consisting of supportive care and subsequently GFD.

**Key words:** Celiac disease; Celiac crisis; Malabsorption; Malnutrition; Diarrhea

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**Core tip:** Celiac disease is well recognized as having a broad spectrum of presentations. Among them, celiac crisis is a rare but potentially life-threatening clinical feature, which has been reported in both pediatric and adult celiac disease cases. Several case reports have been published so far in adults and our aim was to summarize the current literature in order to better delineate the patients’ profile with respect to possible triggers, clinical characteristics, laboratory workup and management of celiac crisis.

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**INTRODUCTION**

Celiac disease (CD) is a systemic, immune-mediated disease, primarily affecting the small bowel, which occurs in genetically predisposed individuals and is triggered by dietary gluten exposure[1-3]. For many years, CD was considered to be a disease of childhood, being well known as the prototype of malabsorption in pediatric population. In adults, CD has a different phenotype, frequently presenting with mild digestive signs and symptoms or with extraintestinal features such as anemia, early osteoporosis, chronic fatigue, unexplained infertility or ataxia[2-5].

Celiac crisis (CC) is a rare but potentially life-threatening clinical feature of CD, which has been reported in both children and adults. It was first described in 1953, in a case series of 35 children with a fatality rate of 9%[6-8]. Clinically, CC has a brutal onset with profuse diarrhea, severe dehydration, hemodynamic instability, profound electrolytic and metabolic disturbances, being considered an acute, fulminant manifestation of CD[9,10]. This acute onset and rapidly progressing gastrointestinal symptoms of CC, accompanied by metabolic, electrolyte and hemodynamic compromise usually requires hospitalization and intensive care support. Recognition of this condition can be challenging in clinical practice, as infectious causes and not CD are usually thought of in such a clinical scenario. CC diagnosis comprises the acute malabsorptive state with positive CD-serology and histology. An immune stimulus can sometimes be identified as a precipitating factor for CC such as infections or recent surgery. Treatment consists of intensive nutritional support and gluten-free diet.

CC is not very well documented in the literature, with only a handful of case reports and case series published. Actually, currently available guidelines do not include yet this entity neither in children, nor in adults[2,3,5]. It is however classified as a complication of CD in a recent phenotypic classification[11]. Most consider it a heraldic manifestation of CD, but it has been also reported as an acute flare of previously untreated CD or in CD patients with dietary transgressions[12].

We herein conducted a review of CC cases reported in adults and tried to summarize the clinical, laboratory and histological characteristics of CC patients.

**MATERIALS AND METHODS**

***Search strategy and article selection***

The literature was systematically searched using the term "celiac crisis" (and its variant "coeliac crisis") in two databases, PubMed/MEDLINE and EMBASE. We restricted the search for articles published from January 1970 onwards. The articles identified from this search were checked to have at least access to the article abstract in English and then the abstract was assessed for relevance with the topic.We included all articles matching these criteria and reporting on adults (over 18 years old).We excluded articles referring to pediatric cases (patients under 18 years old). For the remaining articles, we searched for the full-text version and we also checked their references for additional possible articles matching the topic that could have been missed on the initial database search (Figure 1). Full-text in English was available for 26/29 articles, while the remaining three were in Spanish[13], French[14] and Turkish[15] language, and data regarding clinical, biological, endoscopy and histology were collected after translating the case presentation. All cases included were counted only one time.

**RESULTS**

***Demographics***

Altogether 42 cases presented in 29 articles were found with the above-described search, of which two articles presented 2 cases, another case series of 12 cases and the remaining each one case. Demographics and clinical characteristics of patients are summarized in Table 1*.*

Among the 42 cases, median age was 50 years (range 23 to 83), higher in males (62 *vs* 45, *P* = 0.002) and there was a female predominance (female: male ratio 2:1). Amid the reviewed cases, only 5 were previously known CD patients - in whom poor adherence to diet was noted, while the remaining 37 (88.1%) got diagnosed by means of their presentation as CC.

***Clinical manifestations***

From the clinical point of view, all patients reported diarrhea and in about two thirds of them significant weight loss was documented. Only in one case it is mentioned that the weight was not affected, while in the rest of the cases presented this information was missing. Also, signs of dehydration were described, like tachycardia, functional renal impairment or arterial hypotension (Table 1).

Interestingly, the malabsorption syndrome associated with the CC lead to clinical pictures like altered hemostasis (bleeding diathesis or thrombosis) in 4 patients, neurologic manifestations (tetany, paresthesia, neuropathy or quadriparesis probably in the setting of hypocalcemia or hypokalemia) in 6 patients and cardiovascular involvement (firing of an implantable cardiac defibrillator) in one patient.

A possible CC precipitating factor was described in 11/42 of the cases, as follows: trauma - 1, surgery - 3 (one for small bowel obstruction by Meckel diverticulum, two after pancreatico-duodenectomy/Whipple procedure), pancreatitis - 1, infections - 4 (Clostridium difficile colitis - 1, herpes simplex esophagitis - 1, urinary tract infection - 1, Cytomegalovirus infection - 1), birth - 1, or Bell’s palsy - 1.

Altogether 6 out of the 42 cases associated other autoimmune diseases, namely 2 with type 1 diabetes mellitus, one rheumatoid arthritis, one autoimmune hypothyroidism, one autoimmune hepatitis and another with Sjogren and Raynaud's disease.

***Laboratory data and diagnostic approach***

Anemia, prolonged international normalized ratio, hypoalbuminemia, hypokalemia and hypocalcemia were seen in a substantial number of cases, reflecting the malabsorptive state in these patients. Metabolic acidosis was also reported in a high proportion of cases. Anemia, hypoalbuminemia, coagulation disturbances and deficiency of vitamin B12, vitamin D or folate were found when tested. Laboratory work-up of reported cases is summarized in Table 2.

Anti-tissue transglutaminase antibody (tTG) testing was noted in 23 cases, yielding 87% positivity. Anti-endomysial antibodies (EMA) was positive in 15 out of 17 CC cases reporting this determination (88.2%). Some of the patients were diagnosed using anti-gliadin antibodies (AGA), while in 3 articles no CD-specific serology was reported. Naturally, the laboratory tests used varied largely.

Small-bowel biopsy to confirm CD was done in 100% of the adult CC cases analyzed. It is to note that the CD histological intestinal pattern was advanced, classified as Marsh 3 and 4. A clear distribution of Marsh stages (3 a/b/c) could not be done because of the insufficient data reported in the articles included regarding the histological features of biopsies.

***Treatment and evolution under gluten free diet***

All patients required hospitalization with fluid resuscitation, correction of acid-base or electrolyte imbalances and nutritional support. There was good evolution with the gluten free diet (GFD) in the reported cases, except one, in whom death was recorded due to refeeding syndrome). About one in five patients (8/42 - 19%) the treatment by steroids was noted for the CC management.

**DISCUSSION**

Despite being first described in 1953[6-8], it was not until 2010 that CC had its first diagnostic criteria set, proposed by Jamma *et al*[16]. Characterizing a case series of 12 patients, the CC was defined as an acute onset or rapid progression of the gastrointestinal symptomatology attributable to CD requiring hospitalization and/or parenteral nutrition along with at least 2 of the following: (1) Signs of severe dehydration including hemodynamic instability and/or orthostatic changes; (2) Neurologic dysfunction; (3) Renal dysfunction, creatinine level > 2.0 g/dL; (4) Metabolic acidosis, pH < 7.35; (5) Hypoproteinemia (albumin level, <3.0 g/dL); (6) Abnormal electrolyte levels including hypernatremia/hyponatremia, hypocalcemia, hypokalemia, or hypomagnesemia; and (7) Weight loss > 5 kg.

CC is only rarely encountered in clinical practice, having an estimate of under 1% of all CD cases[16]. Only case reports and small case series have been reported so far in the literature. We herein collected data on 42 adult CC cases (all fulfilling the diagnostic criteria proposed by Jamma *et al*[16]) and aimed to summarize the characteristics of these patients with regard to clinical, laboratory and histological data and their outcome under GFD.

Among the 42 CC cases there was a female predominance (2:1), which parallels the higher frequency of CD seen in women (2.3:1)[17]. CC was the inaugural feature of CD in 37/42 cases, while the remaining 5 were previously diagnosed CD patients in whom non-compliance probably triggered the CC. In these known CD patients’ non-adherent to diet, a differential diagnosis with refractory CD should be considered as this can have a poor outcome also[18].

From a clinical point of view, the CC cases included in this review presented with severe diarrhea, weight loss and sometimes hemodynamic instability. Most frequent laboratory alterations reported were metabolic acidosis, anemia, hypocalcaemia, hypoalbuminemia, and hypokalemia, consequence of the profound malabsorptive state. In some of the cases, the electrolyte imbalances lead to neurologic or cardiologic manifestations, which could be the main presenting feature in CC; a high index of suspicion is needed among physicians with regard to these atypical and very rare presentations, being previously shown that there is poor awareness in regard to CD non-intestinal features[19]. Not least, CC can also present with bleeding diathesis, which was the case for 4/42 of the reviewed cases; as previously reported, hemorrhagic events in CD patients encompass a wide range of clinical manifestations such as gastrointestinal bleeding, hemoptysis, epistaxis, hematuria, hematomas or ecchymosis[20].

This acute, stormy presentation of CD has been postulated by some authors to be triggered by a stimulus such as surgery, infection or pregnancy[16]. Among the 42 reviewed cases, one in four of patients had a recent major medical event/intervention which could have worsen the baseline pathology; it is however still early to sustain here a link. Moreover, we have to consider that an anterior or associated intestinal infection makes the differential diagnosis with CC very difficult. It might be useful to even consider the concomitance of an infection with intestinal tropism an exclusion criterion for the CC in CD patients or to carefully consider the differential diagnosis in such cases.

Regarding the CD positive diagnosis, although some cases have been diagnosed using AGA as a serological marker, most of the patients were either tTG or EMA positive. Small-bowel biopsies were carried out in all patients, revealing enteropathy with different grades of severity, most with advanced histology changes (Marsh 3c stage). Although exact distribution for sub-stages Marsh 3 a/b/c could not be done due to insufficient histological data from the case reports, its usefulness is questioned in a recent consensus paper which concluded that sub-classification of Marsh 3 stage should be abandoned[21].

Evolution under GFD was favorable in all patients, with improved clinical and biological status, except one reported death due to refeeding syndrome[22]. Steroid use was reported in some of the CC patients. Recent reports however question the role of steroids in CC[23] and this is backed up by cases reports when ongoing immunosuppression with corticosteroids and azathioprine for autoimmune hepatitis[24] or prednisone for Bell’s palsy[24] did not prevent the CC occurrence. There is also the concern of increased electrolyte depletion under corticosteroids treatment[22].

In conclusion, CC is a rare, but severe and possibly life-threatening clinical form of CD. We herein present a review of adult CC cases reported in the literature to date, aiming to raise awareness about this entity by better defining these patients’ profile in regard to possible triggers, clinical presentation, laboratory workup alterations, management and outcome.

**ARTICLE HIGHLIGHTS**

***Research background***

Celiac disease (CD) is a well recognized as a clinical chameleon, which is responsible for the high underdiagnosis rates of this common digestive condition. One of its presenting features is celiac crisis (CC), a potentially life-threatening acute malabsorptive state accompanied by metabolic and electrolyte disturbances and hemodynamic instability, usually requiring hospitalization and intensive care. Only a handful of case-reports have been published so far in the literature, both in adults and children, and currently available guidelines are not mentioning it at all.

***Research motivation***

We aimed to perform a systematic review focused on CC in order to better delineate the possible triggers, clinical features, diagnostic work-up and treatment measures. Only case reports or case series were published so far in the literature, and so, another objective was raising awareness about this condition as a possible heraldic feature of CD.

***Research objectives***

The main objective was to get a clear characterization of CC by summarizing all case-reports with regard to clinical manifestations, laboratory data, diagnostic and therapeutic approach. Also, we meant to get some insight about the possible trigger factors of CC.

***Research methods***

For this purpose, we performed a systematic review of the published case reports by searching the literature in two major databases, PubMed and EMBASE. All abstracts meeting inclusion criteria were processed, and relevant articles were read in full-text and further analyzed for the specific objectives.

***Research results***

Our review summarizes available literature on the occurrence of CC in adults, respectively 42 cases reported in 29 articles. Common clinical features (profuse diarrhea, hemodynamic instability, weight loss, renal impairment) and particular ones (neurologic, cardiovascular or hematologic) were described, along with possible triggers (infections, surgery, pregnancy). Besides the laboratory alterations secondary to the acute malabsorptive state, the diagnostic approach included CD-serology testing and histology. Management and outcome, referring to intensive care support, need for steroids and evolution under gluten-free diet was also analyzed.

***Research conclusions***

To the best of our knowledge, this review is the first to summarize clinical, diagnostic and therapeutic approach of a rare but potentially life-threatening presenting feature of CD, by an extensive analysis of currently available data. While definition and characteristics of the CC were clearly described, and gaps in understanding this conditions were also outlined.

***Research perspectives***

This research presents the main characteristics of the CC occurrence in adult CD patients and also there is a need to increase awareness of this condition. Further research is warranted to elucidate the pathological mechanism triggering CC.

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**Table 1 Celiac disease published cases – clinical characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Index** | **No**  | **Age (yr)** | **Sex** | **Weight loss** | **BMI**(kg/m2) | **Time from the CD diagnosis** | **Previous GFD/ compliance** | **Favorable evolution under GFD** |
| [26] | 1 | 43 | F | 20 kg/12 mo | 14.7 | 3 yr | Yes, non-compliance | Yes |
| [22] | 1 | 28 | F | - | 14.0 | 21 yr | Yes, non-compliance | - |
| [10] | 1 | 26 | F | - | - | 0 | No | Yes |
| [27] | 1 | 24 | F | 4-5 kg/1 wk | 17.5 | 0 | No | Yes |
| [28] | 1 | 69 | M | No | - | 0 | No | Yes |
| [25] | 1 | 46 | F | - | - | 0 | No | Yes |
| [12] | 1 | 31 | F | 14 kg/1 mo | 17 | 0 | No | Yes |
| [29] | 1 | 43 | M | 35 kg/6 mo | 11 | 0 | No | Yes |
| [30] | 2 | 8275 | FM | -- | -- | 00 | NoNo | YesYes |
| [31] | 1 | 64 | F | 10 kg | - | 0 | No | Yes |
| [32] | 1 | 52 | F | Yes | - | 0 | No | - |
| [33] | 1 | 30 | F | 9 kg/1 mo | 21.5 | 0 | No | Yes |
| [34] | 1 | 83 | M | - | - | 0 | No | Yes |
| [35] | 1 | 67 | M | 18 kg/6 mo | - | 0 | No | Yes |
| [16] | 12 | mean 58.9(34-74) | 8F/4M | 12/12 (5-15 kg) | - | 11/12 – 01/12 - ? | 11/12 – No1/12 - Yes, non-compliance  | 12/12 – Yescorticosteroids 6/12 |
| [14] | 1 | 26 | F | - | - | 0 | No | Yes |
| [24] | 1 | 50  | F | - | - | 0 | No | Yes |
| [36] | 1 | 23 | F | - |  | 0 | No | Yes |
| [37] | 1 | 58 | M | 20 kg/2 mo | - | 0 | No | Yes |
| [38] | 1 | 49 | F | 35 kg/3 mo | - | - | No | Yes |
| [39] | 1 | 56 | F | 15 kg | - | 2 yr | Yes, non-compliance | Yes, corticosteroids |
| [40] | 1 | 38 | M | Yes | - | 0 | No | Yes |
| [41] | 1 | 50 | M | 13 kg/2 mo | - | 0 | No | Yes |
| [15] | 1 | 37 | F | Yes | - | 0 | No | Yes |
| [13] | 1 | 26 | F | - | 19.9 | 2 yr | Yes, non-compliance | Yes, prednisone |
| [42]  | 1 | 30 | F | 15 kg/3 yr | - | 0 | No | Yes |
| [8]  | 2 | 7555 | MF | Yes- | 14.7- | 00 | NoNo | Yes |
| [43]  | 1 | 36 | F | 4 kg/9 d | 16.3 | 0 | No | Yes |
| [44] | 1 | 58 | M | 15 kg | 17.3 | 0 | No | Yes |

BMI: Body mass index; CD: Celiac disease; GFD: Gluten-free diet.

**Table 2 Celiac disease published cases – paraclinical characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Index** | **No**  | **Diagnosis** | **Hemogram** | **Coagulation** |
| **Biopsy** | **EMA** | **tTG** | **DGP/AGA** |
| [26] | 1 | Yes, Marsh 3C | - | P, 608 u | - | Hb – L (7.8 g/dL), PLT – L | INR – H (2.1), aPTT – H (45 s) |
| [22] | 1 | Yes | P | P | P | - | - |
| [10] | 1 | Yes | - | P (> 100 u) | - | Hb – H (15.8 g/dL) | - |
| [27] | 1 | Yes, Marsh 3C | - | P (99 u/mL) | - | Hb – L (9.3 g/dL) | INR – H (3.2) |
| [28] | 1 | Yes | - | P (132 u) | - | Hb – L (4.8-12.2 g/dL) | INR – H (1.3) |
| [25] | 1 | Yes, Marsh 3C | - | P (48 u) | P/(39 u) | Hb – L (11.0 g/dL) | - |
| [12] | 1 | Yes | - | - | - | - | INR – H (3.5) |
| [29] | 1 | Yes, Marsh 4 | - | P (19 ui/mL) | - | - | - |
| [30] | 2 | Yes | P (3+) | P (200 Ru/mL) | - | Hb – L (8.1 g/dL), PLT – L (180000/dL)  | - |
| Yes | P (+1) | P (200 Ru/mL) |  | Hb – L (7.6 g/dL), PLT – L (156000/dL) | - |
| [31] | 1 | Yes, Marsh 4 | P | P (> 200 U/mL) | P | Hb – L (8.7g/dL) | - |
| [32] | 1 | Yes | - | - | - | Hb – L  | - |
| [33] | 1 | Yes | P (>1/1280) | - | - | Hb – NR (12.3g/dL) | - |
| [34] | 1 | Yes | P | N | - | - | - |
| [35] | 1 | Yes, Marsh 3 | N | N | N | Hb – NR (12.4 g/dL), PLT – L (160000/dL) | - |
| [16] | 12 | Yes 12/12, ≥ Marsh 3a | - | P, 10/11 | - | - | - |
| [14] | 1 | Yes, Marsh 3 | P (92 U/mL) | - | P/(20U/mL) | - | - |
| [23] | 1 | Yes | P (1:160) | P (15 EU/mL) | - | - | - |
| [36] | 1 | Yes, Marsh 3b | - | P (33.9 u/L) | P/(41.9u/L) | Hb – NR, PLT – L (94000/dL) | - |
| [37] | 1 | Yes, Marsh 4 | - | P (> 200 U/mL) | - | Hb – L (4.7 g/dL) | - |
| [38] | 1 | Yes, Marsh3C | P | P | - | Hb – L (7.2 g/dL), PLT – L (257000/dL) | INR – H (> 1.5), aPTT – H (154 s) |
| [39] | 1 | Yes, Marsh 4 | N | N | - | - | - |
| [40] | 1 | Yes, Marsh 3c | P(35.9 u) | P (20.6 u) | - | Hb – NR (15.2 g/dL) | INR – H (1.6) |
| [41] | 1 | Yes, Marsh 3 | P (158.7) | P (> 200 U/mL) | - | Hb - L (9.4 g/dL) | -  |
| [15] | 1 | Yes, Marsh 3 | P | P | AGA P | Hb - L (8 g/dL) | - |
| [13] | 1 | Yes, Marsh 3c | - | P (23.4, positive > 12) | AGA P (27.4) | HT - L (18%) | PT < 10% |
| [42]  | 1 | Yes, Marsh 3b  | - | - | AGA P (IgA 63.4, IgG 111.1) | Hb - L | - |
| [8]  | 2 | Yes, Marsh 3a; Yes, Marsh 3b | P; P | - | AGA N; AGA P | Hb - L (5.9 /dL); Hb - L (7.9 /dL) | PT prolonged (19 s); PT prolonged (18 s) |
| [43]  | 1 | Yes, Marsh 3c | - | - | - | Hb - L | - |
| [44] | 1 | Yes, Marsh 3c  | P (1:640) | P (142) | AGA P | Hb - L (11.6 g/dL) | INR – H (1.6) |

L: Low; H: High; N: Normal; M: Masculine; Hb: Hemoglobin; P: Positive, N: Negative: NR: Normal ranges, HT: Hematocrit; AGA: anti-gliadin antibodies; aPPT: Activated partial thromboplastin time; CD: Celiac disease; DGP: Anti-deamidated gliadin antibodies; EMA: Anti-endomysial antibodies; INR: International normalized ratio; PLT: Platelets; PT: Prothrombin time; tTG: Anti-tissue transglutaminase antibodies.

**Figure 1 Flowchart for the articles considered for the final analysis.**