Central and Extrapontine Myelinolysis in the Setting of Hyperglycemia

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Osmotic demyelination syndrome (ODS) was first described by Adams et al[1] in 1959 as a combination of quadriparesis, pseudobulbar paralysis, and the distinctive myelin loss in the pons, attributable to alcoholism or malnutrition. ODS has since been commonly attributed to rapid correction of chronic hyponatremia. Other reported etiologies include alcohol withdrawal, liver transplantation, hypokalemia, hypernatremia, as well as severe hyperglycemia[2–6] (Supplementary References [e1–e20]). Here, we describe a case of ODS associated with diabetic ketoacidosis and review the existing literature on hyperglycemia-related ODS.

Case Report

A 61-year-old right-handed man with type II diabetes mellitus, hypertension, hyperlipidemia, and necrotic fasciitis of his right lower extremity was found unconscious and brought to the emergency department. On presentation, the patient was lethargic and hypotensive (blood pressure: 85/50 mm Hg). Initial laboratories showed hyperglycemia (700 mg/dL), high anion gap (25 mEq/L), elevated serum ketones (3.37 mmol/L), and hyperlactatemia (5.8 mmol/L). He was treated for diabetic ketoacidosis and sepsis, followed by a right above-knee amputation. The neurology service was consulted on day 7 due to persistent dysarthria, disorientation, and quadriplegia despite resolution of hyperglycemia and sepsis.

On neurologic assessment, the patient was alert and oriented to self but unable to provide a clear timeline for his symptoms. His cranial nerve examination was intact. The motor examination was notable for quadriplegia with trace movements in the legs, hyperreflexia, and a positive Hoffman sign. The sensory examination was intact to light touch, pin prick, and proprioception.

The cervical-spine magnetic resonance image (MRI) was unremarkable. Brain MRI showed symmetric diffuse bilateral diffusion restriction and T2 fluid-attenuated inversion recovery abnormalities in the bilateral perirolandic regions, occipital lobes, and pons without contrast enhancement suggesting ODS (Figure 1). Cerebrospinal fluid analysis was within normal limits (white blood cells = 1/mm^3, red blood cells = 1/mm^3, protein = 46 mg/dL, glucose = 73 mg/dL with a serum glucose = 102, negative gram stain and meningitis/encephalitis panel). His serum sodium levels were within normal limits at admission and remained stable throughout hospitalization. There was a drop in serum glucose levels from 700 mg/dL to 245 mg/dL and change in osmolarity from 377 to 347 mOsm/kg on the first day of hospitalization (Supplementary Figure 1). Based on clinical and radiologic features, and in the absence of other etiologies, we suggest that the findings were due to the hyperosmolar state secondary to diabetic ketoacidosis.

He was discharged for intense patient rehabilitation after 24 days of hospitalization. Upon discharge, he was completely alert and oriented and able to lift the amputated stump of his right leg and move his left leg within the plane of gravity. He demonstrated trace movements in his left arm. No significant improvement was seen in the right arm at discharge. No further clinic follow-up is available at the time of this writing.

Discussion

This report illustrates a rare case of ODS in the setting of hyperglycemia. We performed a literature search in PubMed, Google Scholar, and Embase and found 25 cases reporting this association. A summary of these cases is presented in Supplementary Table 1. Supplementary Figure 2 illustrates the flow diagram of literature screening. Supplementary Table 2 lists the literature search terms.

There are 2 possible explanations for the pathogenesis of ODS, osmotic shifts due to rapid correction of the hyperosmolar state, or a hypertonic insult that overwhelms the neuronal compensatory capacity. Rapid osmotic shifts resulting from rapid correction of a hyperosmolar state lead to an efflux of osmolytes or influx of water into brain cells and cause neuronal damage. This is the proposed mechanism in the rare instances of ODS in the setting of rapid correction of hypernatremia.[3,7] An alternative explanation is a hypertonic insult in which the serum or extracellular space becomes hypertonic, overwhelming the compensatory mechanism of neuronal cell bodies and leading to astrocytic lesions and demyelination.[3,6] Serum glucose does not contribute to osmolality as much as serum sodium. However, both

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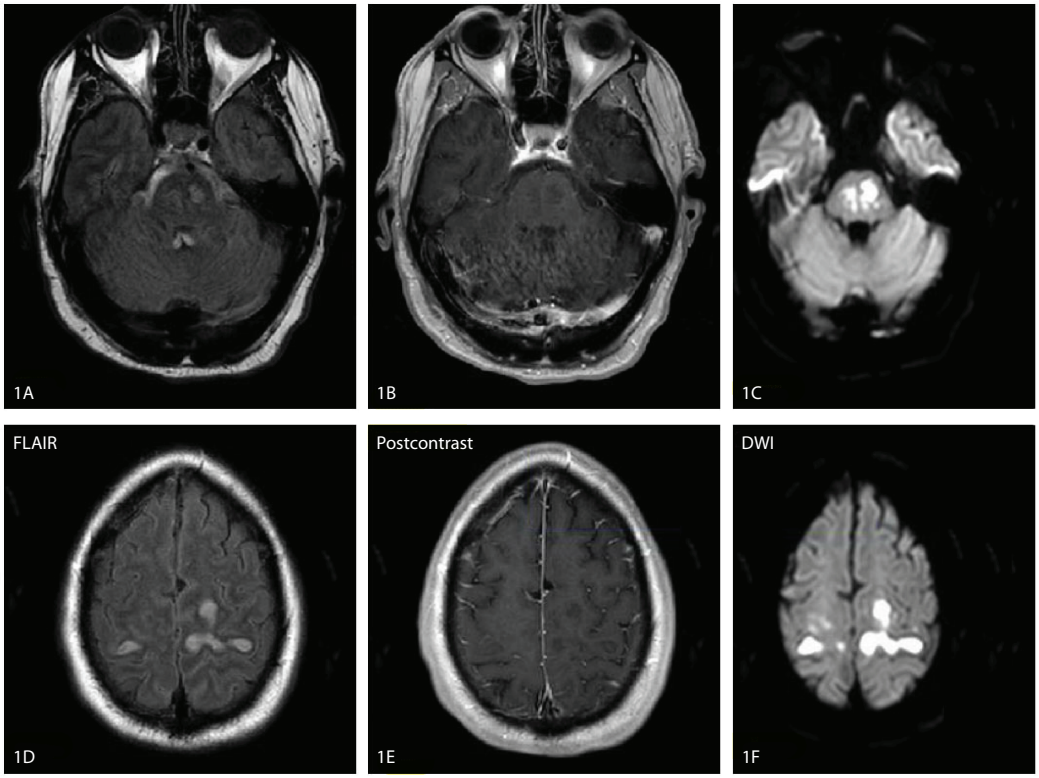
Figure 1. The Patient's Brain MRI Is Notable for Patchy Diffusion Restriction in the Central Pons and Perirolandic Regions (1C and 1F); Corresponding T2 FLAIR Abnormalities Are Evident (1A and 1D); Postcontrast Sequences Show No Contrast Enhancement (1B and 1E)



Abbreviations: DWI = diffusion weighted imaging, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging.

mechanisms have been proposed to cause ODS with dramatically elevated serum glucose levels[4] (Supplementary References [e1–e20]). The duration of glucose and sodium elevation is unclear in most of these cases given their rarity and absence of laboratory data prior to presentation.

ODS prevention is focused on slow correction of the hyperosmolar state.[1–3] Treatment of ODS includes supportive care and treating the underlying condition. The outcomes are variable, ranging from near complete recovery to a completely dependent state or even death (Supplementary Table 1). Treatments with glucocorticoids, intravenous immunoglobulin, intravenous thyrotropin-releasing hormone, and plasma exchange have been tried, but additional studies are warranted before their implementation in clinical practice[5] (Supplementary References [e8]).

Conclusion

Severe hyperglycemia is an uncommon and possibly underreported cause of ODS. The proposed underlying mechanisms are a direct hyperosmolar insult or the osmotic shifts resulting from the rapid correction of the hyperosmolar state.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Central and Extrapontine Myelinolysis in the Setting of Hyperglycemia

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List of Supplementary Material for the article

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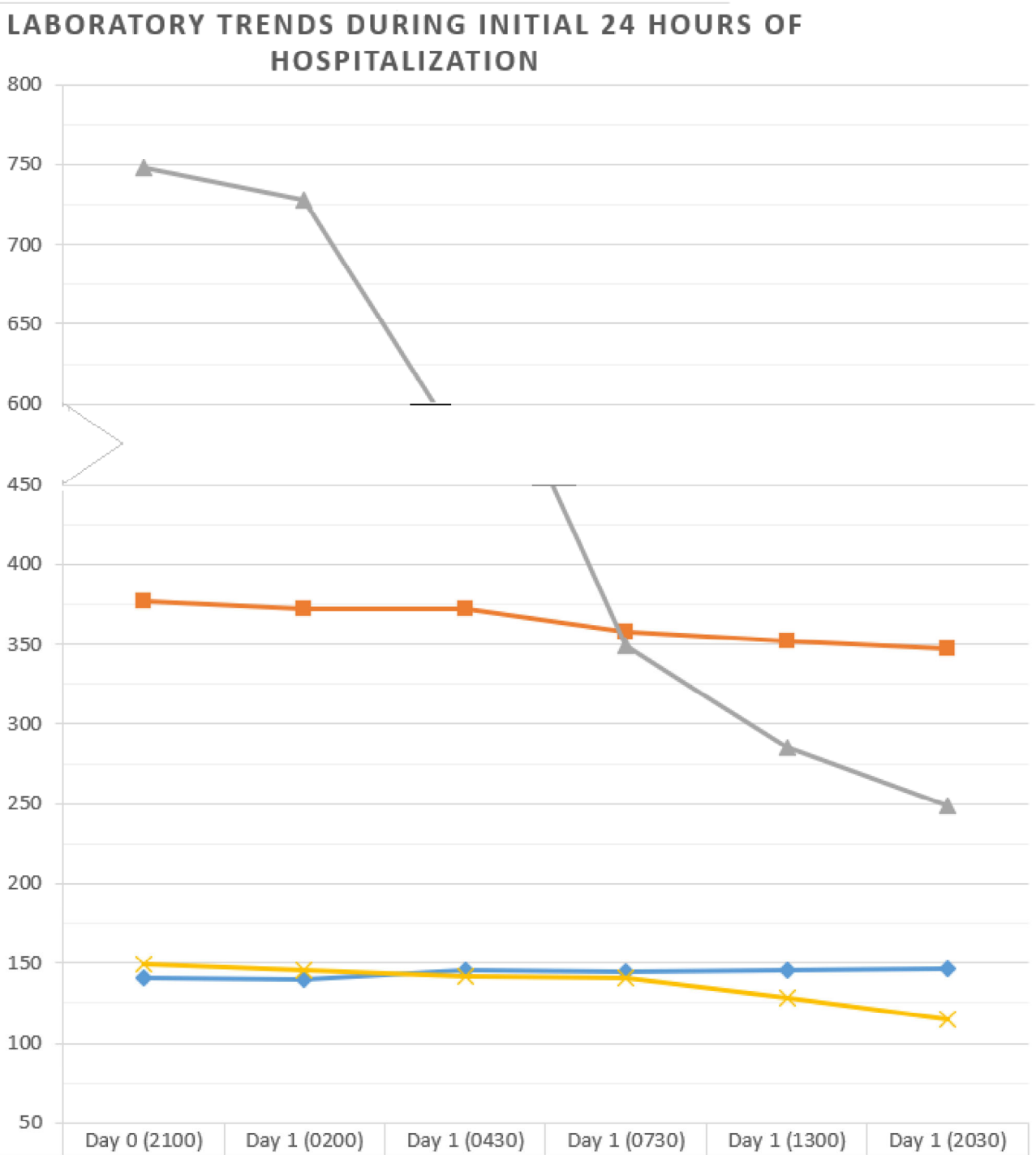
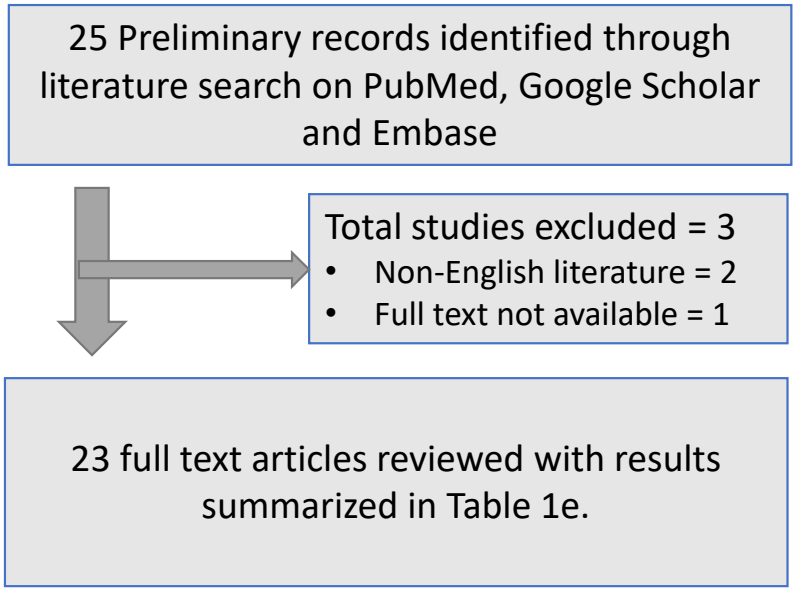
Supplementary Figure 1



	Day 0 (2100)	Day 1 (0200)	Day 1 (0430)	Day 1 (0730)	Day 1 (1300)	Day 1 (2030)
Sodium (mEq/L)	141	140	145	144	145	146
Osmolarity (mOsm/Kg)	377	372	372	358	352	347
Glucose (mg/dl)	748	728	569	349	285	249
BUN (mg/dl)	149	145	142	141	128	115



Supplementary Figure 2: Flow Diagram of Literature Screening

Supplementary Table 1: Literature Summary of Cases With Osmotic Demyelination Syndrome Associated With Hyperglycemia

Case Report	Age (years)	Sex	Glucose (mg/dl)	Osmolality (milli osmoles/Kg	Na (mEq/L)	BUN (mg/dl)	Hb A1c %	K (mEq/L)	Presentation	Outcomes
ODS cases attributed to hyperglycemic hyperosmolar state										
Our Case	61	M	748	374	141	145	10.9	4.7	Found unconscious followed by persistent dysarthria and quadriparesis.	Discharge to inpatient rehab at 1 month. Improved mobility and swallowing but required total care.
Hirosawa et al (e1)	55	M	1011	324	126	43.8	17.8	3.2	AMS x 3 days and dysmetria.	Return to baseline over several weeks
Saini et al (6)	45	F	491	307	132	4	18	4.3	Ataxia, R UE pronator drift x 2 weeks	Gradual improvement in gait by second week
Pliquett et al (e2)	55	M	524	296	133	-	17.6	-	Dysmetria and Dysarthria x 5 days. Liver cirrhosis	Discharged to outpatient rehab Able to walk by 3 months
Hegazy et al (4)	43	F	828	-	181	11		4.6	AMS. Brisk plantar response developed during admission	Complete recovery by week 4
McComb et al (e3)	54	F	954	-	169				Obtunded	Deceased at 21 days
Mao et al (e4)	55	M	685	318	134	-	17.5	4.3	R focal seizures which evolved into EPC, R hemiplegia.	Regain of function by 1 m
Guerrero et al (5)	25	M	> 700	-	-	-	-	-	L hemiparesis developed as AG closed	-
Rodríguez-Velver et al (e5)	47	F	838	320	133	21	10.1	4.6	AMS and GTC. Worsening weakness on 24 hours	Return to baseline by 6 months
Kusumoto et al (e6)	87	F	1000	459	179	-	10.8	5.1	Fever, involuntary trunk and UE movements followed by coma	Return of spontaneous speech reported on 1 year followup
Gouveia et al (e7)	38	M	1225	412	154	38		5.4	AMS x 5 days, h/o chronic alcoholism	Remained poorly arousable, transferred to inpatient rehab
Yoshikawa et al (e8)*	84	F	465	308	113	168	-	6.3	AMS, worsened on HD 8.	Died in a few weeks
Bline et al (e9)*	14	F	> 600		130	64	13.8	2.8	Obtunded and emesis x 4days. Decline in mental status on HD 6.	Return to baseline by week 6
Kim et al (e10)	61	M	627	324	133	43.9	18.1	3.4	Dysarthria, dysphagia, dysmetria x 10 days. H/O cirrhosis	Gradually regained swallowing and mobility over weeks.
Kote et al (e11)	37	F	482	327.66	140	30.5	8.8	3.35	Dysarthria and dysmetria x 10-14 days. Exam decline after 6 hours of initiating treatment	Deceased at 15 days
Kumar et al (e12)	62		542	316	135	38	10.6	3.8	Dysphagia, dysarthria, and ataxia x 10-14 days	Improved dysphagia, dysarthria and walk independently upon discharge.
Lee et al (e13)	36	M	823	336	145	-	-	-	Dysphagia, dysarthria, and ataxia Chronic alcoholism	Dysphagia and ataxia resolved by 1 month, Dysarthria persisted at 4-month follow up.
Sharma et al (e14)	20	F	402	318	142		14.2	4.2	Dysarthria and generalized weakness x 15 days	Return to baseline by 30 days.
Yoong et al (e15)	53	M	594.6	340	135		14	4.6	Frequent falls and dysarthria x 2 months	Near complete recovery reported
Ramineni et al (e16)	50	M	546	318	136	66	13	3.6	Dysarthria, ataxia and generalized weakness x 10 days	Mild dysarthria at 1 month. Independent in all ADLs
Talluri et al (e17)	45	M	178	317	140	95		3.9	Intermittent ataxia, dysarthria and pseudobulbar affect	Return to baseline at 8 weeks
Cases attributed to treatment of hyperglycemic hyperosmolar state										
O'Malley et al (e18)	49	F	1910	399	134	23.3		2.2	Drowsy. No focal deficits. Flaccid quadriparesis noted on day 9 when weaned off sedation	Inpatient rehab, near complete recovery at 6 months
Burns et al (e19)	93	M	524	343	137	48		4.6	AMS and emesis. Ataxia developed 48 hours after admission	Improved gait at 1 month
Hsieh et al (e20)	29	M	646	-	138	-	-	2	AMS x 3 days. Declined 40 hours after admission	Remained vent dependent x 6 weeks, discharged to rehab.

*Unclear if acute treatment played any role in development of ODS
Abbreviations: AMS = Altered Mental Status; UE = Upper extremities; R = Right, L = Left
H/O = History of; GTC = Generalized tonic clonic seizure; HD = Hospital day

Supplementary Table 2: Literature Search Terms Used for the Review of Osmotic Demyelination Syndrome Associated With Hyperglycemia

- Osmotic Demyelination Syndrome
- Osmotic Pontine Myelinolysis
- Extra pontine Myelinolysis
- Hyperglycemia
- Hyperosmolar Hyperglycemia
- Diabetic Ketoacidosis

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