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INVOLUNTARY MUSCULAR MOVEMENTS AS AN ADVERSE REACTION TO SACUBITRIL/VALSARTAN IN A PATIENT WITH CARDIOMYOPATHY AND MULTIPLE COMORBIDITIES: A CASE REPORT

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ABSTRACT

Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor used in heart failure with reduced ejection fraction, is known to cause hypotension, hyperkalaemia and renal impairment, whereas involuntary muscular movements are a rare neuromuscular reaction reported mainly through post-marketing surveillance. We describe a 43-year-old man with cardiomyopathy, heart failure with recovered ejection fraction, non-cirrhotic portal hypertension, biopsy-confirmed diabetic nephropathy, haemolytic anaemia and miliary tuberculosis who developed non-painful, sporadic involuntary jerks of the upper and lower limbs within 12–72 hours of starting sacubitril/valsartan 24/26 mg twice daily, the lowest recommended dose. Hyponatraemic, uraemic, hypoglycaemic, septic and hepatic encephalopathy and seizure disorder were considered and excluded on clinical and biochemical grounds. The drug was withdrawn, and the movements resolved

completely within 24–48 hours without specific treatment; rechallenge was not attempted. Causality was assessed as probable by the World Health Organization–Uppsala Monitoring Centre criteria, with a Naranjo score of 5 and severity level 3 on the Hartwig–Siegel scale. This case extends the reported patient profile to a younger patient with recovered ejection fraction and severe multisystem disease, in whom combined hepatic and renal impairment may have raised exposure to the active metabolite LBQ657. Clinicians starting sacubitril/valsartan in patients with impaired organ clearance should remain alert to this reaction and report suspected cases to pharmacovigilance centres.

KEYWORDS: Sacubitril/valsartan; angiotensin receptor–neprilysin inhibitor; involuntary movements; adverse drug reaction; pharmacovigilance; heart failure with recovered ejection fraction.

INTRODUCTION

Sacubitril/valsartan, a fixed-dose combination of the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker valsartan, is the first angiotensin receptor–neprilysin inhibitor (ARNI) approved for the management of heart failure with reduced ejection fraction (HFrEF) in adults with New York Heart Association (NYHA) class II–IV symptoms.[1] Its pharmacology rests on two complementary mechanisms: inhibition of neprilysin, a zinc-dependent endopeptidase that clears natriuretic peptides, bradykinin and other vasoactive substrates, through the active metabolite LBQ657,[2] combined with angiotensin II receptor blockade. In the PARADIGM-HF trial, this dual strategy reduced cardiovascular death and heart failure hospitalisation by 20% compared with enalapril.[1]

Hypotension, hyperkalaemia and renal impairment, all predictable from its haemodynamic and renin–angiotensin–aldosterone system effects, constitute the established adverse-effect profile.[1] Neuromuscular events, by contrast, went largely undetected in the pivotal trials. Bejan-Angoulvant and colleagues were the first to document this signal formally, reporting three older male patients with decompensated heart failure who developed non-painful, intermittent myoclonic limb and head movements within 12 hours to four days of starting sacubitril/valsartan; all resolved after drug withdrawal. A concurrent search of the WHO VigiBase database found 40 reports of related movement disorders, including spasms, twitches, dyskinesia, clonus and myoclonus, attributed to the drug.[3] Rawla and colleagues subsequently described rhabdomyolysis attributed to sacubitril/valsartan without any statin co-prescription, establishing direct skeletal muscle toxicity as a distinct adverse effect.[4]

We present an additional case in a younger patient with cardiomyopathy, heart failure with recovered ejection fraction (HFrecEF) and severe multisystem comorbidity, a clinical context not previously reported for this adverse reaction.

MATERIALS AND METHODS

Study design and ethical considerations

This is a single-patient case report based on clinical documentation during hospital admission, including history, examination, laboratory investigations and imaging performed as part of routine clinical care. Written informed consent was obtained from the patient for the use and publication of his clinical data. This study was conducted in accordance with the Declaration of Helsinki. As a single-patient educational case report, this work does not constitute human subjects research and was determined to not require Institutional Review Board (IRB) approval. Written informed consent was obtained from the patient for treatment and for open-access publication of anonymized clinical data, laboratory findings, and images.

Exclusion of alternative causes

Alternative causes of the involuntary movements, including hyponatraemic encephalopathy, uraemic encephalopathy, hypoglycaemia, sepsis-related encephalopathy, hepatic encephalopathy and seizure disorder, were evaluated on clinical and biochemical grounds.

Causality and severity assessment

Causality between sacubitril/valsartan and the adverse event was assessed independently using three instruments: the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality categories, the Naranjo Adverse Drug Reaction Probability Scale[5] and the Hartwig–Siegel severity assessment scale.[6]

RESULTS AND DISCUSSION

Patient background

The patient was a 43-year-old male of moderate build with the following diagnoses. Non-cirrhotic portal hypertension (NCPH) with a prior episode of oesophageal variceal haemorrhage, managed with endoscopic variceal ligation and splenic artery embolisation; upper gastrointestinal endoscopy on 8 April 2025 showed a few dilated veins at the distal oesophagus consistent with early oesophageal varices, erosions in the gastric body and antrum, and features of hiatus hernia with antral gastritis. Cardiomyopathy with heart failure: sacubitril/valsartan was prescribed by the treating cardiologist on the basis of documented

prior reduced left ventricular systolic function, and a follow-up echocardiogram in June 2025 showed a left ventricular ejection fraction (LVEF) of 55–60% with gross concentric left ventricular hypertrophy (LVH), consistent with HFrecEF following prior guideline-directed medical therapy with carvedilol and other agents.

He also had type 2 diabetes mellitus with poor glycaemic control (HbA1c 11.9%), complicated by biopsy-confirmed diabetic nephropathy class III (Kimmelstiel–Wilson nodular lesions; interstitial fibrosis and tubular atrophy [IFTA] score 2), haemolytic anaemia, and miliary tuberculosis recently commenced on rifampicin, isoniazid and pyrazinamide.

Abdominal and pelvic ultrasound on 5 July 2025 demonstrated splenomegaly (17.5 cm) with peripheral wedge-shaped hypoechoic areas in the superior pole consistent with splenic infarcts, multiple dilated perisplenic vascular channels (maximum diameter 2.3 cm), moderate ascites, and raised bilateral renal cortical echogenicity. These findings corroborated NCPH after splenic artery embolisation, with concurrent renal parenchymal disease relevant to LBQ657 clearance. Liver stiffness on transient elastography was 16.2 kPa. Serum creatinine was 1.6–1.8 mg/dL with nephrotic-range proteinuria.

Drug initiation and adverse reaction

Sacubitril/valsartan was started at sacubitril 24 mg/valsartan 26 mg twice daily, the lowest recommended starting dose. The patient was haemodynamically stable and neurologically intact at initiation. His concurrent medications were carvedilol, torsemide, finerenone, olmesartan, omeprazole, short-acting and premixed insulin, pyridoxine, calcitriol and the anti-tubercular regimen. No statin was prescribed.

Within 12–72 hours of the first dose, he developed non-painful, sporadic, asynchronous involuntary jerks of the upper and lower limbs. Episodes were brief and intermittent. There was no loss of consciousness, tongue-biting, urinary incontinence or post-ictal drowsiness, effectively ruling out a generalised seizure. Neurological examination between episodes was normal, and haemodynamics remained stable throughout.

Sacubitril/valsartan was the only pharmacological addition in this period. Plain magnetic resonance imaging (MRI) of the brain, obtained on 23 April 2026 at a subsequent hospitalisation, showed bilateral symmetrical areas of restricted diffusion with T2/FLAIR hyperintensity involving the anteromedial pons (corticospinal tract, central tegmental bundle,

medial lemniscus and medial longitudinal fasciculus), consistent with osmotic demyelination syndrome (ODS); diffuse cerebral and cerebellar atrophy disproportionate for age was also noted. This finding was temporally remote from the initial events and was attributed to rapid sodium correction at a later admission; it was not present at the time of the involuntary movement episode. Sacubitril/valsartan was withdrawn, and the movements ceased completely within 24–48 hours. Rechallenge was not attempted given the patient's haemodynamic vulnerability.

Laboratory investigations

Laboratory findings on day 1 (22 April 2026) and day 2 (23 April 2026) are summarised in Table 1.

Table 1: Laboratory investigations on day 1 (22 April 2026) and day 2 (23 April 2026).

Investigation	Day 1	Day 2	Reference range
Haematology			
Haemoglobin (g/dL)	7.9	8.5	13.0–18.0
Total WBC (cells/cumm)	3,100	3,100	4,000–11,000
Neutrophils (%)	80	—	40–75
Lymphocytes (%)	15	—	20–50
Monocytes (%)	2	—	1–6
Eosinophils (%)	3	—	2–10
Platelets (/cumm)	92,000	1,02,000	1,50,000–4,00,000
RBC ($\times 10^6/\mu L$)	2.59	—	3.5–5.0
MCV (fL)	87.8	—	82–101
MCH (pg)	30.6	—	27–32
MCHC (%)	34.8	—	32–36
RDW (%)	10.6	—	12–15
Haematocrit (%)	22.7	24.4	37–54
ESR (mm/hr)	17	20	15–20
Biochemistry			
Random blood sugar (mg/dL)	561.9	—	60–140
HbA1c (%)	11.9	—	<6.0 (normal)
Serum urea (mg/dL)	65.6	60.0	15–39
Serum creatinine (mg/dL)	1.8	1.6	0.6–1.3
Serum sodium (mEq/L)	126.0	136.0	135–153
Serum potassium (mEq/L)	5.5	5.0	3.5–5.5
Serum chloride (mEq/L)	103.0	113.0	95–105
Total bilirubin (mg/dL)	2.1	—	0.2–1.0
Direct bilirubin (mg/dL)	0.7	—	0.1–0.4
Indirect bilirubin (mg/dL)	1.4	—	0.1–0.6
Total protein (g/dL)	6.1	—	5.5–8.0
Serum albumin (g/dL)	3.5	—	3.5–5.0
Serum globulin (g/dL)	2.6	—	1.8–3.0

A/G ratio	1.3:1	—	1.5–2.5:1
AST/SGOT (U/L)	12.1	—	Up to 40
ALT/SGPT (U/L)	13.6	—	Up to 41
Serum ALP (U/L)	171.1	—	35–140
Urinalysis (day 2 only)			
Urine protein	—	3+	Nil
Urine bilirubin	—	3+	Nil
Urobilinogen	—	1+	Nil
Urine blood	—	3+	Nil
Leucocytes (/hpf)	—	25–50	0–2
Pus cells (/hpf)	—	2–5	0–2

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HbA1c = glycated haemoglobin; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; RBC = red blood cell count; RDW = red cell distribution width; WBC = white blood cell count; ESR = erythrocyte sedimentation rate; — = not repeated on that day.

Causality assessment

Causality was assessed as probable by WHO-UMC criteria on all four counts: a plausible temporal relationship, a positive dechallenge, no identifiable alternative cause, and consistency with an existing pharmacovigilance signal. The Naranjo algorithm applied independently yielded a score of 5 (Table 2), confirming the probable classification. On the Hartwig–Siegel severity scale, the reaction was graded level 3: the drug was discontinued, forfeiting an evidence-based therapeutic option, although the movement disorder itself required no pharmacological treatment or supportive intervention.

Table 2: Naranjo Algorithm For Causality Assessment.

Question	Score	Maximum	Result
Are there previous conclusive reports of this reaction?	+1	+1	
Did the adverse event appear after the suspected drug was administered?	+2	+2	
Did the adverse reaction improve upon drug discontinuation (dechallenge)?	+1	+1	
Did the adverse event reappear upon re-administration (rechallenge)?	0	+2	
Were there alternative causes that could have produced the reaction?	0	+2	
Did the reaction reappear following placebo administration?	0	+1	
Was the drug detected in the blood at toxic concentrations?	0	+1	
Was the reaction more severe with dose escalation or less severe with reduction?	0	+1	

Did the patient have a similar reaction to the same or related drug previously?	0	+1	
Was the adverse event confirmed by any objective evidence?	+1	+1	
Total score	5		Probable

Score interpretation: 0 = doubtful; 1–4 = possible; 5–8 = probable; ≥9 = definite.

Comparison with Previous Reports

Several features distinguish this case from the Bejan-Angoulvant series.[3] The patient was considerably younger (43 versus 65–79 years) and carried a far heavier burden of multiorgan disease. The echocardiographic context is also distinctive: a follow-up study showed LVEF of 55–60% with gross concentric LVH, consistent with HFrecEF, a recognised outcome of sustained guideline-directed medical therapy. The ARNI had been prescribed on the basis of prior documented reduced systolic function. HFrecEF does not invalidate the indication or weaken causality; it reflects successful cardiac remodelling, and the adverse reaction itself occurred at the very outset of ARNI exposure, before any updated echocardiographic data from this admission were available to the prescribing team.

Proposed Mechanism

The most plausible mechanism is central neprilysin inhibition. LBQ657 crosses the blood–brain barrier and inhibits enkephalin degradation in nigrostriatal and mesolimbic pathways; the resulting enkephalin excess is thought to perturb dopaminergic motor circuitry, generating involuntary movements.[7] Rodent studies confirm that enkephalinase blockade alters D1/D2-mediated motor behaviour, although this was not reproduced in primate models, a discrepancy that partly accounts for why the neuromuscular signal was overlooked during clinical development.[7]

Pharmacokinetic Considerations

Pharmacokinetic vulnerability was probably central to why this patient reacted at a dose that most patients tolerate.[2] Both LBQ657 and valsartan rely on hepatic metabolism and renal elimination. Concurrent portal hypertension, elevated liver stiffness (16.2 kPa), hypoalbuminaemia and chronic kidney disease collectively reduce first-pass metabolism, impair protein binding and slow LBQ657 clearance, producing systemic drug exposure well in excess of what the prescribed dose would generate in a patient with intact organ function. The anti-tubercular regimen adds a further unpredictable element: rifampicin is a potent CYP3A4/P-glycoprotein inducer that would ordinarily accelerate sacubitril clearance, but this

effect operates in the setting of simultaneous hepatic impairment and isoniazid-mediated CYP inhibition, making the net pharmacokinetic outcome difficult to predict.

The absence of any statin rules out the previously reported statin–ARNI myotoxic interaction[4,8] and implicates sacubitril/valsartan as the independent causative agent. The serum sodium of 126 mEq/L at presentation raised the question of hyponatraemic encephalopathy, but the involuntary movements resolved fully within 24–48 hours of stopping the drug, without sodium correction or any neurological intervention, making a metabolic aetiology implausible.

Limitations and Clinical Implications

Limitations are inherent to the single-case design: no rechallenge was performed (clinically unjustifiable), and plasma drug concentrations were not measured. Despite these constraints, the combination of temporal plausibility, a clean dechallenge response and systematic exclusion of alternatives constitutes a coherent causal case. Clinicians starting sacubitril/valsartan in patients with hepatic or renal comorbidity should document a brief neuromuscular baseline, counsel the patient about this rare but recognisable reaction, and submit reports to national pharmacovigilance registries.[9,10]

CONCLUSION

Involuntary muscular movements associated with sacubitril/valsartan are uncommon but real. This report broadens the documented patient profile to a younger individual with HFrecEF and extensive multiorgan comorbidity. Dual hepatic and renal impairment, in a complex polypharmacy context, probably amplified LBQ657 exposure sufficiently to lower the threshold for central neuromuscular toxicity, even at the minimum starting dose. The reaction resolved without specific treatment once the drug was stopped, underlining that recognition and prompt withdrawal are the key clinical actions. A structured neuromuscular baseline assessment before initiating ARNI therapy is prudent in patients with significant organ dysfunction, and systematic pharmacovigilance reporting remains essential to refine prescribing guidance for this vulnerable population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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