

Diabetic ketoacidosis, refractory hypokalemia, and acquired arginine vasopressin resistance preceding osmotic demyelination syndrome: A possible pathophysiological cascade

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ABSTRACT

Osmotic demyelination syndrome (ODS) is classically linked to rapid correction of chronic hyponatremia, but dynamic osmotic changes during treatment of diabetic ketoacidosis (DKA) may also cause ODS. A 22-year-old man with schizophrenia receiving aripiprazole and clozapine presented with DKA after prolonged poor intake and 30-kg weight loss. Blood glucose at presentation was 399 mg/dL and fell to 146 mg/dL within 2 h. Sodium rose from 140 to 148.9 mmol/L within 11 h and peaked at 149.4 mmol/L, while potassium reached 2.0 mmol/L and remained severely low through early 18 December despite replacement. After glycemic control, persistent dilute urine despite serum hyperosmolality suggested acquired partial arginine vasopressin resistance. He subsequently developed hypophonia, dysarthria, rigidity, bradykinesia, tremor, urinary incontinence, and gait impairment. Brain magnetic resonance imaging showed changes suggestive of ODS. The sequence supports a cascade linking DKA, profound potassium depletion, insulin-related intracellular shift, hypokalemia-associated concentrating failure, hypotonic water loss, and cumulative hyperosmolar stress to ODS.

Key words: Arginine vasopressin resistance, Clozapine, Diabetic ketoacidosis, Hypernatremia, Osmotic demyelination syndrome, Refractory hypokalemia

Diabetic ketoacidosis (DKA) causes major deficits of water and electrolytes. Although serum potassium may initially be normal or elevated because of insulin deficiency and acidosis, total-body potassium is depleted by osmotic diuresis, vomiting, and urinary ketoanion loss; insulin therapy and correction of acidosis may then unmask severe hypokalemia [1]. Second-generation antipsychotics, including clozapine and aripiprazole, have been associated with new-onset diabetes and DKA [2]. Sustained hypokalemia can impair collecting duct water handling by reducing aquaporin-2 expression and promoting its degradation, producing renal resistance to arginine vasopressin (AVP) [3,4]. The term AVP resistance (AVP-R) is now preferred to nephrogenic diabetes insipidus [5]. Osmotic demyelination syndrome (ODS) usually follows overly rapid correction of chronic hyponatremia, but hyperglycemia, hypernatremia,

malnutrition, and hypokalemia may also contribute to osmotic injury [6-11].

We report a young man in whom DKA, persistent severe hypokalemia, an acquired urinary concentrating defect, and pontine demyelination occurred in sequence, and we developed a unifying pathophysiological hypothesis.

CASE REPORT

A 22-year-old man with schizophrenia of approximately 4-year duration on aripiprazole 20 mg/day and clozapine 25 mg at night was brought to the emergency department on December 16, 2025. During the preceding 3 months, he had markedly reduced food intake and lost approximately 30 kg. Nausea and vomiting worsened over 5 days, polyuria was present for about 10 days, and drowsiness for 2 days.

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He was tachycardic at 128/min, tachypneic at 26/min, drowsy but arousable, and irritable. Emergency random blood glucose was 399 mg/dL. The first laboratory panel showed sodium 140 mmol/L, potassium 3.04 mmol/L, chloride 107 mmol/L, urea 16.88 mg/dL, and creatinine 1.11 mg/dL. Glycated hemoglobin (HbA1c) was 10.96%, and urine ketones were strongly positive (80 mg/dL). Arterial blood gas analysis showed severe metabolic acidosis (pH 6.90, HCO₃⁻ 3 mmol/L, PaCO₂ 18 mmHg, PaO₂ 95 mmHg). DKA was diagnosed, and intravenous fluids, titrated intravenous regular insulin, and intensive electrolyte replacement were started.

Capillary glucose fell from 399 to 173 mg/dL within 1 h and to 146 mg/dL by 2 h, followed by marked variability with subsequent values ranging from 132 to 423 mg/dL. Sodium increased from 140 to 148.9 mmol/L within approximately 11 h and peaked at 149.4 mmol/L on 17 December. Potassium fell to 2.0 mmol/L and remained 2.04–2.38 mmol/L through early 18 December despite intravenous and oral replacement. It transiently rose to 4.09 mmol/L and thereafter stabilized with continued replacement (Table 1). The pattern was interpreted as profound total-body potassium depletion due to poor intake, vomiting, osmotic diuresis, and ketoanion loss, compounded by insulin-mediated intracellular shift. Preserved C-peptide (2.01 ng/mL) was documented after stabilization.

As consciousness improved, a distinct neurological syndrome became evident: Hypophonic and slurred speech, generalized rigidity and bradykinesia, mask-like facies, postural and intermittent resting tremor, slow short-stepped gait, impaired independent ambulation, and urinary incontinence. Antipsychotic-induced parkinsonism was considered, but the abrupt onset during a severe osmotic-electrolyte disturbance prompted neuroimaging. Brain magnetic resonance imaging (MRI) performed on 22 December demonstrated a predominantly symmetric central pontine T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesion with pontine swelling. Diffusion-weighted imaging

(DWI) showed only minimal true diffusion restriction, with much of the DWI hyperintensity attributable to edema/T2 shine-through. There was relative preservation of the peripheral pontine tissue and corticospinal tracts. No definite extrapontine demyelinating lesions involving the basal ganglia, thalami, cerebellum, or cerebral white matter were identified on the available images (Fig. 1).

Polyuria and polydipsia persisted after glycemic improvement. On 26 December, sodium was 146 mmol/L and measured serum osmolality was 300.72 mOsm/kg, whereas urine osmolality was only 133.96 mOsm/kg. On 28 December, serum osmolality was 303.59 mOsm/kg with urine osmolality 188.7 mOsm/kg. The disproportionately dilute urine despite serum hyperosmolality supported an acquired concentrating defect. In the context of prolonged hypokalemia and no documented hypothalamic-pituitary lesion, partial AVP-R secondary to hypokalemia was suspected (Table 2). Free-water and electrolyte management and rehabilitation were continued.

Neurological and urinary symptoms progressively improved. At follow-up, speech was clear; hypophonia, rigidity, and bradykinesia had resolved, and he was able to walk independently. Follow-up brain MRI on February 16, 2026, showed resolution of the acute pontine edema with residual trident-shaped central pontine T2/FLAIR hyperintensity and relative sparing of the peripheral corticospinal tracts, consistent with central pontine osmotic demyelination (Fig. 2).

DISCUSSION

The case can be organized into a six-step, mutually reinforcing cascade.

First, newly recognized diabetes – possibly facilitated by second-generation antipsychotic exposure – combined with prolonged poor intake to produce DKA. A systematic review found cases with clozapine, aripiprazole, olanzapine, risperidone, and quetiapine, often in relatively young individuals; mechanisms

Table 1: Serial biochemical trajectory during hospitalization

Date	Na (mmol/L)	K (mmol/L)	Glucose (mg/dL)	Key finding
16 December	140.0	3.04	312.36	First laboratory panel; emergency RBS 399 mg/dL; HbA1c 10.96%; creatinine 1.11 mg/dL
16 December	148.9	2.00	—	Sodium rose 8.9 mmol/L in approximately 11 h
17 December	149.4	2.30	—	Peak measured sodium
18 December	145.6	2.04	228.63	Corrected Na ≈147.7 mmol/L; effective osmolality ≈303.9 mOsm/kg
18 December	145.0	4.09	—	Transient response after potassium replacement
19 December	144.0	3.03	237.32	Potassium subsequently stabilized with continued replacement
22 December	141.9	4.23	—	MRI showed pontine lesion compatible with ODS
26 December	146.0	3.42	91.35	Serum Osm 300.72; urine Osm 133.96 mOsm/kg; C-peptide 2.01 ng/mL
28 December	146.2	4.14	155.3	Serum Osm 303.59; urine Osm 188.7 mOsm/kg
30 December	144.0	3.64	—	Electrolytes stable during clinical improvement

RBS: Random blood sugar, HbA1c: Glycated hemoglobin, MRI: Magnetic resonance imaging, ODS: Osmotic demyelination syndrome, Osm: Osmolality. Corrected sodium and effective osmolality are shown only for paired sodium and glucose values

Table 2: Condensed clinical timeline

Period	Clinical findings	Interpretation/management
Pre-admission	Three months of poor intake and ~30-kg weight loss; 10 days of polyuria; 5 days of vomiting; 2 days of drowsiness	Dehydration, catabolism, evolving hyperglycemic crisis
16 December	RBS 399 mg/dL; severe acidosis and ketonuria; Na 140→148.9; K 3.04→2.0 mmol/L	DKA treatment with IV fluids, insulin, and intensive K replacement
17–18 December	Na peaked at 149.4 mmol/L; K remained 2.04–2.38 mmol/L; neurological syndrome emerged	Profound K depletion with insulin-related intracellular shift; osmotic injury considered
22 December	MRI showed a symmetric central pontine lesion without definite extrapontine demyelination	ODS favored over isolated drug-induced parkinsonism
26–30 December	Serum Osm 300.72–303.59 mOsm/kg with urine Osm 133.96–188.7 mOsm/kg; subsequent clinical improvement	Acquired concentrating defect/partial AVP-R suspected; free-water and electrolyte management continued

RBS: Random blood sugar, DKA: Diabetic ketoacidosis, IV: Intravenous, ODS: Osmotic demyelination syndrome, Osm: Osmolality, AVP-R: arginine vasopressin resistance

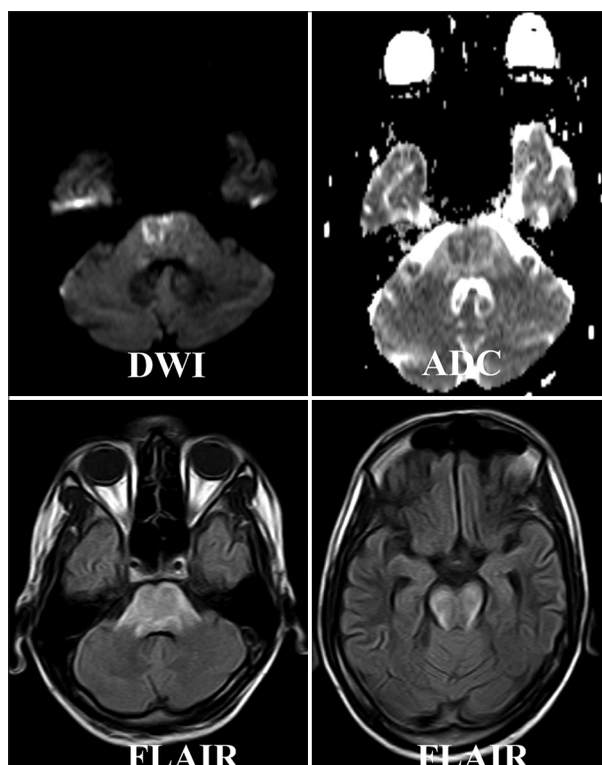


Figure 1: Initial brain magnetic resonance imaging obtained on December 22, 2025. Axial diffusion-weighted imaging (DWI), apparent diffusion coefficient, and fluid-attenuated inversion recovery images demonstrate a predominantly symmetric central pontine signal abnormality with pontine edema/swelling. DWI shows minimal true diffusion restriction, with much of the increased signal representing T2 shine-through. The distribution and clinical context were suggestive of early central pontine osmotic demyelination

appear heterogeneous and may include insulin resistance, impaired beta-cell function, and autoimmune diabetes [2]. In our patient, HbA1c 10.96% and estimated mean glucose 259.88 mg/dL confirmed antecedent dysglycemia, whereas preserved C-peptide of 2.01 ng/mL after stabilization indicated preserved endogenous insulin secretion.

Second, osmotic diuresis, vomiting, ketoanion excretion, and inadequate intake created a massive total-body potassium deficit. The potassium course is central. Potassium declined from 3.04 to 2.0 mmol/L during the 1st day of DKA therapy and remained between 2.04

and 2.38 mmol/L through early 18 December despite replacement. Such values imply a major total-body deficit.

Third, insulin therapy and correction of acidosis shifted potassium into cells, explaining why serum potassium remained severely low despite replacement [1,2].

Fourth, sustained hypokalemia likely impaired collecting duct water handling. Experimental and clinical literature shows that potassium depletion downregulates aquaporin-2 and promotes its autophagic degradation, producing renal resistance to AVP and dilute polyuria [3,4]. However, a formal water-deprivation test, copeptin measurement, and quantified desmopressin challenge were not documented; therefore, AVP-R should be regarded as clinically suspected rather than definitively proven.

Fifth, DKA therapy changes several effective osmoles simultaneously: Glucose falls, sodium rises as water shifts back intracellularly, potassium is administered, and extracellular volume is restored. Thus, the osmotic exposure was not a simple monotonic correction but a rapid, multidirectional trajectory.

Sixth, prolonged malnutrition, approximately 30 kg weight loss, and severe hypokalemia may have reduced cellular osmotic resilience, making pontine white matter susceptible to demyelination [6–11]. The hypothesis is therefore not that severe hypernatremia alone caused ODS but that a rapid multidirectional change in effective osmolality during DKA treatment was amplified by free-water loss and impaired cellular adaptation.

The imaging differential of a central pontine lesion includes acute pontine infarction, inflammatory demyelination, rhombencephalitis, brainstem-predominant posterior reversible encephalopathy syndrome (PRES), infiltrative pontine glioma, and toxic-metabolic encephalopathies. Pontine infarction was less likely because of the symmetric central distribution, relative peripheral sparing, and minimal true diffusion restriction rather than a vascular-territorial pattern. Inflammatory demyelination and rhombencephalitis generally produce asymmetric or multifocal lesions, often with additional cerebral, spinal, or inflammatory abnormalities. Brainstem-predominant PRES predominantly reflects vasogenic edema and usually



Figure 2: Follow-up brain magnetic resonance imaging on February 16, 2026. Axial diffusion-weighted imaging, T2-weighted, and fluid-attenuated inversion recovery images demonstrate resolution of the acute pontine edema with residual trident-shaped symmetric central pontine hyperintensity and relative sparing of the peripheral corticospinal tracts, characteristic of central pontine osmotic demyelination

occurs in an appropriate hypertensive or renal setting, while an infiltrative glioma would be expected to demonstrate persistent or progressive expansion rather than subsequent radiological resolution. The symmetric central pontine distribution, relative sparing of peripheral fibers, trident-shaped appearance on follow-up MRI, temporal association with profound osmotic and electrolyte disturbances, and subsequent radiological improvement therefore strongly favored ODS.

CONCLUSION

A young man with DKA, antecedent chronic hyperglycemia, and profound refractory hypokalemia developed persistent hypotonic urinary dilution followed by a pontine demyelinating syndrome. The proposed cascade – massive potassium depletion, insulin-mediated intracellular shift, hypokalemia-associated partial AVP-R, free-water loss, and cumulative osmotic stress – offers a coherent explanation without requiring extreme hypernatremia. Simultaneous monitoring of glucose trajectory, measured and corrected sodium, potassium, serum and urine osmolality, urine output, and neurological status may permit earlier recognition and risk mitigation for ODS in hyperglycemic emergencies.

AUTHORS' CONTRIBUTIONS

Dr. Sravanthi managed the patient and contributed to the literature review and manuscript preparation. Dr. Sailesh conceptualized the study, drafted the manuscript, and contributed to the literature review. Dr. Ramakrishna, Dr. Goli Charan, and Dr. Bhargavi contributed to patient management and critical revision of the manuscript. Dr. Manoj Kanaparti reviewed and interpreted the radiological investigations. All authors approved the final manuscript.

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