Celiac Crisis Is a Rare but Serious Complication of Celiac Disease in Adults

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BACKGROUND & AIMS: Celiac crisis is a life-threatening syndrome in which patients with celiac disease have profuse diarrhea and severe metabolic disturbances. Celiac crisis is rare among adults and not well documented. To improve awareness of this condition and to facilitate diagnosis, we reviewed cases of celiac crisis to identify presenting features, formulate diagnostic criteria, and develop treatment strategies. **METHODS:** Cases of biopsy-proven celiac disease were reviewed. Celiac crisis was defined as acute onset or rapid progression of gastrointestinal symptoms that could be attributed to celiac disease and required hospitalization and/or parenteral nutrition, along with signs or symptoms of dehydration or malnutrition. **RESULTS:** Twelve patients met preset criteria for celiac crisis; 11 developed celiac crisis before they were diagnosed with celiac disease. Eleven patients had increased titres of transglutaminase antibodies and 1 had immunoglobulin A deficiency. Results of biopsy analyses of duodenum samples from all patients were consistent with a Marsh 3 score (33% with total villous atrophy). Patients presented with severe dehydration, renal dysfunction, and electrolyte disturbances. All patients required hospitalization and intravenous fluids, 6 required corticosteroids, and 5 required parenteral nutrition. All patients eventually had a full response to a gluten-free diet. **CONCLUSIONS: Celiac crisis has a high morbidity and, although rarely described, occurs in adults and often has a clear precipitating factor. Patients who present with severe unexplained diarrhea and malabsorption should be tested for celiac disease; treatment with systemic steroids or oral budesonide should be considered. Nutritional support often is required in the short term but most patients ultimately respond to gluten avoidance.**

Keywords: Steroids; Treatment; Tissue Transglutaminase; Enteropathy.

Celiac crisis is a life-threatening syndrome in which celiac disease causes acute dramatic metabolic derangements. Common manifestations of celiac crisis include severe diarrhea, hypoproteinemia, and metabolic and electrolyte disturbances significant enough to require hospitalization.[1,2] The term *celiac crisis* was first noted in the literature in 1953 when Andersen et al[3] and Di Sant'Agnese[4] reported the clinical course of 58 children with celiac disease, 35 of whom presented with celiac crisis. In this series, children with celiac crisis were noted to have a case fatality rate of 9%. Celiac crisis continues to be associated with a high morbidity rate,[5,6] mandating immediate identification and treatment; however, since this initial report no individual publication has described more than 3 cases.

Further, celiac crisis had been thought of primarily as a childhood ailment, much as celiac disease itself was until recently. In addition, it has been suggested that celiac crisis is becoming less frequent because of earlier diagnosis of celiac disease made possible by the great advances in diagnostic modalities over the past decades,[7] although there are little data to support this statement. To date, fewer than 10 cases of celiac crisis in adults have been reported in the literature,[5–10] and for this reason celiac disease rarely is considered in adults presenting with acute severe diarrheal illness, even when infectious etiologies have been excluded.

The mainstays of treatment of celiac crisis are initiation of a gluten-free diet, parenteral fluid replacement and nutritional support, and, in most cases, corticosteroids. However, all reports in the modern literature describe only 1 or 2 cases and again the majority of these are in pediatric populations.[1] The lack of reported cases makes it difficult to gain an appreciation of the true spectrum of celiac crisis in adult patients. To improve awareness of celiac crisis and to facilitate diagnosis, we reviewed cases of celiac crisis seen at 2 major referral centers for celiac disease: Beth Israel Deaconess Medical Center in Boston, MA, and the Mayo Clinic in Rochester, MN. The study was approved by the institutional review boards of the Mayo Foundation and Beth Israel Deaconess Medical Center.

Methods

Because there are no standardized diagnostic criteria for celiac crisis, literature was first reviewed to define working criteria for case selection. Consensus among investigators was reached and celiac crisis was defined as follows: acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least 2 objective signs of malnutrition, dehydration, or electrolyte disturbance (as listed in Table 1). We then reviewed cases of biopsy-proven celiac disease seen at Beth Israel Deaconess Medical Center, Boston, MA, and the Mayo Clinic, Rochester, MN, from 2000 to 2008. All patients met standard diagnostic criteria for celiac disease including modified Marsh classification 3a or higher, and either positive tissue transglutaminase antibodies (tTG), endomysial antibody, or deamidated gliadin peptides antibodies serology, or positive

Abbreviations used in this paper: Ig, immunoglobulin; tTG, tissue transglutaminase.

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Table 1. Definition of Celiac Crisis

Acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least 2 of the following:
Signs of severe dehydration including hemodynamic instability and/or orthostatic changes
Neurologic dysfunction
Renal dysfunction, creatinine level, >2.0 g/dL
Metabolic acidosis, pH <7.35
Hypoproteinemia (albumin level, <3.0 g/dL)
Abnormal electrolyte levels including hypernatremia/hyponatremia, hypocalcemia, hypokalemia, or hypomagnesemia
Weight loss, >10 lb

HLA DQ2 or DQ8 and clinical response to treatment with a gluten-free diet.[11] Demographic data along with symptoms at presentation, presence of electrolyte abnormality, weight loss, administration of total parenteral nutrition, systemic steroid therapy, Marsh grade, HLA type, immunoglobulin (Ig)A tTG level at the time of celiac crisis, and time to recovery were collected from the medical records (Table 2).

Results

Twelve adult patients with biopsy-proven celiac disease met the earlier-described criteria for celiac crisis. Because of the participating institutions' status as referral centers, actual incidence is difficult to estimate. However, between the 2 centers approximately 1200 patients with celiac disease were diagnosed over the study duration, reflecting an incidence of celiac crisis of less than 1% in patients with celiac disease.

Of the 12 cases, 8 were women and 4 were men, the mean age at diagnosis was 58.9 years overall; 63.5 years in men and 56.6 years in women (P = NS). Eleven of 12 patients developed celiac crisis before diagnosis of celiac disease. One patient who had known celiac disease before development of celiac crisis had not been following a gluten-free diet. Of the 11 patients for whom tTG was available, one patient had IgA deficiency, and all of the other patients had increased IgA tissue transglutaminase titers, 8 of 9 with levels greater than 4 times the upper limit of normal. Biopsies of the duodenum in all patients revealed villous atrophy and were consistent with a Marsh 3 score. Of 12 cases, HLA type was available for 10, of which 9 were HLA positive for DQ2 and 1 was positive for DQ8. Three of 12 patients had other autoimmune disorders: rheumatoid arthritis (case 3), autoimmune hypothyroidism (case 5), and Sjögren syndrome and Raynaud disease (case 12). Also notable, 2 patients had osteoporosis (cases 7 and 9), 1 had osteopenia (case 6), 2 had type 2 diabetes mellitus (cases 9 and 10), and 1 had nonalcoholic steatohepatitis (case 5). Three of 12 patients had capsule endoscopy confirming features of villous atrophy in the proximal small intestine (cases 7, 8, and 11).

Five patients had a major medical event before, and possibly precipitating, their celiac crisis: 1 presented less than 2 months post partum (case 1), another patient presented 2 weeks after small-bowel obstruction followed by exploratory laparotomy and removal of Meckel diverticulum (case 2), a third patient presented immediately after an episode of gallstone pancreatitis (case 4), and 2 patients presented 1 week after pancreaticoduo-

Table 2. Demographic and Clinical Characteristics

Patient	Age, *y*	Sex	Serology	Symptoms	Weight loss, *lb*	Electrolyte abnormality	Marsh grade/IELs	TPN	Steroids	HLA	Hospital stay, *d*	Time to recover, *wk*
1	34	F	tTG 113	D	15	Metabolic acidosis	3b/50	+	+	DQ 8	7	8
2	51	M	tTG >200 EMA +	D	20	↓ Ca, ↓ K, ↓ Na, ↓ Alb, Metabolic acidosis, ARF (Cr, 3.1)	3c/50	+	+	DQ 2	11	20
3	48	F	IgA deficiency tTG 0	V, D, Orthostatic changes	30	↓ Ca, ↓ K	3b[a]	–	–	DQ 2	4, 3	40
4	70	M	tTG >100	V, D, ↑ HR abdominal pain	10	↓ K	3a[a]	–	–	NA	NA	24
5	48	F	NA	D, ↑ HR, Neuropathy	21	NA	3a/50	–	–	DQ 2	7	NA
6	68	F	tTG 6 reference, (0–5)	V, D, ↓ BP	30	↓ K, ↑ Na ↓ Alb	3a[a]	+	+	DQ 2	5	32
7	67	F	tTG 250	D, ↓ BP	28	↓ Ca, ↓ Alb	3c/100	–	–	DQ2	8	30
8	74	F	tTG 24.5	D, Tetany	30	↓ Ca, ↓ K, ↓ Mg ↓ Alb	3c/60	–	+	NA	7	8
9	65	M	tTG 21.3 EMA+	D, Tetany	20	↓ Ca	3a/40	+	–	DQ2	10	16
10	68	M	tTG 117 EMA+	D, Tetany	20	↓ Ca, ↓ Alb	3b/60	+	–	DQ2	11	24
11	65	F	tTG 22	D	40	↓ Ca, ↓ Mg, Metabolic acidosis, ARF (Cr, 2.6)	3c/80	–	+	DQ2	13	24
12	49	F	tTG 83.7 EMA+	D	10	↓ Mg	3a/50	–	+	DQ2	4	24

IEL, number of intraepithelial lymphocytes per 100 epithelial cells; TPN, total parenteral nutrition; F, female; D, diarrhea; M, male; EMA, endomysial antibody; ↓, decrease; NA, not available; Ca, calcium; K, potassium; Na, sodium; Alb, albumin; ARF, acute renal failure; Cr, creatinine; V, vomiting; HR, heart rate; BP, blood pressure; ↑, increase; Mg, magnesium.
[a]IEL count not available.

denectomy (Whipple procedure) because of presumed pancreatic or ampullary malignancy (cases 9 and 10).[12]

Patients presented with severe dehydration, renal dysfunction presenting as increased creatinine level, and electrolyte disturbances such as hypokalemia, hypocalcemia, and hyponatremia requiring replacement of these electrolytes. Of these, hypocalcemia was most common (6 patients) with tetany reported in 3 patients. Per diagnostic criteria, all patients required hospitalization and intravenous fluids, and 5 patients required parenteral nutrition. Six patients required corticosteroids including intravenous prednisolone followed by tapering doses of oral prednisone starting at 60 mg (case 2), prednisone 40 mg then budesonide 9 mg/d (cases 6 and 8), budesonide 9 mg/d (cases 2 and 11), and prednisone 30 mg then budesonide 9 mg/d (case 12). All patients adopted a strict gluten-free diet and had a rapid clinical response within 2 weeks; however, nutritional support and/or treatment with corticosteroids was necessary in a minority of patients for up to 40 weeks.

Discussion

Celiac disease is an immune-mediated enteropathy characterized by malabsorption and villous atrophy triggered by gluten proteins.[13] Currently, in most adult cases, even untreated celiac disease has an indolent course with gastrointestinal symptoms and nutritional abnormalities, but does not result in severe or life-threatening illness. This is in stark contrast to the past when celiac disease was known as a severe disease of childhood. Although data do suggest that celiac disease is becoming more common overall,[14,15] it is unclear whether the dramatic change in clinical spectrum is owing to early recognition and treatment, improved diagnosis of milder cases, or an actual change in the nature of celiac disease over time.

The term *celiac crisis* has been used since the 1950s to describe the acute, fulminant form of celiac disease.[3] Clinically, it is characterized by severe diarrhea, dehydration, and metabolic disturbances including hypokalemia, hyponatremia, hypocalcemia, hypomagnesemia, and hypoproteinemia. Traditionally, celiac crisis was associated with a high mortality rate; however, medical care has progressed greatly over the past half century and no recent deaths from celiac crisis have been reported in the literature since Lloyd-Still et al[16] described the successful treatment of 3 cases of celiac crisis in children with corticosteroids in 1972.

The reason why some individuals present with celiac crisis whereas the vast majority of patients with celiac disease run a much more mild course is unclear; however, there is likely a combination of severe mucosal inflammation, immune activation, and disruption of normal patterns of motility. Similar to celiac disease in general, celiac crisis in this series appears to be precipitated often by a general immune stimulus such as surgery, infection, or pregnancy, as has been described previously.[17–19] However, it is unclear if celiac crisis in adults occurs at disease onset or if celiac disease is present but undiagnosed until a trigger leads to disease exacerbation. It is notable that in 5 of the 12 patients, symptom onset clearly occurred immediately after surgery.[12] It is possible that the combination of celiac disease with a second intestinal insult (Whipple resection) could result in more severe symptoms.

It is notable that all 11 patients, in whom initial laboratory results were available, had either high titer IgA tTG or IgA deficiency, suggesting that standard diagnostic testing is adequate for initial evaluation of celiac crisis in acutely ill individuals. In addition, in all patients, small intestinal biopsy revealed marked villous atrophy, and given the prolonged time to recovery of many of these patients, data from the initial biopsy were clinically valuable. As with all celiac disease, gluten withdrawal with nutritional support is the treatment of choice, and 50% of patients responded quickly to these interventions alone. For individuals not responding promptly to gluten restriction, treatment with prednisone or budesonide was efficacious, and all patients were able to wean off of steroids completely within 8 months (mean, 5.3 mo; range, 4–7 mo) with eventual good response to a gluten-free diet alone.

In summary, we present data on 12 adult individuals presenting with celiac crisis over the past 8 years. This series provides new information regarding the spectrum of celiac crisis and celiac disease in general. In addition, the diagnostic criteria developed for this project may be of benefit in helping clinicians to diagnose and treat celiac crisis more promptly in adult patients. We believe that celiac disease should be considered in the differential diagnosis of all patients presenting with an acute onset of severe diarrhea with metabolic disturbances once common infectious etiologies have been ruled out. Any patient found to have an increased IgA tTG or IgA deficiency in this setting should be placed on a gluten-free diet and have a small intestinal biopsy performed as soon as possible. Corticosteroids should be considered in cases of celiac crisis when a gluten-free diet, in conjunction with fluid and electrolyte repletion, does not result in rapid improvement.

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Conflicts of interest

The authors disclose no conflicts.

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