JCEM Case Reports, 2024, **2**, luae205
https://doi.org/10.1210/jcemcr/luae205
Advance access publication 4 November 2024
Case Report

Hypoglycemia Associated With Hypermobile Ehlers-Danlos Syndrome

Hamayle Saeed,[1,2] Amanda Sheehan,[1] and Mary-Elizabeth Patti[1,2]

[1]Research Division, Joslin Diabetes Center, Boston, MA 02215, USA
[2]Harvard Medical School, Boston, MA 02215, USA

Correspondence: Mary Elizabeth Patti, MD, Research Division, Joslin Diabetes Center, 1 Joslin Pl, Boston, MA 02215. Email: mary.elizabeth.patti@joslin.harvard.edu.

Abstract

Hypoglycemia in the absence of diabetes is often multifactorial and challenging to diagnose definitively. We present a case report and an expanded series of adult females with reactive hypoglycemia who were diagnosed with Ehlers-Danlos syndrome (EDS). These patients exhibited predominantly postprandial hypoglycemia, with some fasting and activity-induced episodes. Clinical findings included autonomic dysfunction, gastrointestinal symptoms, and joint hypermobility. Interventions focused on medical nutrition therapy, continuous glucose monitoring, and, in some cases, medication. Many patients continued to experience hypoglycemic episodes despite treatment. Key learning points include the potential association between hypermobile EDS and hypoglycemia, the importance of confirming the Whipple triad, and the need for multidisciplinary management. This case series highlights the need for further research into the prevalence and pathophysiology of hypoglycemia in EDS.

Key Words: Ehlers-Danlos syndrome, hypoglycemia, glucose metabolism, hypermobility, autonomic dysfunction, connective tissue disorders

Introduction

Hypoglycemia without diabetes is often defined by timing or provocative factors, such as fasting, postprandial, exercise-induced, or mixed patterns. Symptoms, reflecting parasympathetic and sympathetic activation, may include sweating, tremor, dizziness, palpitations, fatigue, hunger, and anxiety. Severe hypoglycemia may lead to neuroglycopenia, with difficulty concentrating, confusion, loss of consciousness, seizure, and coma. Given the nonspecific nature of symptoms, confirming hypoglycemia requires fulfilling the Whipple triad: documented hypoglycemia during symptoms and resolution after normalization of glucose [1].

Diagnostic evaluation in adults focuses on excluding autonomous insulin secretion due to insulinoma, insulin-like factors produced by nonislet cell tumors, adrenal insufficiency, malnutrition, other illnesses, congenital disorders, long QT syndrome [2], alcohol use, and medication side effects. Achieving a definitive diagnosis can be challenging, especially for postprandial hypoglycemia. Reactive hypoglycemia can occur after upper gastrointestinal surgery (eg, bariatric surgery, esophagectomy, gastrectomy, fundoplication) but has also been described in dysautonomia [3], nonsurgical rapid gastric emptying, and other forms of intestinal dysmotility [4] However, the etiology of reactive hypoglycemia remains undefined for many patients. Diagnostic evaluation is often complicated by significant symptom overlap between reactive hypoglycemia and other conditions that cause postprandial symptoms without hypoglycemia, including dumping syndrome, orthostatic hypotension, cardiac arrhythmias, and dysautonomia.

We report a series of patients with documented reactive hypoglycemia associated with Ehlers-Danlos syndrome (EDS), a group of connective tissue disorders characterized by joint instability, skin hyperextensibility, and tissue fragility [5]. Associated conditions may include dysautonomia, postural orthostatic tachycardia syndrome [6], intestinal dysmotility, hernias, headaches, fatigue, chronic pain, seizure, and mast cell activation syndrome [7]. EDS is likely underdiagnosed, with some patients seeking care for years before diagnosis.

Case Presentation

A 33-year-old female with an established clinical diagnosis of hypermobile EDS (hEDS) was referred for evaluation of possible hypoglycemia during hospitalization for seizure-like activity. Seizure-like activity had occurred 2 hours after breakfast, during an outpatient visit when she reported fatigue, malaise, and diaphoresis; capillary glucose was 65 mg/dL (3.6 mmol/L, reference range: 70-100 mg/dL; 3.9-5.6 mmol/L). The patient was hospitalized; after an overnight fast, she reported palpitations, lethargy, sweating, and dizziness. Capillary glucose was 61 mg/dL (3.4 mmol/L); symptoms were relieved promptly with juice.

She reported the onset of similar symptoms during high school, including weakness, sweating, shakiness, and piloerection, particularly after activity on warm days. An oral glucose tolerance test performed at an external institution revealed venous glucose of 45 mg/dL (2.5 mmol/L) at 2 hours, prompting the diagnosis of reactive hypoglycemia.

At age 28, she sustained 2 concussions after head trauma, followed by multiple seizure-like events. Video electroencephalography during symptomatic events was negative for epileptic seizures, with diagnosis of nonepileptic seizures. Worsening nonepileptic seizure frequency prompted emergency room evaluation; capillary glucose was 51 mg/dL (2.8 mmol/L). IV

Received: 6 August 2024. **Editorial Decision:** 17 October 2024. **Corrected and Typeset:** 4 November 2024

dextrose improved glucose to 70 mg/dL (3.9 mmol/L), but a subsequent fall to 50 mg/dL (2.8 mmol/L) was associated with recurrent seizure-like activity. Inadequate nutrition was deemed the likely cause, despite stable body mass index 23 kg/m^2.

The patient reported recurrent symptoms of weakness, fatigue, dizziness, sweating, thirst, shakiness, palpitations, impaired memory, difficulty concentrating, slow thinking, and confusion; home glucose monitoring revealed capillary glucose <60 mg/dL (3.3 mmol/L). Episodes typically occurred 2 hours after breakfast, with activity >10 minutes, hot weather, showering, and occasionally in fasting and midnocturnal states. She experienced 10+ events requiring emergency room evaluation due to loss of consciousness.

hEDS had been diagnosed with a Beighton score of 9/9, characterized by joint hypermobility, recurrent joint dislocations; hyperextensible skin; atrophic scarring; dental crowding with a high, narrow palate; striae unrelated to weight gain/loss; recurrent abdominal hernia; piezogenic heel papules; and chronic widespread pain. Mitral regurgitation was noted on echocardiogram. Additional diagnoses included postural orthostatic tachycardia syndrome (POTS), small fiber neuropathy, dysautonomia, Raynaud syndrome, orthostatic hypotension, pleural effusions, biliary dyskinesia, gastroesophageal reflux, constipation, goiter, hearing loss, polycystic ovarian syndrome, intestinal bacterial overgrowth, migraine, iron deficiency anemia, and vitamin B12 deficiency. There was no history of hypoglycemia during infancy or childhood, upper gastrointestinal surgery, disordered eating, or adrenal insufficiency. Weight was stable for several years with a body mass index 22 to 23 kg/m^2. Surgical history included repair of meniscus and wrist ligaments. Medications included levalbuterol, multivitamins, B-complex, vitamin D3, and magnesium, with stable usage over time.

The patient's family history included maternal hEDS and paternal type 2 diabetes, overweight, hypertension, and hyperlipidemia. There was no family history of hypoglycemia; multiple endocrine neoplasia; or disorders of adrenal, pituitary, parathyroid, or pancreas.

Diagnostic Assessment

Laboratory testing after overnight fasting on 3 separate occasions showed normal venous glucose (81-89 mg/dL [4.5-4.9 mmol/L]; reference range: 70-100 mg/dL [3.9-5.6 mmol/L]) and appropriate β-cell peptides (insulin 2.7-3.9 μIU/mL [18.7-27 pmol/L]; reference: <18.4 μIU/mL [128 pmol/L]), proinsulin <7.5 pmol/L (reference: < 8.8 pmol/L), C-peptide 0.60-0.85 ng/mL [0.20-0.28 nmol/L] (reference: 0.8-3.85 ng/mL [2-9.6 nmol/L]). Morning cortisol (13-14 μg/dL [359-386 nmol/L]; reference: 5-25 μg/dL [138-690 nmol/L]) and postcosyntropin cortisol, TSH, gastrin, IGF1, IGF2, and prolactin were normal. Abdominal computed tomography and brain magnetic resonance imaging were unremarkable. During an inpatient fast, she developed chest pressure, palpitations, paresthesias, and confusion at 36 hours, with concurrent plasma glucose of 51 mg/dL (2.8 mmol/L). Glucose increased by 15 mg/dL (0.83 mmol/L) 30 minutes after glucagon administration, consistent with a lack of excessive insulin action during prolonged fast. At fast termination, there was appropriate suppression of insulin (2.3 μIU/mL [16 pmol/L]; reference range for prolonged fast: <3 μIU/mL [20.8 pmol/L]), proinsulin (4.5 pmol/L; reference: <5 pmol/L), and C-peptide (0.55 ng/mL [0.18 nmol/L]; reference: <0.2 nmol/L [0.6 ng/mL]), with normal glucagon (57 pg/mL [57 ng/L]; reference: 50-100 pg/mL [50-100 ng/L]) and robust induction of ketogenesis (β-hydroxybutyrate 5.7 mmol/L; reference for prolonged fast: >2.7 mmol/L).

The overall assessment was predominantly reactive hypoglycemia, potentially related to disordered autonomic control of glucose metabolism in the context of prior traumatic brain injuries, intestinal dysmotility, and EDS. Although the majority of available glucose levels were capillary samples, low capillary glucose corresponded closely with venous samples during fasting.

Treatment

Initial treatment included a Dexcom G6 continuous glucose monitor (CGM), uncooked cornstarch, and glucagon for emergency use. Medical nutrition therapy focused on frequent small meals with low glycemic index foods. Despite meticulous adherence, CGM revealed sensor glucose <70 mg/dL (3.9 mmol/L) for 3% to 12% of all readings, most commonly postbreakfast, postactivity, and during midnocturnal hours (range: 42-147 mg/dL [2.3-8.2 mmol/L]).

Outcome and Follow-up

The patient was followed in a hypoglycemia-focused clinic, and her clinical status remained stable.

Additional patients with EDS and similar patterns of confirmed hypoglycemia were recognized in our hypoglycemia-focused clinic (Tables 1 and 2). Most patients had a confirmed hEDS diagnosis; 69% had an EDS family history. Autonomic dysfunction (dysmotility, dysautonomia, neuropathy, POTS, orthostatic hypotension, and mast cell activation syndrome) was common. All patients experienced reactive hypoglycemia; 61% also reported fasting hypoglycemia. Minimum plasma and capillary glucose were 47 (2.6 mmol/L) and 39 mg/dL (2.1 mmol/L), respectively. These observations suggested a strong association between EDS and hypoglycemia.

Discussion

We report documented hypoglycemia occurring in patients with EDS. Hypoglycemia symptoms were most common postprandially but also after activity, short-term fasting, and delayed meals. Symptoms were confirmed by venous, sensor, and/or capillary glucose. Some individuals experienced neuroglycopenia, loss of consciousness, and seizures.

EDS is a hereditary connective tissue disorder with 13 defined subtypes, all characterized by abnormalities in connective tissue [8, 9]. hEDS is the most common form, with a primarily autosomal dominant inheritance pattern, but specific genes remain unidentified. Diagnosis relies on clinical criteria including the hEDS checklist and Beighton scoring, with an exam demonstrating hypermobility, skin extensibility, and atrophic scarring. Additional features include dysautonomia [10, 11], POTS, dysmotility/gastrointestinal complaints [12], recurrent hernias, dislocations/subluxations, headaches, fatigue, and pain. Gastrointestinal manifestations include both structural (hernias, rectoceles, prolapse) and functional (dysmotility) abnormalities [13]. Dysautonomia may encompass altered sympathetic reactivity, potentially related to neuropathy, connective tissue laxity, and vasoactive medications [11].

Table 1. EDS related history

Case #	Age	Sex	BMI	EDS diagnosis	EDS family history	Dysmotility	Dysautonomia	Neuropathy	POTS	Orthostatic hypotension	MCAS
1	20	F	26	Yes, h_EDS	+	+	MALS	–	+	+	+
2	42	F	40	Yes, h_EDS	–	–	Suspected	Suspected	+	–	–
3	26	F	25	Yes, EDS III	+	+	+	Suspected	+	–	+
4	44	F	25	Yes, h_EDS	–	+	+	+	–	+	Suspected
5	40	F	18	Yes, h_EDS	Adopted	+	+	Suspected	–	+	–
6	35	F	22	Yes, h_EDS	+	+	+	+	+	–	–
7	33	F	22	Suspected h_EDS	–	+	+	+	+	+	–
8	61	F	27	Yes, h_EDS	+	–	–	–	–	–	–
9	57	F	39	Yes, h_EDS	+	–	–	–	–	–	–
10	57	F	20	Yes, Classic EDS	+	+	Suspected	–	–	–	–
11	29	F	24	Yes, h_EDS	+	–	–	–	–	–	–
12	22	F	24	Hypermobility syndrome	+	+	Suspected	+	+	+	+
13	34	F	34	Yes, h_EDS	+	+	Suspected	–	+	+	–

+ indicates diagnosed presence; – indicates absence.

Abbreviations: BMI, body mass index; EDS, Ehlers-Danlos syndrome; hEDS, hypermobile Ehlers-Danlos syndrome; MALS, median arcuate ligament syndrome; MCAS, mast cell activation syndrome; POTS, postural orthostatic tachycardia syndrome.

Symptoms of palpitations, diaphoresis, dizziness, fatigue, nausea, anxiety, brain fog, cognitive changes, blurred vision, and loss of consciousness may overlap between EDS-related disorders and hypoglycemia. Therefore, careful documentation of glucose at the time of symptoms is required in order to fulfill the Whipple triad; venous glucose is preferred for diagnosis, as alterations in blood flow may reduce the accuracy of capillary and sensor glucose measurements, potentially yielding falsely low values. Professional (masked) continuous glucose monitoring with a symptom, activity, and meal diary can be helpful to assess patterns but not for diagnosis.

The diagnostic approach for possible hypoglycemia (Fig. 1) begins with a comprehensive history, examination, and verification of the Whipple triad (low venous glucose at the time of symptoms or multiple capillary glucose measurements if venous sampling is not feasible).

If the Whipple triad criteria are met, hypoglycemia is confirmed. Subsequent evaluation is aimed at defining the etiology of hypoglycemia using a critical sample by measuring β-cell peptides (insulin, proinsulin, C-peptide), β-hydroxybutyrate, cortisol, and possibly other hormones. If samples at the time of documented hypoglycemia are not available, prolonged fasting may be needed to assess the contribution of β-cell peptides and to fully exclude those disorders requiring distinct therapy, such as insulinoma or other tumors, noninsulinoma pancreatogenous hypoglycemia syndrome, autoimmune hypoglycemia, malnutrition, side effects of medications or supplements, and hormone deficiencies (eg, adrenal insufficiency). In hypoglycemia with predominant reactive (postprandial or postexercise) patterns, potential causes include upper gastrointestinal surgery, autoimmune hypoglycemia, insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome, or drug-related factors. If the patient does not respond to initial management (eg, medical nutrition therapy, acarbose, CGM), further laboratory testing, imaging for localization, and/or prolonged fasting should be considered.

The index patient described in this report had previously had an oral glucose tolerance test; however, this is not recommended as part of the evaluation, as it is nonphysiologic and induces hypoglycemia in 10% of healthy people [14].

A relationship between EDS and hypoglycemia has not been previously described to our knowledge. Possible etiologic factors linking EDS to hypoglycemia may include intestinal dysmotility, dysautonomia, and Chiari malformation. In our experience, β-cell peptides are appropriately suppressed at the time of hypoglycemia in EDS-associated hypoglycemia.

Gastrointestinal manifestations, including dysmotility, are common in hEDS. Notably, rapid gastric emptying may contribute to postprandial hypoglycemia in affected individuals [15, 16]. Gastric emptying studies may be considered based on symptom patterns. Disordered eating, reduced caloric intake, or malabsorption could reduce gluconeogenesis and/or glycogen stores [17, 18]. Celiac disease, gluten intolerance, Crohn's disease, reflux esophagitis, and mast cell activation disorders may be more prevalent in EDS, potentially contributing to dysregulation of gut and immune function [17, 19, 20].

EDS-associated autonomic dysfunction could influence hypoglycemia via several mechanisms. First, recurrent hypoglycemia may impair counterregulation in response to declining glucose, reducing awareness of hypoglycemia (hypoglycemia-associated autonomic failure) and increasing vulnerability to hypoglycemia [21]. Second, autonomic dysfunction could alter neuronal responses to hypoglycemia. Glut2-dependent glucose-sensing neurons regulate insulin secretion through vagal firing [22], while hypothalamic nutrient sensing modulates hepatic glucose production via autonomic projections to the liver [23].

Small fiber neuropathy is common in EDS [24]. Individuals with hEDS and gastrointestinal symptoms also score higher on orthostatic domains in autonomic symptom scales [25, 26]. Altered blood flow could also result in falsely low capillary and sensor glucose readings, underscoring the importance of venous glucose levels for diagnosis.

Chiari malformation (type I) is associated with EDS [27]. It may cause altered intracranial pressure, resulting in vagal hypertonia. In turn, vagal stimulation of pancreatic islets

Table 2. Hypoglycemia-related history

Case #	Hypoglycemia onset (age)	Fasting hypoglycemia	Reactive hypoglycemia	Minimum reported plasma glucose [reference range: 70-100 mg/dL; 3.9-5.6 mmol/L]	Minimum reported capillary glucose [reference range: 70-100 mg/dL; 3.9-5.6 mmol/L]	Hypoglycemia family history
1	Childhood	–	+	42 mg/dL (2.3 mmol/L)	28 mg/dL (1.6 mmol/L)	–
2	18	–	+	61 mg/dL (3.4 mmol/L)	47 mg/dL (2.6 mmol/L)	+
3	22	+	+	46 mg/dL (2.6 mmol/L)	40 mg/dL (2.2 mmol/L)	–
4	38	+	+	40 mg/dL (2.2 mmol/L)	50 mg/dL (2.8 mmol/L)	–
5	14	+	+	52 mg/dL (2.9 mmol/L)	36 mg/dL (2.0 mmol/L)	NA
6	30	+	+	54 mg/dL (3.0 mmol/L)	51 mg/dL (2.8 mmol/L)	–
7	30	+	+	50 mg/dL (2.8 mmol/L)	45 mg/dL (2.5 mmol/L)	–
8	58 (post-RYGB)	–	+	NA	40 mg/dL (2.2 mmol/L)	NA
9	44 (post-RYGB)	–	+	NA	38 mg/dL (2.1 mmol/L)	–
10	Adulthood	+	+	47 mg/dL (2.6 mmol/L)	40 mg/dL (2.2 mmol/L)	+
11	Childhood	+	+	32 mg/dL (1.8 mmol/L)	30 mg/dL (1.7 mmol/L)	+
12	Childhood	+	+	NA	30 mg/dL (1.7 mmol/L)	–
13	Adulthood (pre-VSG)	–	+	NA	31 mg/dL (1.7 mmol/L)	–

+ indicates presence; – indicates absence.
Abbreviations: NA, not available; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy.

can increase insulin stimulation. Chiari malformation effects on the brainstem may also cause dysregulation of counterregulatory mechanisms [28].

If EDS is suggested on the basis of history and examination, the short (<10-minute) hEDS Diagnostic Checklist may be a useful screening tool. If the patient meets clinical criteria, referral to a geneticist or other clinician experienced in differentiating EDS from other connective tissue disorders is recommended.

As with all patients with established hypoglycemia, management requires a multidisciplinary team. Although no established guidelines exist, management is informed by experience in treating hypoglycemia associated with other conditions. Individualized medical nutritional therapy should focus on adequate macronutrient intake and minimizing gastrointestinal symptoms while considering preferences and intolerances. Limiting carbohydrates to only low glycemic index (complex)

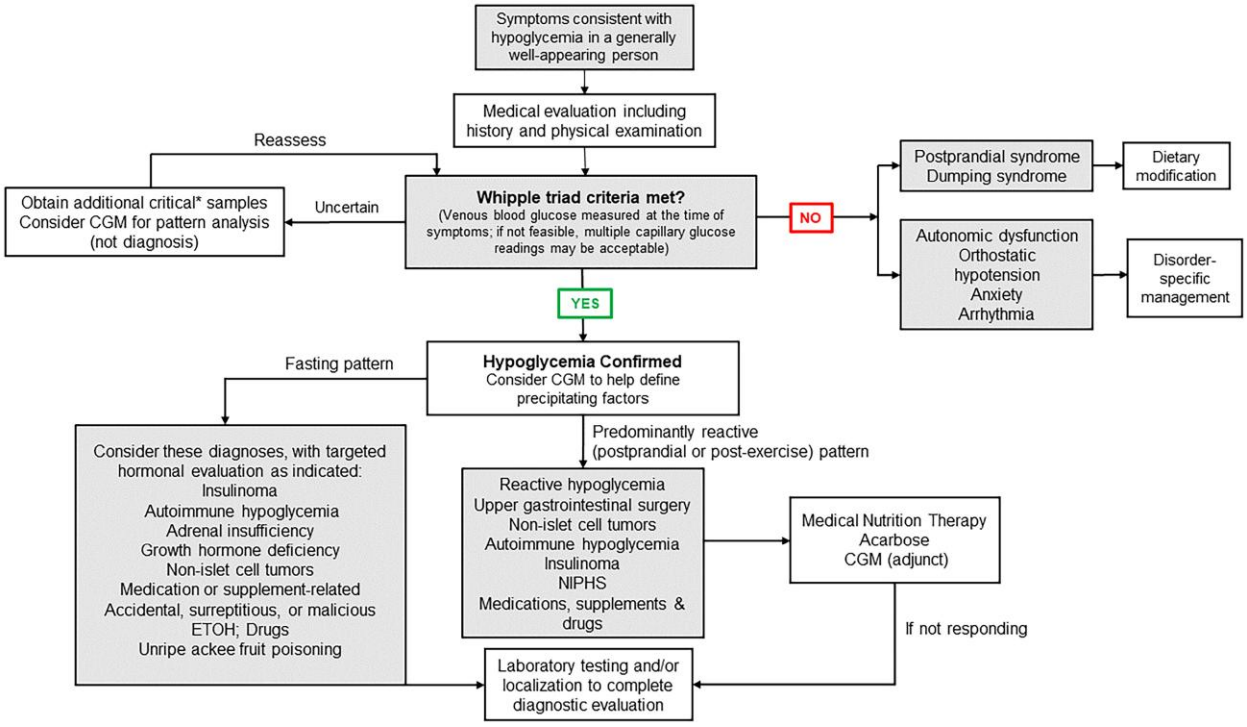

Figure 1. Evaluation of individuals with possible hypoglycemia. *Critical sample indicates blood sample at time of documented hypoglycemia.

carbohydrates (20-30 g for meals, 10-15 g for snacks) and ensuring adequate protein intake can be helpful. Alcohol should be avoided as it can worsen hypoglycemia. Uncooked cornstarch or related products may be used before activity, bedtime, or other vulnerable periods [29].

If dietary measures are insufficient and safety is compromised, medications may be indicated, such as acarbose, especially in individuals with rapid gastric emptying. While additional medications can be considered based on glycemic patterns and severity, complete elimination of hypoglycemia is unlikely with current options.

Personal CGMs with alarms, despite lower accuracy at low glucose ranges, may help individuals with severe hypoglycemia and unawareness to identify impending episodes and initiate treatment to prevent severe hypoglycemia. If a CGM is not available, glucose monitoring 1 to 3 hours after meals, with activity or exercise, and when symptomatic can be helpful. Even with a CGM, patients should be educated to recognize healthy glucose patterns and encouraged to verify low sensor glucose readings with capillary measurements. Patients should ensure their fingers are warm and well-perfused to avoid falsely low readings, especially in those with Raynaud phenomenon.

In summary, we observe that hypoglycemia can occur in individuals with EDS and may present with largely postmeal and activity-induced patterns. Thus, if a rigorous diagnostic workup of a patient with established hypoglycemia does not yield a specific diagnosis, clinicians should consider evaluation for EDS using clinical criteria. We recognize that both EDS and hypoglycemia are uncommon, and ascertainment bias could confound the association. Future research will be required to assess the prevalence of hypoglycemia in EDS cohorts, dissect relationships between glucose and possible hypoglycemic symptoms, and define the pathophysiology underlying this potential association.

Learning Points

- EDS can be associated with hypoglycemia, with largely postprandial or activity-induced patterns.
- Gastrointestinal manifestations, such as dysmotility and rapid gastric emptying, are common in EDS and may contribute to postprandial symptoms and hypoglycemia.
- Autonomic dysfunction in EDS may impair counterregulation, increasing vulnerability to and reducing awareness of hypoglycemia.
- Overlapping symptoms between hypoglycemia and EDS-related disorders necessitate confirmation of the Whipple triad through documentation of glucose patterns and symptoms and careful evaluation to exclude other disorders.
- Management of hypoglycemia in hEDS requires a multidisciplinary approach, with medical nutrition therapy focusing on low glycemic index carbohydrates, adequate protein intake, and uncooked cornstarch and medications as needed.

Contributors

All authors made individual contributions to authorship. H.S.: writing and manuscript revision; A.S.: writing and manuscript revision; M.E.P.: supervision, project administration, review and editing, and final approval of the manuscript. All authors reviewed and approved the final draft.

Funding

National Institutes of Diabetes and Digestive and Kidney Diseases (P30 DK036836), award DK 121995 (to M.E.P.).

Disclosures

M.E.P. acknowledges investigator-initiated research grant support from Dexcom, site investigator on a sponsored clinical trial (Recordati), consulting fees from MBX, Spruce Biosciences, and membership on data safety monitoring board (Fractyl).

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

References

1. Cryer PE, Axelrod L, Grossman AB, *et al*. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728.
2. Mateo CR, Patti ME. Long QT Syndrome and Risk for Hypoglycemia in a Postbariatric Surgery Patient: Bariatric Times. 2019. https://bariatrictimes.com/long-qt-syndrome-postbariatric-surgery/
3. Goedhart C, Gall N, Lulsegged A. A retrospective observational-cohort study of the relationship between reactive hypoglycaemia to postural orthostatic tachycardia syndrome (PoTS). Endocrine Abstracts. 2016-05-13 2016;41(EP235). https://www.endocrine-abstracts.org/ea/0041/ea0041ep235
4. Middleton SJ, Balan K. Post-prandial reactive hypoglycaemia and diarrhea caused by idiopathic accelerated gastric emptying: a case report. *J Med Case Rep*. 2011;5(1):177.
5. Malfait F, Francomano C, Byers P, *et al*. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):8-26.
6. Celletti C, Borsellino B, Castori M, *et al*. A new insight on postural tachycardia syndrome in 102 adults with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder. *Monaldi Arch Chest Dis*. 2020;90(2):10.4081/monaldi.2020.1286.
7. Brock I, Prendergast W, Maitland A. Mast cell activation disease and immunoglobulin deficiency in patients with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder. *Am J Med Genet C Semin Med Genet*. 2021;187(4):473-481.
8. Castori M, Voermans NC. Neurological manifestations of Ehlers-Danlos syndrome(s): a review. *Iran J Neurol*. 2014;13(4):190-208.
9. Galan E, Kousseff BG. Peripheral neuropathy in Ehlers-Danlos syndrome. *Pediatr Neurol*. 1995;12(3):242-245.
10. Castori M, Camerota F, Celletti C, *et al*. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. *Am J Med Genet A*. 2010;152A(3):556-564.
11. De Wandele I, Rombaut L, Leybaert L, *et al*. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum*. 2014;44(1):93-100.
12. De Wandele I, Calders P, Peersman W, *et al*. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum*. 2014;44(3):353-361.

13. Alomari M, Hitawala A, Chadalavada P, *et al*. Prevalence and predictors of gastrointestinal dysmotility in patients with hypermobile Ehlers-Danlos syndrome: a tertiary care center experience. *Cureus*. 2020;12(4):e7881.
14. Hogan MJ, Service FJ, Sharbrough FW, Gerich JE. Oral glucose tolerance test compared with a mixed meal in the diagnosis of reactive hypoglycemia. A caveat on stimulation. *Mayo Clin Proc*. 1983; 58(8):491-496.
15. Middleton SJ, Balan K. Idiopathic accelerated gastric emptying presenting in adults with post-prandial diarrhea and reactive hypoglycemia: a case series. *J Med Case Rep*. 2012;6(1):132.
16. Fikree A, Chelimsky G, Collins H, Kovacic K, Aziz Q. Gastrointestinal involvement in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):181-187.
17. Bandsma RH, Mendel M, Spoelstra MN, *et al*. Mechanisms behind decreased endogenous glucose production in malnourished children. *Pediatr Res*. 2010;68(5):423-428.
18. Baeza-Velasco C, Lorente S, Tasa-Vinyals E, Guillaume S, Mora MS, Espinoza P. Gastrointestinal and eating problems in women with Ehlers-Danlos syndromes. *Eat Weight Disord*. 2021;26(8):2645-2656.
19. Beckers AB, Keszthelyi D, Fikree A, *et al*. Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: a review for the gastroenterologist. *Neurogastroenterol Motil*. 2017;29(8):10.1111/nmo.13013.
20. Seneviratne SL, Maitland A, Afrin L. Mast cell disorders in Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet*. 2017;175(1):226-236.
21. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes*. 2005;54(12): 3592-3601.
22. Thorens B. Neural regulation of pancreatic islet cell mass and function. *Diabetes Obes Metab*. 2014;16 Suppl 1(S1):87-95.
23. Bisschop PH, Fliers E, Kalsbeek A. Autonomic regulation of hepatic glucose production. *Compr Physiol*. 2015;5(1):147-165.
24. Cazzato D, Castori M, Lombardi R, *et al*. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. *Neurology*. 2016;87(2):155-159.
25. Do T, Diamond S, Green C, Warren M. Nutritional implications of patients with dysautonomia and hypermobility syndromes. *Curr Nutr Rep*. 2021;10(4):324-333.
26. Thwaites PA, Gibson PR, Burgell RE. Hypermobile Ehlers-Danlos syndrome and disorders of the gastrointestinal tract: what the gastroenterologist needs to know. *J Gastroenterol Hepatol*. 2022;37(9):1693-1709.
27. Tarani L, Del Balzo F, Costantino F, *et al*. Chiari type I malformation, syncope, headache, hypoglycemia and hepatic steatosis in an 8-year old girl: a causal association? *Pediatr Rep*. 2010; 2(1):e8.
28. Henderson FC, Austin C, Benzel E, *et al*. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):195-211.
29. Suhl E, Anderson-Haynes SE, Mulla C, Patti ME. Medical nutrition therapy for post-bariatric hypoglycemia: practical insights. *Surg Obes Relat Dis*. 2017;13(5):888-896.