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Celiac crisis is a rare but serious complication of celiac disease in adults

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Abstract

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 tTG 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.

Conclusion—Celiac crisis has a high morbidity and, although rarely described, occurs in adults and often has a clear precipitating factor. Patients that 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 is often required in the short term but most patients ultimately respond to gluten avoidance.

Keywords

steroids; treatment; tissue transglutaminase; enteropathy

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Introduction

Celiac crisis is a life threatening syndrome where 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' is first noted in the literature in 1953 when Anderson and di Sant-Agnese reported the clinical course of 58 children with celiac disease, 35 of whom presented with celiac crisis.[3, 4] In this series, children with celiac crisis were noted to have a case fatality rate of nine percent. Celiac crisis continues to be associated with a high morbidity[5, 6], mandating immediate identification and treatment, however, since this initial report, no individual publication has described more than three cases.

Further, celiac crisis had been thought of primarily as a childhood ailment, much as celiac disease itself was until recently. Additionally, it has been suggested that celiac crisis is becoming less frequent due to earlier diagnosis of celiac disease made possible by the great advances in diagnostic modalities over the past decades[7], although there is little data to support this statement. To date, less than 10 cases of celiac crisis in adults have been reported in the literature[5–10], and for this reason, celiac disease is rarely 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 modern literature describe only one or two 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. In order to improve awareness of celiac crisis and to facilitate diagnosis, we reviewed cases of celiac crisis seen at two major referral centers for celiac disease; Beth Israel Deaconess Medical Center in Boston, MA and Mayo Clinic in Rochester, MN.

Methods

As 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 'acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least two 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 in Boston, MA and Mayo Clinic in Rochester, MN from 2000–2008. 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 (EMA) or deamidated gliadin peptides antibodies (DGP) serology, or positive HLA DQ2 or DQ8 and clinical response to treatment with a gluten free diet (GFD).[11] Demographic data along with symptoms at presentation, presence of electrolyte abnormality, weigh loss, administration of total parenteral nutrition (TPN), systemic steroid therapy, Marsh grade, HLA type, IgA tissue transglutaminase level at the time of celiac crisis, and time to recovery were collected from the medical records.

Results

Twelve adult patients with biopsy proven celiac disease met the above criteria for celiac crisis. Due to the participating institutions status as referral centers, actual incidence is difficult to estimate. However, between the two centers approximately 1200 patients with celiac disease

were diagnosed over the study duration reflecting an incidence of celiac crisis of less than one percent in patients with celiac disease.

Of the 12 cases, 8 were women and 4 were men, mean age of diagnosis was 58.9 years overall; 63.5 years in men and 56.6 years in women (p=NS). 11 of 12 patients developed celiac crisis prior to diagnosis of celiac disease. One patient who had known celiac disease prior to 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 others had elevated IgA tissue transglutaminase titers, eight of nine 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), Sjogren syndrome and Raynaud's disease (case 12). Also notable, two patients had osteoporosis (cases 7 and 9), one had osteopenia (case 6) two had type 2 diabetes mellitus (case 9 and 10) and one had nonalcoholic steatohepatitis NASH (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 prior to, and possibly precipitating, their celiac crisis: 1 presented less than two months post partum (case 1), another two weeks after small bowel obstruction followed by exploratory laparotomy and removal of Meckel's diverticulum (case 2), a third immediately after an episode of gallstone pancreatitis (case 4), and two presented one week after pancreaticoduodenectomy (Whipple procedure) because of presumed pancreatic or ampullary malignancy (cases 9 and 10).[12]

Patients presented with severe dehydration, renal dysfunction presenting as elevated creatinine level, and electrolyte disturbances like hypokalemia, hypocalcemia and hyponatremia requiring replacement of these electrolytes. Of these, hypocalemia was most common (6 patients) with tetany reported in 3. Per diagnostic criteria, all patients required hospitalization and intravenous fluids and five required parenteral nutrition. Six patients required corticosteroids including intravenous prednisolone followed by tapering doses of oral prednisone starting at 60 mg (case2), prednisone 40 mg then budesonide 9 mg/day (cases 6 and 8), budesonide 9 mg/day (cases 2 and11), and prednisone 30 mg then budesonide 9 mg/day (case 12). All patients adopted a strict gluten free diet and had a rapid clinical response within two weeks, however, nutritional support and/or treatment with corticosteroids was necessary in a minority 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. While data do suggest that celiac disease is becoming more common overall[14, 15] it is unclear whether the dramatic change in clinical spectrum is due 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 last half century and no recent deaths

from celiac crisis have been reported in the literature since Lloyd-Still described the successful treatment of three cases of celiac crisis in children with corticosteroids in 1972.[16]

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. Like celiac disease in general, celiac crisis in this series appears often to be precipitated by a general immune stimulus such as surgery, infection or pregnancy as has been previously described.[17–19] However, it is unclear if celiac crisis in adults occurs at disease onset or if celiac disease has 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 intestestinal insult (Whipple resection) could result in more severe symptoms.

It is notable that all 11 patients in whom initial labs are 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. Additionally, 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 was 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 were efficacious, and all patients were able to wean off of steroids completely within 8 months (mean 5.3, Range 4 to 7) 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 eight years. This series provides new information regarding the spectrum of celiac crisis and celiac disease in general. Additionally, the diagnostic criteria developed for this project may be of benefit in helping clinicians to more promptly diagnose and treat celiac crisis 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 elevated IgA tTG or IgA deficiency in this setting should be placed on a gluten free diet and 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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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 >2.0 g/dL
Metabolic acidosis: pH <7.35
Hypoproteinemia (Albumin < 3.0 g/dL)
Abnormal electrolytes including: hyper/hyponatremia, hypocalcemia, hypokalemia or hypomagnesemia
Weight loss > 10 lbs

Table 2

Demographic and clinical characteristics

Pt	Age	Gender	serology	Symptoms	Weight loss (lb)	Electrolyte abnormality	Marsh grade/IELs	TPN	steroids	HLA	Hospital stay	Time to recover
1	34	F	tTG 113	D	15	Acidosis	3b/50	+	+	DQ 8	7 days	8 weeks
2	51	M	tTG >200 EMA +	D	20	↓Ca, ↓K, ↓Na, ↓Alb, Acidosis, ARF (Cr- 3.1)	3c/50	+	+	DQ 2	11 days	20 weeks
3	48	F	IgA def. tTG 0	V, D, Orthostasis	30	↓Ca, ↓K	3b*	_	_	DQ 2	4 days, 3 days	40 weeks
4	70	M	tTG >100	V, D, ↑HR Abd. pain,	10	↓K	3a*	_	_	NA	NA	24 weeks
5	48	F	NA	D, ↑HR, Neuropathy	21	NA	3a/50	_	_	DQ 2	7days	NA
6	68	F	tTG 6 (ref. 0 – 5)	V, D, ↓BP	30	↓K, ↑Na ↓Alb	3a*	+	+	DQ 2	5 days	32 weeks
7	67	F	tTG 250	D, ↓BP	28	↓Ca, ↓Alb	3c/100	-	-	DQ2	8 days	30 weeks
8	74	F	tTG 24.5	D, Tetany	30	↓Ca, ↓K, ↓Mg ↓Alb	3c/60	-	+	NA	7 days	8 weeks
9	65	M	tTG 21.3 EMA+	D, Tetany	20	↓Ca	3a/40	+	-	DQ2	10 days	16 weeks
10	68	M	tTG 117 EMA+	D, Tetany	20	↓Ca, ↓Alb	3b/60	+	-	DQ2	11 days	24 weeks
11	65	F	tTG 22	D	40	↓Ca, ↓Mg, Acidosis, ARF (Cr. 2.6)	3c/80	-	+	DQ2	13 days	24 weeks
12	49	F	tTG 83.7 EMA+	D	10	↓Mg	3a/50	-	+	DQ2	4 days	24 weeks

↓ - decrease, ↑- increase, Abd. Pain- abdominal pain, Acidosis- metabolic acidosis, Alb- albumin, ARF- acute renal failure, BP- blood pressure, Ca- calcium, Cr- creatinine, D- diarrhea, EMA- endomysial antibody, F-female, HLA- human leukocyte antigen, HR- heart rate, IELs- number of intraepithelial lymphocytes per 100 epithelial cells, *-IEL count not available, IgA def.- Immunoglobulin A deficiency, K- potassium, lb- pounds, M- male, Mg- magnesium, Na- sodium, NA- not available, Orthostasis- orthostatic changes, TPN- total parenteral nutrition, V- vomiting, tTG- IgA anti-tissue transglutaminase antibody