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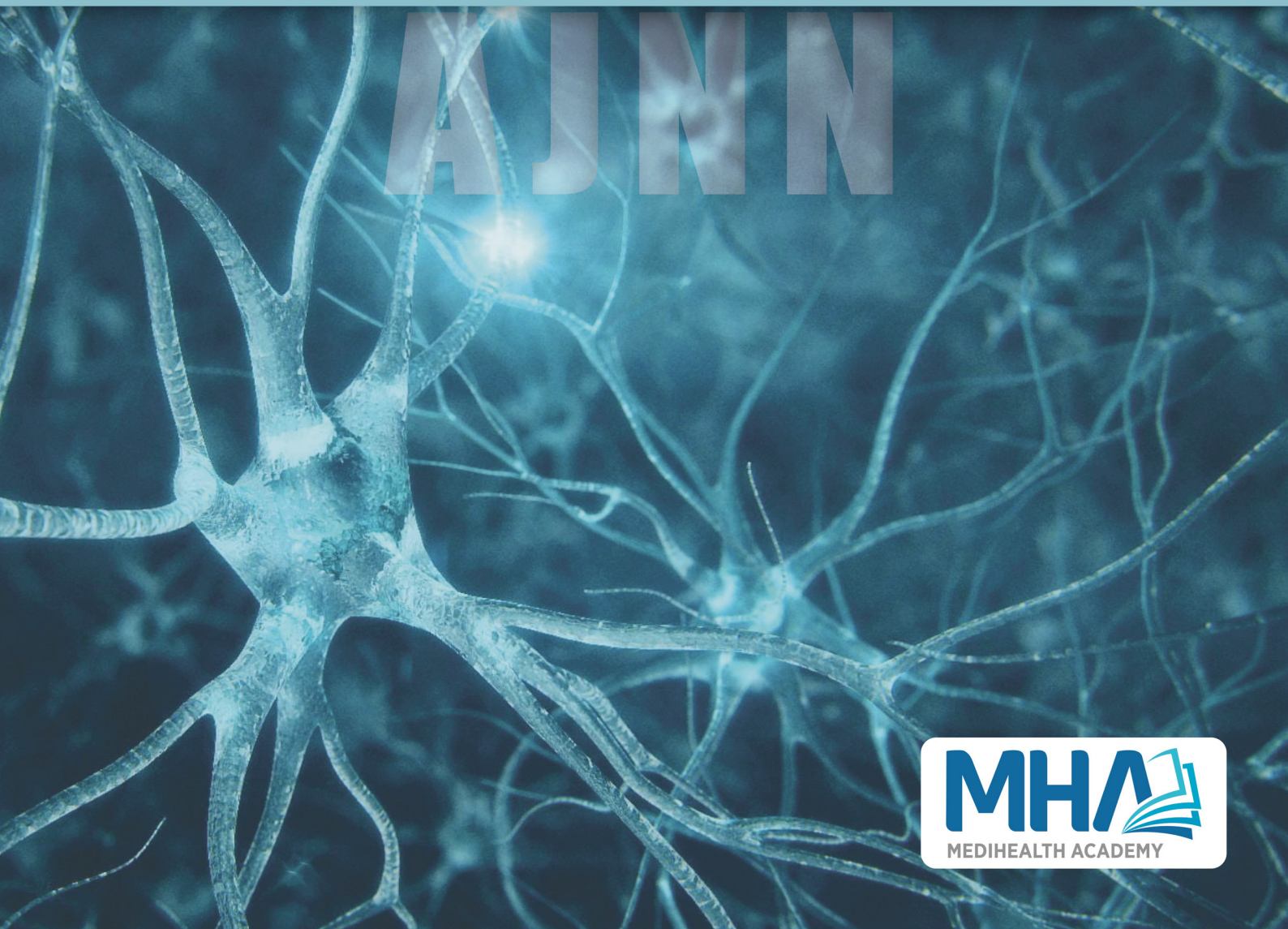

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Original Article

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Electroclinical aspects of diabetic neuropathy in the city of Ouagadougou

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ABSTRACT

Aims: Diabetic neuropathy (DN) is one of the most common microvascular complications of diabetes mellitus, often leading to severe sensorimotor disability. This study aimed to identify factors associated with the severity of electroneuromyographic (ENMG) involvement among diabetic patients followed in Ouagadougou, Burkina Faso.

Methods: We conducted a cross-sectional analytical study including 64 patients with clinically diagnosed DN who underwent electrodiagnostic (EDX) evaluation. Sociodemographic, clinical, and biological data were collected. Neuropathy severity was classified as mild/moderate or severe/very severe. Bivariate and multivariate logistic regression analyses were performed, with a significance level set at $p<0.05$.

Results: The mean age was 64.6±8 years, with a slight female predominance (53.1%). In bivariate analysis, severe EDX involvement was significantly associated with a diabetes duration ≥10 years [OR=6.55; 95% CI (1.95-21.9); p=0.002] and age ≥65 years [OR=3.33; 95% CI (1.15-9.61); p=0.024]. In multivariate analysis, only diabetes duration ≥10 years remained an independent predictor of severity [adjusted OR=5.32; 95% CI (1.52-18.5); p=0.009].

Conclusion: The severity of DN was mainly linked to long-standing diabetes, emphasizing the need for early screening and strict glycemic control.

Keywords: Diabetic neuropathy, electroneuromyography, severity, associated factors, Burkina Faso

INTRODUCTION

Diabetic neuropathy (DN) is the most common chronic complication of diabetes mellitus (DM) and a leading cause of peripheral neuropathy worldwide.[1] It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in individuals with diabetes after exclusion of other potential causes.[2]

DN affects approximately 1% to 7% of the general population, with higher prevalence in individuals over 50 years of age and a slight female predominance.[3] It complicates both type 1 diabetes (T1D) and type 2 diabetes (T2D).[3,4] Reported prevalence varies widely, ranging from 7% to 80% depending on study design and diagnostic criteria.[5] DN encompasses several clinical syndromes, including distal symmetric polyneuropathy (the most common form, accounting for approximately 75% of cases), autonomic neuropathy, cranial neuropathies, mononeuropathies, radiculoplexopathies, diabetic neuropathic cachexia, and treatment-induced neuropathy.[6,7]

The diagnosis of DN is based on both clinical and electrophysiological evidence.[2] Electroneuromyography (ENMG) is a key diagnostic tool for functional assessment, allowing confirmation of diagnosis and characterization of the underlying pathophysiological mechanism, including axonal, demyelinating, or mixed neuropathies.[3] Although not always required for the diagnosis of typical clinical forms, ENMG is essential for detecting subclinical or mild neuropathy.[8] In Burkina Faso, ENMG remains a relatively recent diagnostic modality, with limited availability and a small number of trained specialists.

The prevalence of DN increases with disease duration, reaching approximately 34% after 25 years of diabetes, as reported in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.[9] Similar findings have been reported in the EURODIAB prospective study.[10] In contrast, more than half of individuals with T2D develop signs and symptoms of

diabetic peripheral neuropathy during their lifetime.[11,12] The prevalence of painful DN is also high, reaching 20% to 30% even in newly diagnosed or early-stage T2D, as demonstrated in large contemporary cohorts such as ADDITION, GRADE, and SEARCH.[13,14]

Data on DN in sub-Saharan Africa remain limited. In Burkina Faso, published studies addressing its prevalence, risk factors, and electrophysiological characteristics are scarce. A local study conducted in 2018 reported a prevalence of DN of 80.7%.[15] In that cohort, distal polyneuropathy accounted for 81.8% of cases and autonomic neuropathy for 72.7%, with poor glycemic control observed in 38.8% of patients. However, the electrophysiological characterization of neuropathy was not addressed.[15]

We conducted this study to characterize the electrodiagnostic (EDX) profile of DN in our setting and to identify its associated clinical and metabolic determinants.

METHODS

This study was conducted with the approval of the Institutional Ethics Committee of Saint Camille Hospital in Ouagadougou (Date: 09.11.2023, Decision No: 2023-11-09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

This was a descriptive, cross-sectional, prospective study conducted over a nine-month period, from January 1, 2024, to September 30, 2024.

The study was conducted in two neurophysiology centers in Burkina Faso: the electro-neurophysiology unit of the Neurology Department at Saint Camille Hospital in Ouagadougou (HOSCO) and the neurophysiology unit at Agir Clinic.

The study population included all diabetic patients who underwent ENMG at both sites during the study period. Patients with a history of peripheral neuropathy due to causes other than diabetes (e.g., vitamin deficiency, alcoholism, or chemotherapy) were excluded. Patients who did not provide informed consent were also excluded.

Data collection was performed after approval from the Ethics and Research Committees of Saint Camille Hospital in Ouagadougou and Agir Clinic.

All included patients underwent a complete neurological examination and ENMG. Data were collected using a standardized case report form, including epidemiological, clinical (history and neurological examination findings), and electrophysiological data.

Clinical assessment tools included:

- A 128-Hz tuning fork, a brush, and a monofilament for assessment of sensory modalities (proprioceptive, tactile, nociceptive, and vibratory) and foot ulcer risk.
- A reflex hammer for assessment of deep tendon reflexes
- A blood pressure monitor and stethoscope for evaluation of cardiovascular autonomic neuropathy (CAN)
- Scales and a measuring tape for body-mass index (BMI) calculation and nutritional assessment
- The DN4 questionnaire for screening painful diabetic neuropathy (PDN)
- The Visual Analog Scale (VAS) for pain intensity assessment

ENMG was performed using Micromed and Natus devices.

ENMG procedures: Nerve conduction studies were performed using standard laboratory techniques with surface stimulation and recording.

Motor conduction studies focused bilaterally on four nerves: the deep peroneal, posterior tibial, median, and ulnar nerves.

Sensory conduction studies included the median and ulnar nerves in the upper limbs and the sural nerve in the lower limbs.

Needle electromyography was performed in selected cases.

Laboratory standards for ENMG interpretation were based on those described by Emmanuel Fournier.[16,17]

Abnormal nerve conduction parameters were defined according to standard neurophysiological guidelines (Fournier, 2018).[16] Lower-limb abnormalities included motor conduction velocity (MCV)<40 m/s, distal motor latency (DML)>4.5 ms, and sural sensory nerve action potential (SNAP) amplitude <5 µV.

The HOSCO reference values are presented in Table 1.

Table 1. HOSCO ENMG standards

Motor nerves	**Distal latency**	**Amplitude**	**Speed**	**F wavelatency**
Median	<3.7 ms	>6 mV	>48 m/s	≤32 ms
Ulnar	<3.2 ms	>6 mV	>50 m/s	≤32 ms
Radial	<3.4 ms	>6 mV	>50m/s	
Axillary (circumflex)	<4.5 ms	>4 to 6 mV		
Musculocutaneous UL			>50 m/s	
Fibular (CFN)	<5 ms	>3mV	>42 m/s	≤56 ms
Tibial (TN)	<5.5 ms	>5mV	>42 m/s	≤56 ms
Sensory nerves	**Amplitude**		**Speed**	
Median	15Uv		>45 m/s	
Ulnar	>10Uv		>45Mv	
Radial	>15Uv		>50m/s	
Musculocutaneous UL	10Uv		>50m/s	
Sural	>10uV		>40m/s	
Musculocutaneous LL	>10Uv		>40m/s	

UL: Upper limb, CFN: Common fibular nerve, TN: Tibial nerve, LL: Lower limb

The severity of ENMG abnormalities was classified according to a system adapted from Baba et al.[18] as follows:

- **Mild (early):** Isolated conduction abnormalities or mild amplitude reduction limited to lower-limb nerves.
- **Moderate:** Significant amplitude reduction and slowing of conduction velocities in the lower limbs without upper-limb involvement.
- **Severe:** Absence of recordable sensory or motor responses in at least two lower-limb nerves.
- **Very severe:** Diffuse axonal loss with absent responses extending to upper-limb nerves (median and ulnar).

Operational definitions:

- **Diabetes mellitus:** Fasting plasma glucose >7 mmol/L (126 mg/dl) on two separate measurements after at least 8 hours of fasting, or random plasma glucose >11.1 mmol/L (200 mg/dl) in the presence of typical symptoms (weight loss, polyuria, polydipsia).
- **Diabetic neuropathy (DN):** Clinical diagnosis based on history and neurological examination, defined by subjective symptoms (paresthesia, neuropathic pain) and/or objective signs (sensory loss, weakness, muscle atrophy, reduced or absent deep tendon reflexes, cranial nerve involvement).
- **Polyneuropathy:** Simultaneous involvement of multiple peripheral nerves.
- **Mononeuropathy:** Involvement of a single peripheral nerve.
- **Polyradiculoneuropathy:** Diffuse involvement of peripheral nerves and nerve roots.
- **Painful diabetic neuropathy (PDN):** DN4 score ≥4.
- **Cardiovascular autonomic neuropathy (CAN):** Orthostatic hypotension defined as a drop in systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg within 3 minutes of standing.
- **Digestive autonomic neuropathy (DAN):** Presence of gastroparesis and/or enteropathy (chronic constipation, diarrhea, or fecal incontinence).
- **Urogenital autonomic neuropathy (UGAN):** Bladder dysfunction, urinary retention, urgency, erectile dysfunction/retrograde ejaculation in male, or anorgasmia in female.
- **Sudomotor dysfunction:** Anhidrosis of the lower limbs and/or hyperhidrosis of the face and trunk.
- **Chronic renal failure (CRF):** Patients receiving treatment for renal failure or with estimated glomerular filtration rate (eGFR)<90 ml/min.
- **Dyslipidemia:** Defined by lipid-lowering therapy or LDL-c >1.8 mmol/L in high-risk patients, or >2.5 mmol/L in other diabetic patients.
- **Sedentary lifestyle:** Physical inactivity defined as <30 minutes of moderate-to-vigorous physical activity per day.
- **Diabetes control:** Assessed using glycated hemoglobin (HbA1c) and fasting plasma glucose levels.

RESULTS

Descriptive Study

A total of 64 patients with DN were recruited, representing 20% of all ENMG examinations performed during the study period. The mean age was 64.6±8 years (range: 45-81 years), with a slight female predominance (53.1%; female-to-male ratio: 1.13). Most patients resided in urban areas (84.4%) and were married (75.0%). Retired individuals represented the largest socio-professional group (40.6%). The sociodemographic characteristics of the study population are summarized in Table 2.

Table 2. Sociodemographic characteristics (n=64)

Characteristic	Number (n)	Percentage
Age (years) mean±SD: 64.6 years ±8 years (extremes: 45-81 years)		
(45-55)	2	3.1
(55-65)	32	50.0
(65-75)	22	34.4
(75-85)	8	12.5
Gender (gender ratio F/M=1.13)		
Female	34	53.1
Male	30	46.9
Place of residence		
Urban	54	84.4
Rural	10	15.6
Education		
Educated	44	68.7
Not in school	20	31.3
Marital status		
Married	48	75.0
Widowed	16	25
Professional activity		
Retired	26	40.6
Homemaker	18	28.1
Merchant	6	9.4
Civil servant	6	9.4
Private individual	6	9.4
Farmer	2	3.1

SD: Standard deviation, F/M: Female/male

Type 2 DM (T2D) accounted for 96.9% (n=62) of cases. The mean duration of diabetes was 11.3±7.8 years, and 56.2% of patients had a disease duration between 5 and 15 years. All patients were on antidiabetic treatment, with 65.6% managed without insulin. Glycemic control was poor, with 87.5% showing elevated fasting blood glucose levels and 93.8% having HbA1c >7%. Diabetes-related characteristics and glycemic control parameters are presented in Table 3.

Table 3. Diabetes characteristics and glycemic control (n=64)

Characteristic	Number (n)	Percentage
Type of DM		
Type 2 (T2D)	62	96.9
Type 1 (T1D)	2	3.1
Duration of diabetes mellitus (years) average SD: 11.3 years ±7.8 years (extremes: 0.08-39)		
<5	10	15.6
(5-10)	18	28.1
(10-15)	18	28.1
(15-20)	6	9.4
≥20	12	18.8
Relationship to treatment (insulin)		
Non-insulin dependent	42	65.6
Insulin-dependent	12	18.8
Insulin-requiring	10	15.6
Glycemic control (short term)		
Fasting blood glucose >6.1 mmol/L	56	87.5
Fasting blood glucose <6.1 mmol/L	8	12.5
Glycemic control (long term)		
HbA1c >7%	60	93.8
HbA1c <7%	4	6.2

DM: Diyabetes mellitus, SD: Standard deviation, HbA1c: Hemoglobin A1c

Hypertension was the most frequent cardiovascular risk factor (81.3%), followed by sedentary lifestyle (56.3%). The most common chronic complications were heart disease (28.1%) and diabetic nephropathy (12.5%).

Cardiovascular risk factors, diabetes-related complications, and associated comorbidities are detailed in Table 4.

Table 4. Cardiovascular risk factors, diabetes complications, and associated comorbidities (n=64)

Characteristic	Number (n)	Percentage
Associated cardiovascular risk factors		
HBP	52	81.3
Sedentary lifestyle	36	56.3
Dyslipidemia	24	37.5
Obesity	20	31.3
Alcohol	18	28.1
Tobacco	4	6.2
Chronic complications of diabetes		
Heart disease	18	28.1
Diabetic nephropathy	8	12.5
Diabetic retinopathy	6	9.4
Diabetic arteriopathy	4	6.3
Ischemic stroke	2	3.1
Comorbidities associated with neuropathy		
Lumbosciatica	6	9.4
Asthma	2	3.1
Severe weight loss	2	3.1
Polyarthralgia	2	3.1

HBP: High blood pressure

All patients presented at least one sensory symptom. Pain was the most frequent complaint (87.5%), leading to a diagnosis of painful DN (DN4 ≥4) in 84.4% of cases. Autonomic dysfunction was observed in 87.5% of patients, predominantly erectile dysfunction (32.1%). Motor impairment was present in 71.9% of patients. Overall, clinical evaluation showed painful diabetic polyneuropathy in 84.4%, autonomic neuropathy in 78.1%, and generalized peripheral neuropathy in 87.5%.

The clinical manifestations and different forms of DN observed in the study population are presented in Table 5.

Table 5. Clinical manifestations and types of neuropathy diabetic (n=64)

Characteristic	Number (n)	Percentage
Subjective sensory signs (n=64)		
Total pain	56	87.5
Burning pain	44	68.8
Numbness	38	59.4
Tingling	34	53.1
Itching	14	21.9
Neuropathic pain (DN4 ≥4)		
Diagnosed	54	84.4
Objective sensory signs (n=64)		
Hypoesthesia to touch	12	18.8
Hyperesthesia to touch	8	12.5
Motor signs (n=46: 71.9% of N=64)		
Motor deficit LL	16	(34.8%)
Motor deficit of one LL	14	(30.4%)
Motor deficit of one UL	7	15.2
Motor deficit of both UL	9	19.6
Neurovegetative signs (n=56: 87.5% of N=64)		
Erectile dysfunction	18	(32.1%)
Urinary disorders	14	(25.0%)
Sweating disorder	12	(21.4%)
Gastrointestinal disorders	8	(14.3%)
Clinical types of neuropathy (n=64)		
Painful diabetic polyneuropathy	54	84.4
Peripheral neuropathy (total)	56	87.5
Autonomic neuropathy (total)	50	78.1
Urogenital neuropathy	24	37.5
Cardiac autonomic neuropathy	14	21.9
Radiculopathy	4	6.2
Multiple mononeuropathy	2	3.1

DN4: Douleur neuropathique en 4 questions, LL: Lower limb

ENMG was abnormal in 87.5% (n=56) of patients. Quantitative analysis revealed prolonged distal motor latencies and reduced motor and sensory conduction velocities, predominantly in the lower limbs (mean tibial motor conduction velocity: 37.5±10.6 m/s; mean sural sensory amplitude: 4.0±4.7 µV).

Quantitative ENMG findings are summarized in Table 6.

Qualitative analysis showed that 92.8% of abnormal ENMGs were consistent with axonal damage. Chronic length-dependent sensory-motor axonal polyneuropathy was the most frequent electrophysiological pattern (75.0%). Nearly 50% of patients presented with severe or very severe involvement (50.0% of pathological ENMGs).

Table 6. Average quantitative characteristics of ENMG in patients

Nerve		n	Mean/SD	Min	Max	Unit
Median nerve (upper limb)	MCV	56	49.8±7.7	34	67.6	m/s
	DML		8.1±5.3	2.3	15.7	ms
	F wave latency		46.9±9.3	27.5	68	ms
	Motor amplitude		6.1±2.5	1.0	16	mV
	SCV		49.9±11.5	10.8	75.0	m/s
	Sensory amplitude		9.1±13.1	2.0	24	µV
Ulnar nerve (upper limb)	MCV	50	51.8±9.5	27.0	70.0	m/s
	DML		9.8±4.2	3.3	20.2	ms
	F wave latency		48.4±9.3	26.2	68.0	ms
	Motor amplitude		5.5±2.7	0.6	11.7	mV
	SCV		52.3±14.7	22.0	76.7	m/s
	Sensory amplitude		10.1±13.9	1.0	24.0	µV
Fibular nerve (lower limb)	MCV	60	39.8±8.7	17.0	61.7	m/s
	DML		8.7±5.2	1.2	20.4	ms
	F wave latency		48.7±9.9	32.0	83.0	ms
	Motor amplitude		2.7±2.6	0.1	13.3	mV
Tibial nerve (lower limb)	MCV	64	37.5±10.6	15.5	64.0	m/s
	DML		9.1± 5.3	1.0	20.8	ms
	F wave latency		48.7±9.0	28.9	66.0	ms
	Motor amplitude		2.8±2.4	0.1	11.7	mV
Sural nerve (lower limb)	SCV	64	45.8±12.8	20.5	68.8	m/s
	Sensory amplitude		4.0±4.7	0.1	19.0	µV

ENMG: Electroneuromyography, SD: Standard deviation, Min: Minimum, Max: Maximum, MCV: Motor conduction velocity, DML: Distal motor latency, SCV: Sensory conduction velocity

The qualitative ENMG findings and severity classification are presented in Table 7.

Table 7. Qualitative characteristics and classification of ENMG findings (n=56 pathological ENMG)

Characteristic	Number (n)	Percentage
ENMG assessment (n=64)		
Pathological ENMG	56	87.5
Normal ENMG	8	12.5
Dominant pathophysiological type (n=56)		
Axonal damage (axonopathy)	52	92.8
Demyelinating disorder (myelinopathy)	4	7.2
Electrophysiological profile (n=56)		
Sensory-motor axonal polyneuropathy (L-D)	42	75.0
Sensory axonal polyneuropathy (L-R)	6	10.7
Chronic demyelinating polyneuropathy	4	7.1
Other (mono/multifocal, radiculoplexopathy)	4	7.2
Severity of ENMG findings (n=56)		
Early	2	(3.6%)
Moderate	26	(46.4%)
Severe	18	(32.1%)
Very severe	10	(17.9%)

ENMG: Electroneuromyography

Analytical Study

In bivariate analysis, severe ENMG involvement was significantly associated with diabetes duration ≥10 years (OR=6.55; 95% CI: 1.95-21.9; p=0.002), age ≥65 years (OR=3.33; 95% CI: 1.15-9.61; p=0.024), motor impairment (OR=2.52; 95% CI: 0.89-7.09; p=0.078), and diabetic nephropathy (OR=3.50; 95% CI: 0.67-18.2; p=0.131). Factors associated with severe ENMG involvement in bivariate analysis are presented in Table 8.

In multivariate analysis, only diabetes duration ≥10 years remained an independent predictor of severe ENMG involvement (adjusted OR=5.32; 95% CI: 1.52-18.5; p=0.009).

After adjustment, age and motor impairment were no longer significant, suggesting that they act as proxies of diabetes duration rather than independent risk factors (Table 9).

The results of the multivariate logistic regression analysis are presented in Table 9.

DISCUSSION

Our cohort of 64 patients, representing 20% of all ENMG examinations performed at the two study sites during the study period, consisted predominantly of older adults (mean age: 64.6 years) and patients with T2D (96.9%). This distribution reflects the ongoing epidemiological transition and the rising burden of T2D in aging populations in sub-Saharan Africa.[19,20] The slight female predominance (53.1%) and urban residence (84.4%) are consistent with reports from West Africa and likely reflect referral patterns to specialized neurophysiology services concentrated in urban centers.[21,22] The predominance of retired individuals (40.6%) suggests that DN primarily affects patients with long disease duration and reduced occupational activity.

A major finding of this study is the very poor glycemic control observed in our cohort, with 93.8% of patients presenting HbA1c levels >7% and 87.5% exhibiting elevated fasting blood glucose. These proportions are considerably higher than those reported in high-income countries, where glycemic targets are achieved in approximately 25-50% of patients.[24,25] Our findings are consistent with data from sub-Saharan Africa, where chronic hyperglycemia remains a major determinant of diabetic peripheral neuropathy.[26] This sustained metabolic imbalance likely represents a key contributor to microvascular complications, including diabetic neuropathy, and may reflect limited access to optimal diabetes care and structured follow-up.[20]

Hypertension (81.3%), sedentary lifestyle (56.3%), and dyslipidemia (37.5%) indicate a high burden of cardiometabolic comorbidities. These factors are known to synergistically contribute to small fiber dysfunction and axonal degeneration.[27] Their combined impact in African populations warrants further investigation.

Pain was the most frequent clinical manifestation, reported in 87.5% of patients, and painful DN (DN4 ≥4) was diagnosed in 84.4%. This high prevalence likely reflects referral bias. In Burkina Faso, access to ENMG remains limited due to resource constraints and shortage of trained personnel. Consequently, patients referred for EDX evaluation are often those with severe symptoms or refractory neuropathic pain. This selection bias may explain the high proportion of severe and very severe electrophysiological abnormalities (~50%) observed in our cohort and limits extrapolation to the general

Table 8. Factors associated with severe ENMG involvement

Factors	Severe/very severe damage (n=28)	Mild/moderate damage (n=28)	OR (95% CI)	p-value
Duration of diabetes				
≥10 years (vs. <10 years)	24 (85.7%)	13 (46.4%)	6.55 (1.95-21.9)	0.002
Age				
≥65 years (vs. <65 years)	18 (64.3%)	10 (35.7%)	3.33 (1.15-9.61)	0.024
Diabetic nephropathy				
Yes (vs no)	6 (21.4%)	2 (7.1%)	3.50 (0.67-18.2)	0.131
Clinical motor signs				
Yes (vs. no)	20 (71.4%)	14 (50.0%)	2.52 (0.89-7.09)	0.078
Dyslipidemia				
Yes (vs. no)	14 (50.0%)	10 (35.7%)	1.81 (0.64-5.10)	0.266
Hypertension				
Yes (vs no)	24 (85.7%)	21 (75.0%)	1.97 (0.52-7.49)	0.317
Gender				
Male (vs female)	16 (57.1%)	14 (50.0%)	1.34 (0.46-3.91)	0.587
Heart disease				
Yes (vs no)	8 (28.6%)	10 (35.7%)	0.74 (0.24-2.25)	0.601
HbA1c				
≥7% (vs. <7%)	27 (96.4%)	27 (96.4%)	N/A	1.000

ENMG: Electroneuromyography, OR: Odds ratio, CI: Confidence interval, HbA1c: Hemoglobin A1c

Table 9. Multivariate analysis: independent factors for severe ENMG involvement

Independent variables	Reference category	OR	95% CI	p
Duration of diabetes (≥10 years)	<10 years	5.32	1.52-18.5	0.009
Age (≥65 years)	<65 years	1.28	0.33-5.00	0.713
Clinical motor signs	No	1.90	0.51-7.05	0.336
Diabetic nephropathy	No	2.15	0.38-12.1	0.387

ENMG: Electroneuromyography, OR: Odds ratio, CI: Confidence interval

diabetic population. As a result, early and asymptomatic neuropathy is likely underdiagnosed.

Autonomic dysfunction was observed in 87.5% of patients, predominantly erectile dysfunction (32.1%), while motor impairment was present in 71.9%. The coexistence of sensory, motor, and autonomic involvement suggests advanced and diffuse peripheral nerve damage. Similar patterns have been reported in West African cohorts, particularly in Senegal and Mali among patients undergoing ENMG evaluation.[28,29]

EDX studies revealed abnormal findings in 87.5% of patients, with axonal neuropathy accounting for 92.8% of cases. The predominant pattern was chronic length-dependent sensory-motor axonal polyneuropathy (75.0%). This predominance of axonal damage is consistent with experimental and clinical evidence showing that chronic hyperglycemia induces oxidative stress, mitochondrial dysfunction, and accumulation of advanced glycation end products, ultimately leading to axonal degeneration.[30,31]

Approximately half of the patients (50.0%) presented with severe or very severe electrophysiological impairment, a proportion higher than that reported in screening-based cohorts, where milder forms predominate. This finding further supports the hypothesis of delayed diagnosis and late referral in our setting.

Diabetes duration ≥10 years was the only independent predictor of severe ENMG abnormalities (adjusted OR=5.32; 95% CI: 1.52-18.5; p=0.009). This is consistent with large international studies, including EURODIAB and DCCT/EDIC, which identify disease duration as the most consistent risk factor for diabetic neuropathy, independent of glycemic control and other covariates.[32,33] In the study by Tesfaye et al.,[33] the risk of neuropathy increased progressively after 10 years of diabetes, reaching more than a fourfold increase in long-term disease.

Although age ≥65 years was associated with severity in univariate analysis, this association lost significance after adjustment for diabetes duration, suggesting that age mainly reflects cumulative metabolic exposure rather than an independent causal factor. Similar observations have been reported in several African and Asian cohorts.[34-36]

Motor impairment showed a non-significant trend toward association with severe neuropathy (p=0.078), consistent with electrophysiological evidence indicating that motor involvement may become more prominent with increasing neuropathy severity.[37,38] This underscores the importance of early screening before irreversible nerve damage occurs.

Although diabetic nephropathy and dyslipidemia are recognized comorbidities, no significant association was observed in this study. However, previous studies from Kenya and Egypt have reported a moderate association between renal dysfunction and severe neuropathy, possibly reflecting shared microvascular mechanisms.[39,40] This discrepancy may be explained by sample size limitations, cross-sectional design, and heterogeneity in diagnostic criteria.

Overall, our findings are consistent with regional data from sub-Saharan Africa, where studies conducted between 2021 and 2024 report high rates of severe neuropathy and consistently identify disease duration as the main determinant.[41,42] These results suggest that, despite regional

variability, the underlying pathophysiological mechanisms-oxidative stress, microangiopathy, and chronic metabolic injury-are universal but amplified in low-resource settings due to delayed diagnosis and suboptimal glycemic control.[40]

Limitations

This study provides combined clinical and electrophysiological data in a resource-limited African setting. Strengths include prospective data collection and standardized clinical and neurophysiological assessment. However, limitations include the relatively small sample size, two-center design, and absence of longitudinal follow-up, which limit generalizability. Additionally, the lack of quality-of-life assessment and quantitative pain evaluation represents another limitation.

CONCLUSION

This study identified the main determinants of DN severity in our setting. Diabetes duration emerged as the strongest independent predictor of severe EDX impairment, confirming its central role in the progression of diabetic peripheral nerve damage.

Although advanced age and the presence of clinical motor signs were associated with severity in bivariate analysis, they did not retain statistical significance after multivariate adjustment, suggesting that they mainly reflect disease chronicity rather than independent pathogenic factors.

These findings are consistent with recent international and African literature and reinforce the importance of early detection, regular neurophysiological assessment, and strict glycemic control to prevent progression to severe forms and reduce functional disability.

Further longitudinal studies with larger sample sizes are required to confirm these associations and to explore additional metabolic and therapeutic determinants of DN severity.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Institutional Ethics Committee of Saint Camille Hospital in Ouagadougou (Date: 09.11.2023, Decision No: 2023-11-09).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Conceptualization: AZ, AAD, AM; Study Design: AZ, AAD; Methodology: AZ, AAD, MRK, AM; Investigation: AZ; Data Collection: AZ, AAD, MRK; Data Analysis and Interpretation: AZ; Literature Review: AZ; Manuscript Drafting: AZ; Clinical: AAD; Electrophysiological Investigation: AAD; Interpretation of Findings: AAD, MRK, AM; Critical Review of the Manuscript: AAD, MRK, AM; Clinical Investigation: MRK; Study Supervision: AM.

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Original Article

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Assessment of clinical and electrophysiological findings in axillary nerve injury

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ABSTRACT

Aims: This study investigated the association between clinical features and neurophysiological findings in patients with axillary nerve injury (ANI).

Methods: Patients with isolated ANI were included in the study. Muscle strength was evaluated using the Medical Research Council (MRC) scale. Axillary nerve compound muscle action potential (CMAP) amplitude and latency, as well as the presence of positive sharp waves (PSWs), fibrillation potentials, and motor unit action potentials (MUAPs) in the deltoid muscle, were assessed.

Results: Eleven patients with ANI were included in the study (7 male and 4 female). The causes of ANI were humeral fracture in two patients and shoulder dislocation in four patients. The remaining five patients had blunt trauma without any associated fracture or dislocation. A positive correlation was observed between axillary nerve CMAP amplitude and the deltoid muscle MRC score (p=0.016, r=0.700). A negative correlation was found between axillary nerve CMAP latency and the deltoid muscle MRC score (p=0.048, r=-0.670). All patients demonstrated PSWs, fibrillation potentials, or MUAP abnormalities in the deltoid muscle.

Conclusion: This study demonstrated an association between axillary nerve CMAP latency and amplitude and the deltoid muscle MRC score in patients with ANI. These results suggest that axillary nerve CMAP latency and amplitude are valuable neurophysiological measures for the diagnosis and follow-up of ANI. It should also be noted that ANI may occur even in the absence of a fracture or dislocation.

Keywords: Axillary neuropathy, electromyography, nerve conduction study

INTRODUCTION

Axillary nerve injury (ANI) may occur in isolation, most often as a result of shoulder fractures or dislocations.[1-3] It typically presents with weakness of shoulder abduction and sensory loss over the lateral aspect of the shoulder corresponding to the axillary nerve distribution.[1-5] Severe weakness of shoulder abduction can interfere with daily activities, so timely and accurate diagnosis is essential. Both clinical assessment and neurophysiological testing have an important role in diagnosis.[3-7]

On nerve conduction studies, abnormalities in axillary nerve compound muscle action potential (CMAP) latency or amplitude are significant diagnostic findings.[2,4,6] In addition, the presence of positive sharp waves (PSWs), fibrillation potentials, or neurogenic motor unit action potentials (MUAPs) in the deltoid or teres minor muscles provides further electrophysiological evidence of axillary nerve involvement.[5-7] In general, a markedly reduced CMAP amplitude or the absence of MUAPs on neurophysiological testing indicates a poor prognosis, whereas the opposite findings are associated with a favorable outcome.[8-12]

This study aimed to investigate the relationship between neurophysiological test results and clinical findings in isolated ANI in order to identify electrophysiological parameters that may reflect the underlying mechanism and predict clinical outcome.

METHODS

Ethics

This study was conducted with the approval of the Adana City Training and Researches Hospital Institutional Review

Board (Date: 25.09.2025, Decision No: 747). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Patients with isolated ANI who were evaluated at the Clinical Neurophysiology Laboratory of Adana City Training and Research Hospital, University of Health Sciences, between September 2019 and September 2025 were included in the study. ANI was diagnosed in individuals presenting with deltoid muscle weakness and/or sensory abnormalities in the shoulder region corresponding to the sensory distribution of the axillary nerve, together with the presence of PSWs or fibrillation potentials, or MUAPs with neurogenic features in the deltoid muscle.[1,2,4,6] Muscle strength was assessed with the Medical Research Council (MRC) scale. Patients with neurodegenerative disorders or with clinical, neurophysiological, or imaging findings suggestive of brachial plexopathy or cervical radiculopathy were excluded.

Neurophysiological Tests

Nerve conduction studies and needle electromyography (EMG) were performed using a Cadwell Sierra Summit EMG system (Cadwell Laboratories, Kennewick, WA, USA). Neurophysiological assessments were conducted only when the limb temperature was above 32°C; otherwise, cold extremities were warmed prior to testing. For motor and sensory nerve conduction studies, the high- and low-frequency filters were set at 20 Hz-10 kHz and 20 Hz-2 kHz, respectively. Standard techniques were applied for median, ulnar, medial antebrachial cutaneous, lateral antebrachial cutaneous, and radial nerve conduction studies, with surface electrodes used for recording.[12,13]

The axillary nerve conduction study was performed using standard methodology.[14] Stimulation was delivered at Erb's point with surface electrodes, and recordings were obtained from the deltoid muscle using a concentric needle electrode (length: 50 mm, diameter: 0.46 mm; Bionen Medical Devices, Florence, Italy; or 26 G, Natus, Galway, Ireland). The distance between the stimulation and recording sites was measured with a caliper. The upper limit of normal for latency, depending on this distance, ranged from 5.1 to 5.3 ms.[14] The concentric needle electrode was secured with adhesive tape. Following Erb's point stimulation, the position of the electrode was checked during arm movement to ensure that it had not shifted. Three to five CMAPs were recorded. If the CMAPs varied, the test was repeated, and a consistent CMAP was accepted. In cases where no CMAP could be obtained, latency measurements were not included in the analysis, whereas amplitude values were included.

Needle EMG was performed visually using a concentric needle electrode (length: 50 mm, diameter: 0.46 mm; Bionen Medical Devices, Florence, Italy; or 26 G, Natus, Galway, Ireland). The filter settings were 10 Hz-10 kHz. In the clinical neurophysiology laboratory, the deltoid, biceps brachii, triceps, abductor pollicis brevis, and first dorsal interosseous muscles were routinely examined. When tolerated, the cervical paraspinal muscles were also evaluated. The presence of PSWs and fibrillation potentials at rest was carefully noted. MUAPs with amplitudes >3 mV and durations >15 ms were considered neurogenic.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages, whereas numerical variables were presented as mean±standard deviation and range. Correlations between variables were assessed using Spearman's rank correlation test. The strength of the correlation was interpreted according to the correlation coefficient (r) as follows: $r \geq 0.9$ or $r \leq -0.9$, very strong; $0.7 \leq r < 0.9$ or $-0.9 < r \leq -0.7$, strong; $0.5 \leq r < 0.7$ or $-0.7 < r \leq -0.5$, moderate; $0.3 < r \leq 0.5$ or $-0.5 \leq r < -0.3$, weak; and $r < 0.3$ or $r > -0.3$, negligible (15). A p-value <0.05 was considered statistically significant.[15]

RESULTS

The study included 11 patients (seven male, four female) with a mean age of 48.9±17.1 years (range, 24-76). One patient had diabetes mellitus, while the remaining patients had no chronic illnesses. Among the eleven patients with ANI, two injuries were due to humeral fracture and four were related to shoulder dislocation, whereas the remaining five cases were attributed to blunt trauma without any accompanying fracture or dislocation. The mean duration of symptoms was 131.6±129.0 days (range, 38-365). Five patients had right-sided ANI. The mean MRC grade of the deltoid muscle was 1.8±1.3 (range, 0-4). The number of patients with MRC scores of 0, 1, 2, 3, and 4 was 3, 0, 5, 2, and 1, respectively. Five patients had sensory abnormalities in the shoulder area innervated by the axillary nerve.

Axillary nerve CMAPs could not be obtained in two patients. The mean axillary nerve CMAP latency was 11.6±7.7 ms, and the mean amplitude was 0.9±1.1 mV. The number of patients with abnormal neurophysiological findings is summarized in Table 1. Table 2 presents the correlations between clinical and neurophysiological findings. Figure illustrates the positive correlation between the deltoid muscle MRC grade and the axillary nerve CMAP amplitude.

Table 1. The number of patients with abnormal neurophysiological findings

Neurophysiological feature	Number of patients (%)
Abnormal latency*	8 (89)
Absence of axillary nerve CMAP	2 (18)
PSW and/or fibrillation potentials	8 (73)
Neurogenic or absent MUAP	3 (27)
PSW-fibrillation potentials and/or Neurogenic MUAP	11 (100)

In two patients, latency could not be measured as no axillary nerve CMAP was obtained. CMAP: Compound muscle action potential, PSW: Positive sharp wave, MUAP: Motor unit action potential

Table 2. The correlations between clinical and neurophysiological findings

Clinical feature	Latency (ms)	Amplitude (mV)
Age (years)	p=0.949, r=0.025	p=0.245, r=-0.383
Symptom duration (days)	p=0.258, r=-0.422	p=0.352, r=0.311
MRC score of the deltoid muscle	p=0.048, r=-0.670	p=0.016, r=0.700

MRC: Medical Research Council

DISCUSSION

This study examined the association between clinical features and neurophysiological findings, including axillary nerve CMAP latency and amplitude, in patients with ANI.

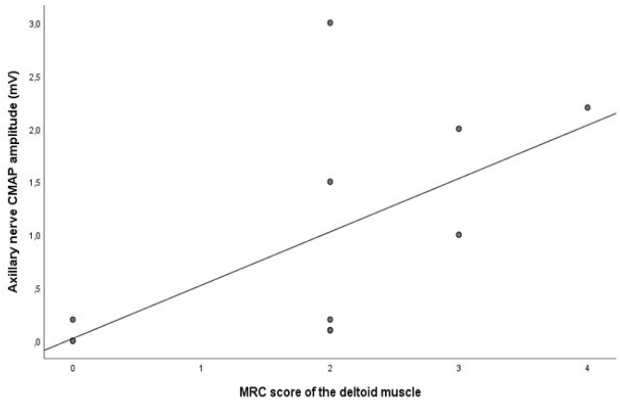

Figure. Correlation between deltoid MRC grade and axillary nerve CMAP amplitude
MRC: Medical Research Council, CMAP: Compound muscle action potential

A significant link was observed between CMAP parameters and muscle strength grades.

A reduced CMAP amplitude is a key finding, as it may indicate axonal degeneration.[8,9,11,12] Previous reports have shown that axonal degeneration is often associated with a poor prognosis. In the present study, a positive correlation between the deltoid muscle MRC score and axillary nerve CMAP amplitude was both expected and significant. Thus, a low axillary nerve CMAP amplitude appears to be a meaningful marker of axonal degeneration and may serve as an important clue for predicting clinical outcome.[5-7,11,12]

Unlike CMAP amplitude, conduction block and slowed nerve conduction velocities may suggest demyelination, which can occur either alone or together with axonal injury.[10,12] In contrast to axonal degeneration, demyelination is generally associated with a more favorable prognosis in nerve injuries.[8-12] In this study, a borderline negative correlation was observed between axillary nerve CMAP latency and the deltoid muscle MRC score. This finding implies that axillary nerve latency may be partly related to muscle strength, although CMAP amplitude seems to have greater clinical relevance in ANI. Nonetheless, the results indicate that axillary nerve CMAP latency, together with CMAP amplitude, can be useful for monitoring the course of ANI.

Isolated ANI most often develops after trauma. Shoulder dislocations and shoulder or humeral fractures account for a considerable proportion of these injuries.[1-3] In the present study, most patients had either shoulder or humeral fractures or shoulder dislocations. However, the occurrence of isolated ANI in some patients without a history of fracture or dislocation is noteworthy, as it indicates that ANI can develop even in the absence of radiologically or clinically evident bone injury.[16,17] The lack of a detectable fracture or dislocation in the shoulder or arm region does not exclude the possibility of ANI. Therefore, ANI should be considered in shoulder trauma accompanied by weakness of shoulder abduction to ensure appropriate evaluation and management.[16,17]

Limitations

Apart from the retrospective design, this study has several limitations. The sample size was relatively small. In addition, the teres minor muscle was not examined with needle EMG, and an axillary nerve sensory conduction study was not performed. It should be noted, however, that sensory conduction studies in the shoulder region are technically challenging. Future studies involving a larger number of patients with ANI, and incorporating needle EMG of the teres minor muscle as well as axillary sensory nerve conduction studies, may provide a clearer understanding of the underlying mechanisms of ANI and contribute to improved management strategies. Conduction block not be assessed because stimulation was not performed at two different sites, which may be considered a limitation of the study. Despite these limitations, the study is valuable in that axillary nerve conduction was assessed using the concentric needle electrode technique, which may have allowed for the identification of meaningful associations between clinical and neurophysiological findings.

CONCLUSION

The results indicate that axillary nerve CMAP amplitude and latency may be associated with the deltoid muscle MRC score. These findings suggest that both indicators may have potential utility as neurophysiological measures in the assessment of ANI. Furthermore, the observation that isolated ANI occurred in all patients following trauma involving blunt trauma, shoulder or humeral fractures, or dislocations supports the view that trauma is a major contributing factor, and also highlights that such nerve involvement may develop even in the absence of overt fracture or dislocation.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Adana City Training and Researches Hospital Institutional Review Board (Date: 25.09.2025, Decision No: 747).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: ŞB, HF; Design: ŞB, HF; Control: ŞB, HF; Data Collection and/or Processing: ŞB, HF; Analysis and/or Interpretation: ŞB, HF; Literature Review: HF; Article Writing: ŞB; Critical Review: ŞB, HF.

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Original Article

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Effect of probiotic supplementation during early enteral nutrition on clinical outcomes in severe traumatic brain injury: a randomized, placebo-controlled trial with blinded outcome assessment

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ABSTRACT

Aims: Severe traumatic brain injury (TBI) is associated with substantial morbidity and mortality. Post-traumatic gut dysbiosis may contribute to adverse outcomes, and probiotic supplementation has been proposed as a therapeutic strategy; however, clinical evidence remains inconclusive. This study aimed to evaluate the effect of probiotic supplementation during early enteral nutrition on clinical outcomes in adults with severe TBI.

Methods: This prospective, randomized, placebo-controlled trial with blinded outcome assessment enrolled 54 adults with severe TBI. Participants on an early enteral feeding protocol were randomized to receive either probiotic supplementation (n=27) or a placebo (n=27). The primary outcome was functional status at three months, assessed using the Glasgow Outcome Score Extended (GOSE), or death before assessment. Secondary outcomes included 30-day mortality, complication rates, and intensive care unit (ICU) length of stay.

Results: The mean age was 37±14.9 years, with a male predominance (8:1). Favorable three-month outcomes occurred in 40.7% of the probiotic group compared with 25.9% of controls (p=0.248). The 30-day mortality rate was numerically higher in the probiotic group, though this difference did not achieve statistical significance (22.2% vs. 11.1%; p=0.273). Overall complication rates (51.9% vs. 66.7%; p=0.268), and mean ICU stay (9±3.25 vs. 9±4.14 days; p=0.401) were similar.

Conclusion: Probiotic supplementation during early enteral nutrition demonstrated no statistically significant improvement in three-month functional outcomes or ICU stay in this trial; the primary findings regarding efficacy remain inconclusive, though the observed numerical differences warrant exploration in larger cohorts.

Keywords: Traumatic brain injury, early enteral nutrition, probiotics, mortality, Glasgow Outcome Score

INTRODUCTION

Traumatic brain injury (TBI) remains a global health crisis, serving as the leading cause of mortality and lifelong morbidity among individuals aged 18-45 years.[1] Within this spectrum, severe TBI-defined by a Glasgow Coma Scale (GCS) score of 3-8-presents a formidable clinical challenge; despite significant advancements in neurosurgical techniques and critical care, short-term and definitive functional recovery for these patients remain frequently poor.[2,3]

Central to the management of severe TBI is the aggressive optimization of nutritional support, as the injury triggers a profound hypermetabolic and catabolic response that rapidly depletes protein and energy reserves.[4] Early enteral feeding (EEF), typically initiated within 24 to 48 hours of injury, is now recognized as a critical pillar of neuro-intensive care.[5] By delivering nutrients directly to the gastrointestinal tract, EEF helps preserve the structural integrity of the gut mucosa, prevents the "starvation effect" that exacerbates systemic inflammation, and is associated with reduced rates of nosocomial infections and improved survival.[5] Despite these clear benefits, achieving full nutritional targets remains a significant clinical hurdle, as post-traumatic gastrointestinal dysfunction often leads to feeding intolerance, thereby necessitating adjunctive strategies to ensure the success of early nutritional interventions.[6]

In the pursuit of novel therapeutic targets, recent research has pivoted toward the impact of secondary systemic injuries. Emerging evidence underscores the importance of the microbiota-gut-brain axis, a bidirectional communication pathway through which post-traumatic gut dysbiosis can exacerbate primary neurological injury.[7] Probiotics, defined as live non-pathogenic microorganisms that confer systemic health benefits, have demonstrated the potential to mitigate this dysbiosis across various clinical settings.[8] By reinforcing gut barrier integrity and improving motility, probiotic supplementation is theorized to prevent secondary infectious complications, reduce the systemic translocation of gut-derived neurotoxins, and ultimately improve clinical and functional recovery.[9,10]

However, the current literature regarding the efficacy of probiotics in neurotrauma is characterized by significant heterogeneity. While some investigations report a potential reduction in mortality and systemic inflammation, others indicate no significant effect on survival or long-term disability.[11,12] This lack of consensus, compounded by a marked paucity of prospective data from Sub-Saharan Africa, highlights a critical knowledge gap.

This study aimed to address this deficit by rigorously evaluating the impact of an EEF protocol combined with multispecies probiotic supplementation on major clinical and functional outcomes in adult patients with severe traumatic brain injury. Specifically, we assessed mortality rates and short-term (3-month) recovery metrics associated with probiotic supplementation during an EEF protocol within a Nigerian tertiary care setting, providing essential data on the efficacy of this intervention in a resource-constrained environment.

METHODS

Ethics

This study was approved by the Ethics Research Committee of the University Teaching Hospital in Ilorin (Date: 10.05.2021, Decision No: ERC PAN/2021/10/020). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

Crucially, all primary and secondary outcome measures were strictly defined a priori before patient enrollment commenced, and no protocol adjustments, criteria modifications, or endpoint revisions were made at any stage during or after the study timeframe.

Informed consent was also obtained from relatives or caregivers for all participants.

Study Design and Population

This study was a prospective, randomized, placebo-controlled trial with blinded outcome assessment conducted at the Division of Neurosurgery, University of Ilorin Teaching Hospital, Kwara State, Nigeria over a 12-month period between January 1, 2023 and December 31, 2023. The study population included all adult patients (aged 18 years and above) presenting to the accident and emergency unit with severe TBI (GCS 3-8) within 24 hours of injury. Exclusion criteria included polytrauma patients (defined as patients sustaining significant injuries to two or more distinct anatomical regions with an Injury Severity Score ≥16) and those with a prior history of probiotic use. Patients with basal skull fractures were also excluded due to the high risk of accidental nasogastric tube misplacement into the intracranial space. Other exclusion criteria included patients with immunocompromised status (e.g., poorly controlled diabetes, HIV), and pregnant patients. A total of 54 eligible patients were recruited.

Sample Size Determination and Randomization

The sample size was calculated using a two-sided test for the comparison of two independent proportions. Based on a previous study from Beck et al.,[13] the expected proportion of unfavorable outcomes in the control group was set at 70%. We hypothesized a clinically meaningful absolute reduction of 40% in the intervention arm, setting the anticipated unfavorable outcome rate for the probiotic group at 30%. Applying a significance level (alpha) of 5% and a statistical power of 80%, the baseline requirement was determined to be 24 patients per group. Accounting for an assumed 10% attrition rate, the final enrollment target was established at 27 patients per group, resulting in a total sample size of 54 participants. The simple random sampling technique was used to allocate patients into either the intervention group or the control group. The random allocation sequence was generated manually by an independent research assistant (a hospital pharmacist) who had no involvement in patient recruitment or clinical care. The research assistant was also responsible for preparing the appropriate agent to be administered in each case i.e. probiotic supplements or sterile water.

To achieve equal block allocation, the pharmacist wrote the group assignments on 54 identical paper slips (27 labeled for the probiotic arm and 27 for the placebo control arm). These slips were mixed in a container and then drawn one by one to populate a master sequence.

Each drawn slip was immediately sealed inside an individual, sequentially numbered, thick opaque envelope. These envelopes were stored securely in the hospital pharmacy. Neurosurgery residents screened and enrolled eligible participants in the accident and emergency unit. After formal enrollment was finalized, the investigator requested the corresponding numbered envelope from the pharmacy, maintaining strict allocation concealment and preventing any selection bias.

Study Protocol and Interventions

The standardized management protocol for severe TBI in our center clinically targets immediate ICU admission for mechanical ventilation, continuous monitoring, stress ulcer prophylaxis, and operative intervention when indicated.

However, due to real-world resource constraints and acute intensive care bed shortages within our setting, universal ICU admission could not be achieved for all participants. While all patients received standardized neurocritical pharmacotherapy, stress ulcer prophylaxis, and surgery when indicated, only 68.5% of the total cohort was managed in the

ICU, while the remaining 31.5% were managed on the general neurosurgery ward, as detailed in our results.

All patients had a size 16 nasogastric (NG) tube passed at admission. The intervention group (group A) received a multispecies tablet form of probiotics, including *Lactobacillus bulgaricus*, *Bifidobacterium longum*, and *Enterococcus faecalis* [six tablets twice daily, delivering a standardized therapeutic dose of 3.0×10^9 colony-forming units (CFUs) per administration]. The tablets were dissolved in 20 ml of sterile water and administered via the NG tube. To mitigate any bias arising from the visual differences between the cloudy probiotic suspension and the clear sterile water placebo, all administrations were handled exclusively by the bedside ward nursing staff. These nurses were entirely un-associated with the research team and played no role in clinical evaluations, treatment decisions, or data collection, thereby preventing any visual unblinding from influencing the study outcomes.

Patients in the control group were administered a placebo (20mls of sterile water twice daily) via the NG tube. An additional 20mls of sterile water was used to flush the NG tube after each dose of the placebo similar to what was done in the intervention arm. The drug and placebo were administered over ten days, commencing on the day of trauma. The probiotic or placebo intervention was initiated on day 1 (within 24 hours of admission), ensuring it was established well before any enteral nutrition commenced. All recruited patients were kept nil per os (NPO) during the first 48 hours post-admission to prioritize primary cardiorespiratory resuscitation, fluid balance, and neuro-intensive stabilization.

Enteral nutrition via the nasogastric tube was formally initiated exactly at the 48-hour mark post-injury, aligning with the upper threshold of EEF guidelines. Due to socio-economic constraints and the high cost of commercial formulas, the feeds consisted of locally prepared, nutrient-dense fortified pap sourced by the patients' relatives. While this formula provided essential macronutrients, the precise daily caloric and protein quantities could not be standardized or individually measured.

The first full 24-hour volume of enteral feeding was completed on the third day of admission, which is why the active feeding schedule is indexed as day 3. This volume-based regimen was successfully tolerated and achieved by approximately 80% of the patients by day 7, progressing according to the following 24-hour tiers:

- Day 3…..125mls of NG tube feeding 6hrly=500mls/day
- Day 4…..250mls of NG tube feeding 6hrly=1000mls/day
- Day 5…..400mls of NG tube feeding 6hrly=1600mls/day
- Day 6…..400mls of NG tube feeding 4hrly=2400mls/day
- Day 7…..500mls of NG tube feeding 4hrly=3000mls/day

Intravenous fluid was reduced at a corresponding rate every day until day 7 when it was discontinued. Patients who did not tolerate this feeding regimen were noted and documented while the feeding schedule was adjusted appropriately to suit such patients. The nasogastric tube was aspirated before each ration of feed was administered. A patient was adjudged not to have tolerated the feed if there was any residual feed aspirated at the time of the next feeding. In that situation, the next feed was skipped while the same schedule for that day was repeated the next day. This was done in conjunction with the nurses who usually fed the patients. While the administering bedside ward nurses were aware of the fluid consistency at the time of delivery, a strict blinded framework was maintained for all other core parties. The patients' relatives, the primary treating neurosurgeons, and the data analysts remained completely blinded to the group assignments throughout the trial.

To secure the integrity of our primary endpoint, the 3-month follow-up evaluation using the Glasgow Outcome Score Extended (GOSE) was conducted by an independent clinical assessor who was completely blinded to the treatment allocation and had no access to the initial ward administration logs.

Unblinding was only done after completion of data collection or earlier in patients with suspected complications of probiotic supplements.

Clinical Outcome Measures

Clinical outcomes were measured using the Glasgow Outcome Score Extended (GOSE), an 8-point scale considered a sensitive measure for TBI recovery. Outcomes were dichotomized into unfavorable (GOSE 1-4) and favorable (GOSE 5-8). This assessment was conducted at three months post-trauma for survivors or at the time of demise for non-survivors. Secondary outcome measureswhich included 30-day mortality rates; lengths of ICU and hospital stay and the frequency of complications such as bed sores, deep venous thrombosis, and surgical site infection in patients while on admission were noted and documented.

Statistical Analysis

Primary and secondary outcome analyses were performed using a strict Intention-to-Treat (ITT) approach encompassing all 54 randomized participants. For the primary 3-month functional outcome evaluation, patients who died prior to assessment were assigned a score of GOSE 1 (death) and categorized within the unfavorable outcome group. Sociodemographic data, clinical and radiological findings (e.g., CT scan results), and outcome scores were recorded in a structured proforma. Data were analyzed using IBM SPSS version 23.0. Data analysis involved comparing proportions and means between the two groups. A p-value of <0.05 was considered statistically significant.

A Consolidated Standards of Reporting Trials (CONSORT) flow chart showing the study progress from enrollment, through allocation, and follow-up, to analysis is shown below **Figure 1**.

RESULTS

Socio-Demographic Characteristics of the Study Population

A total of 54 patients were enrolled in the study, with 27 randomized into the probiotic-supplemented group and 27

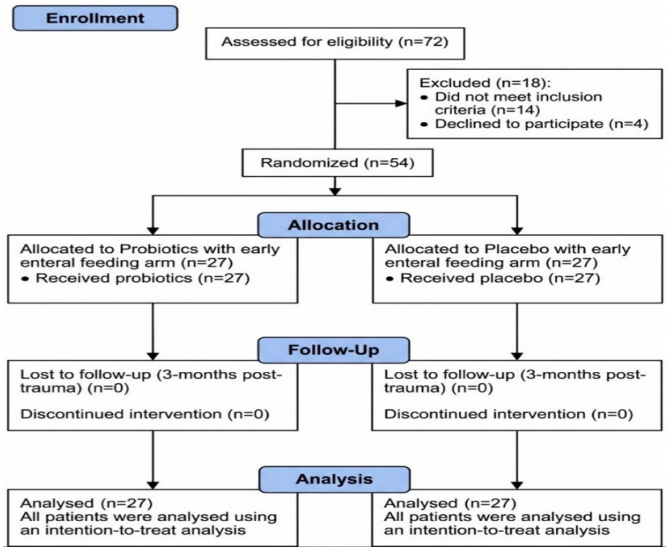

Figure 1. A CONSORT flow chart showing study progress from enrollment, through allocation, and follow-up, to analysis
CONSORT: Consolidated Standards of Reporting Trials

into the placebo group. The mean age of the study population was 37±14.90 years, and 88.9% were males Table 1.

Table 1. Socio-demographic characteristics of the study population n=54

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
Age group (years) n, (%)				1.241	0.743
≤25	7 (25.9)	5 (18.5)	12 (22.2)		
26-35	10 (37.0)	8 (29.6)	18 (33.3)		
36-45	4 (14.8)	6 (22.2)	10 (18.5)		
≥46	6 (22.2)	8 (29.6)	14 (25.9)		
Mean±SD	37±16.2	38±13.8	37±14.9	0.047	0.829
Range	19-75	19-71			
Gender n, (%)				0.001	0.999
Male	24 (88.9)	24 (88.9)	48 (88.9)		
Female	3 (11.1)	3 (11.1)	6 (11.1)		

SD: Standard deviation

Injury mechanism and Cranial CT scan findings

Rider motorcycle road traffic crash was responsible for 51.9% (14 patients) and 55.6% (15 patients) of injuries in the intervention and control groups respectively followed by passenger motorcycle crashes accounting for 18.5% (5 patients) and 14.8% (4 patients) in that order Figure 2. The cranial CT scan findings were also comparable with cerebral edema being the commonest finding in both groups (63.0% and 48.1%) respectively Table 2.

Neurologic Symptoms and Signs

The mean post resuscitation GCS was 7.6±0.6 in the intervention group and 7.3±0.9 in the control group. Seizures occurred in 40.7% (11) and 37.0% (10) of patients in the intervention and control groups respectively. In both groups early post-traumatic seizure was commoner, accounting for 72.7% and 70.0% of cases respectively. No patient had late post traumatic seizure in either group. Vomiting was observed in 33.3% and 25.9% of patients in the probiotics and placebo group respectively. Longitudinal tract deficits were present in 66.7% (18) and 70.4% (19) of patients in the two

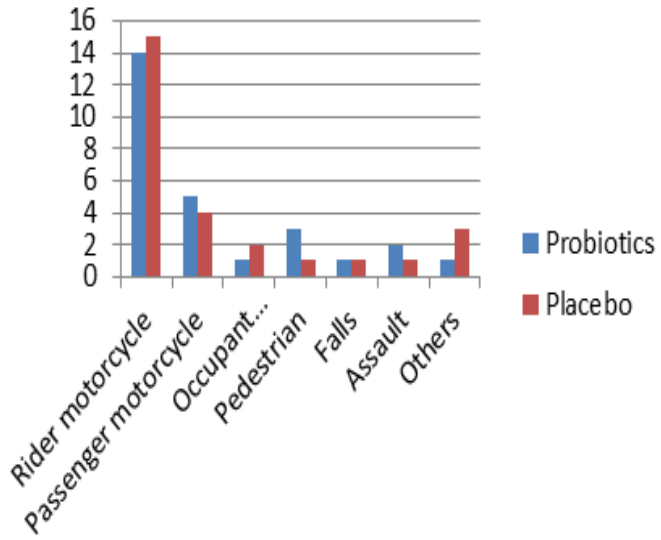

Figure 2. Mechanisms of injury among study participants

Table 2. Cranial CT scan findings in the two groups

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2	p-value
CT scan findings n,(%)					
Fractures	6 (22.2)	11 (40.7)	17 (31.5)	2.146	0.143
EDH	2 (7.4)	5 (18.5)	7 (13.0)	1.477	0.224
ASDH	6 (22.2)	4 (14.8)	10 (18.5)	1.200	0.273
SAH	3 (11.1)	7 (25.9)	10 (18.5)	1.964	0.161
IVH	3 (11.1)	2 (7.4)	5 (9.3)	0.220	0.639
ICH	6 (22.2)	6 (22.2)	12 (22.2)	0.000	1.000
Contusion	12 (44.4)	7 (25.9)	19 (35.2)	2.030	0.154
Edema	17 (63.0)	13 (48.1)	30 (55.6)	1.200	0.273

CT: Computed tomography, EDH: Epidural haematoma, ASDH: Acute subdural haematoma, SAH: Subarachnoid haemorrhage, IVH: Intraventricular haemorrhage, ICH: Intracerebral haemorrhage

groups respectively with hemiparesis being the commonest pattern Table 3, Table 4.

Table 3. Neurologic symptoms among study participants n=54

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
GCS					
At admission	7.1±1.2	7.0±1.0	7.09±1.05	0.128	0.381
Post resuscitation	7.6±0.6	7.3±0.9	7.43±0.77	1.620	0.117
Seizures (n=21)					
Yes	11 (40.7)	10 (37.0)	21 (38.9)	0.078	0.780
No	16 (59.3)	17 (63.0)	33 (61.1)	0.119	0.730[y]
Types of seizure					
Immediate (<24 hours)	3 (27.3)	3 (30.0)	6 (28.6)		
Early (1-7 days)	8 (72.7)	7 (70.0)	15 (71.4)		
Late (>7 days)	0 (0.0)	0 (0.0)	0 (0.0)		
Vomiting				0.355	0.551
Yes	9 (33.3)	7 (25.9)	16 (29.6)		
No	18 (66.7)	20 (74.1)	38 (70.4)		

GCS: Glasgow Coma Scale

Management and Intervention

Among patients in the probiotics group, 77.8% (21) were admitted into the intensive care unit (ICU) while only 59.3%

Table 4. Pupillary sizes, reactivity and long tract deficits

Variables	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
Right pupil size n,(%)				0.250	0.882
<3mm	2 (7.4)	2 (7.4)	4 (7.4)		
3-5mm	22 (81.5)	21 (77.8)	43 (79.6)		
>5mm	3 (11.1)	4 (14.8)	7 (13.0)		
Right pupil reactivity				1.348	0.510
Nil	3 (11.1)	5 (18.5)	8 (14.8)		
Sluggish	10 (37.0)	12 (44.4)	22 (40.7)		
Brisk	14 (51.9)	10 (37.0)	24 (44.4)		
Left pupil size				0.439	0.803
<3mm	3 (11.1)	3 (11.1)	6 (11.1)		
3-5mm	23 (85.2)	21 (77.8)	44 (81.5)		
>5mm	1 (3.7)	3 (11.1)	4 (7.4)		
Left pupil reactivity				0.612	0.736
Nil	2 (7.4)	1 (3.7)	3 (5.6)		
Sluggish	7 (25.9)	9 (33.3)	16 (29.6)		
Brisk	18 (66.7)	17 (63.0)	35 (64.8)		
Long tract deficit				0.085	0.770
Present	18 (66.7)	19 (70.4)	37 (68.5)		
Absent	9 (33.3)	8 (29.6)	17 (31.5)		
Specification of long tract deficit (n=37)	n=18	n=19		0.027	0.986[y]
Right hemiparesis	9 (50.0)	10 (52.6)	19 (51.4)		
Left hemiparesis	9 (50.0)	8 (42.10	17 (45.9)		
Quadriparesis	0 (0.0)	1 (5.3)	1 (2.7)		

Table 5. Management and intervention

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
ICU admission n,(%)				2.146	0.143
Yes	21 (77.8)	16 (59.3)	37 (68.5)		
No	6 (22.2)	11 (40.7)	17 (31.5)		
Duration of ICU admission in days				3.890	0.274
1-5	3 (14.3)	3 (18.8)	6 (16.2)		
6-10	10 (47.6)	8 (50.0)	18 (48.6)		
11-15	8 (38.1)	3 (18.8)	11 (29.7)		
≥ 16	0 (0.0)	2 (12.5)	2 (5.4)		
Mean±SD	9±3.25	9±4.14	9.27±3.61	0.302	0.401
Operative management				2.670	0.102
Yes	10 (37.0)	16 (59.3)	26 (48.1)		
No	17 (63.0)	11 (40.7)	28 (51.9)		
IV mannitol administration				0.092	0.761
Yes	19 (70.4)	20 (74.1)	39 (72.2)		
No	8 (29.6)	7 (25.9)	15 (27.8)		
IV furosemide administration				0.092	0.761
Yes	19 (70.4)	20 (74.1)	39 (72.2)		
No	8 (29.6)	7 (25.9)	15 (27.8)		
Side effect of probiotic administration					
Yes	1 (3.7)	0 (0.0)			
No	26 (96.3)	27 (100.0)			

ICU: Intensive care unit, SD: Standard deviation, IV: Intraventricular

Table 6. GOSE assessments at discharge and at 3-months post-trauma

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
GOS-E assessment					
At discharge n, (%)				0.912	0.340
Favorable outcome	8 (29.6)	5 (18.5)	13 (24.1)		
Unfavorable outcome	19 (70.4)	22 (81.5)	41 (75.9)	0.070	0.244
Category of unfavorable outcomes				1.273	0.736[y]
Death	6 (22.2)	3 (11.1)	9 (16.7)		
Vegetative state	2 (7.4)	1 (3.7)	3 (5.6)		
Lower severe disability	9 (33.3)	15 (55.6)	24 (44.4)		
Upper severe disability	2 (7.4)	3 (11.1)	5 (9.3)		
3rd month (post trauma)					
Favorable outcome	11 (40.7)	7 (25.9)	18 (33.3)	0.817	0.248
Unfavorable outcome	16 (59.3)	20 (74.1)	36 (66.7)		
Category of unfavorable outcomes				0.596	0.742[y]
Death (GOSE 1)	6 (22.2)	3 (11.1)			
Vegetative state	2 (7.4)	1 (3.7)	3 (5.6)		
Lower severe disability	7 (25.9)	11 (40.7)	18 (33.3)		
Upper severe disability	1 (3.7)	5 (18.5)	6 (11.1)		
Residual neurological deficit at 3 months post trauma				0.007	0.936
Yes	12 (57.1)	14 (58.3)	26 (57.8)		
No	9 (42.9)	10 (41.7)	19 (42.2)		

GOSE: Glasgow Outcome Score Extended

(16) in the placebo group were admitted in the ICU. While 37% (10) of patients in the probiotics arm had operative intervention, 59.3% (16) of patients in the placebo group had surgical intervention, p=0.102. In both groups, a similar number of patients had administration of mannitol and furosemide- 70.4% (19) and 72.2% (20) in the probiotics and placebo arms respectively Table 5.

Primary Outcome: Glasgow Outcome Score Extended (GOSE)

At hospital discharge, an intention-to-treat analysis showed favorable outcomes (GOSE 5-8) in 29.6% (n=8) of patients in the intervention group and 18.5% (n=5) of patients in the control group (p=0.340). At the three-month follow-up, retaining all randomized patients with deaths coded as GOSE 1, favorable outcomes occurred in 40.7% (n=11) of the probiotic group compared with 25.9% (n=7) of controls (p=0.248) Table 6.

Secondary Outcomes: Lengths of ICU and Hospital Stay, 30-Day Mortality, and Incidence of Complications

There was no significant difference in the mean length of ICU stay between the two groups (9±3.25 days vs. 9± 4.14 days, p=0.401). The overall mean duration of hospital stay was 19.5±6.9 days in the probiotic arm compared to 24.0±11.8 days in the placebo arm, showing no statistically significant difference (p=0.051). The 30-day mortality rate was 22.2% in the probiotic group compared to 11.1% in the placebo group (Table 7); however, this difference was not statistically significant (p=0.273), and the two cohorts exhibited comparable baseline injury characteristics on cranial CT imaging (Table 2). The proportion of patients who developed complications during admission was 51.9% in the probiotics group and 66.7% in the placebo group. When broken down

Table 7. Secondary outcome measures

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
ICU admission n,(%)				2.146	0.143
Yes	21 (77.8)	16 (59.3)	37 (68.5)		
No	6 (22.2)	11 (40.7)	17 (31.5)		
Duration of ICU admission in days				3.890	0.274
1-5	3 (14.3)	3 (18.8)	6 (16.2)		
6-10	10 (47.6)	8 (50.0)	18 (48.6)		
11-15	8 (38.1)	3 (18.8)	11 (29.7)		
≥ 16	0 (0.0)	2 (12.5)	2 (5.4)		
Mean±SD	9±3.25	9±4.14	9.27±3.61	0.302	0.401
Length of hospital stay in days					
Mean±SD	19.5±6.9	24.0±11.8		-1.702	0.051
Still alive at 30 days post trauma					
Yes	21 (77.8)	24 (88.9)			
No	6 (22.2)	3 (11.1)			
30-day mortality	22.2 %	11.1 %		1.200	0.273

ICU: Intensive care unit, SD: Standard deviation

by specific types, the incidences in the probiotic group versus the placebo group were chest infection (37.0% vs. 48.1%), bed sores (3.7% vs. 18.5%), surgical site infection (11.1% vs. 7.4%), deep venous thrombosis (DVT) (0.0% vs. 3.7%), and other complications (3.7% vs. 7.4%).

DISCUSSION

The primary objective of this randomized controlled trial was to evaluate the effectiveness of EEF supplemented with a multispecies probiotics on the major clinical outcomes, including neurological recovery (GOSE) and mortality, in adult patients with severe TBI. The principal finding was the lack of a statistically significant difference in favorable outcomes as measured by the GOSE at three months post-trauma between the intervention and control groups (p=0.248). This outcome indicates that while the probiotic group demonstrated a higher numerical rate of favorable recovery, the primary findings remain inconclusive due to the limited statistical power of our single-center design. Therefore, our results should not be interpreted as an absence of effect, but rather as an unconfirmed trend that requires evaluation in a larger sample pool. Our results are consistent with findings from some previous preclinical and clinical studies by Kobra et al.,[14] Tan et al.,[15] and Falcao de Arruda et al.,[16] all of whom reported no significant neurologic benefits or improvements in functional recovery with probiotic administration.

Our study noted a higher numerical incidence of 30-day mortality within the probiotic group (22.2% vs. 11.1%), although this variation was not statistically significant (p=0.273). This result contrasts sharply with other studies which have reported a reduction in mortality rates with probiotic use. Asaadi et al.,[17] in a 2024 systematic review and meta-analysis demonstrated that probiotic therapy significantly reduced the risk of 28-day mortality in TBI patients (OR: 0.53; 95% CI: 0.31 to 0.9). However, Sharif et al.[18] in another systematic review and meta-analysis, which included 65 randomized controlled trials with over 8.000 patients, concluded that probiotics probably had no effect on mortality in critically ill patients (RR, 0.95; 95% CI, 0.87-1.04). The study also found no significant difference in in-hospital mortality in critically ill ventilated subjects receiving probiotics compared to controls. These findings suggest that the impact on mortality might not be universally positive across all patient populations or probiotic formulations.

The numerically higher mortality in the probiotics group in this index study raises a concern about the safety of this protocol in the management of severe TBI which may have ethical implications. However, the observed discrepancy in mortality rates may be attributable to subtle baseline differences in injury severity between the two randomized groups. The probiotic cohort exhibited a higher proportion of patients with severe cranial pathologies, specifically cerebral edema (63.0%vs.48.1%) and acute subdural hematoma (22.2% vs. 14.8%). These findings suggest that patients in the intervention group may have suffered a greater force of impact at the time of injury, which typically elicits a more intense inflammatory response in the brain, including severe cerebral edema, thus predisposing them to higher mortality.[19,20] Furthermore, acute subdural hematoma is consistently associated with a higher mortality rate due to the severe concomitant brain parenchymal injuries these patients usually sustain.[21,22] These key confounding variables are highly capable of driving differential mortality rates within a limited sample size. Given this small cohort size and the fact that our calculated risk ratio confidence interval spans widely (95% CI: 0.557-7.187), this mortality signal likely reflects baseline injury discrepancies rather than definitive intervention-related harm. Beyond these baseline discrepancies, while the cohort was statistically justified by initial power calculations to address the primary objective, it remains a relatively compact, single-center sample when examining secondary safety endpoints. Consequently, the observed mortality distribution might reflect a statistical artifact or chance variation driven by baseline clinical imbalances rather than a reproducible intervention risk. While a consistent harmful signal is biologically unexpected in most ICU settings, critical illness factors unique to severe TBI-such as profound gut ischemia, mucosal barrier dysfunction, or the confounding effects of vasopressors and broad-spectrum antibiotics-could theoretically facilitate rare microbial translocation or skew clinical outcomes. Consequently, this mortality trend likely stems from a complex interaction between injury pathophysiology and systemic ICU variables rather than a reproducible risk inherent to the probiotic itself. Crucially, a defining factor influencing these survival trends is the systemic constraint on intensive care resources. While standard international guidelines mandate immediate ICU admission and mechanical ventilation for all severe TBI patients, bed shortages in our environment restricted universal access.

The resulting imbalance in ICU care-where more patients in the probiotic arm received intensive monitoring than in the control arm (77.8% vs. 59.3%)-adds an extraordinary layer of clinical confounding. Therefore, these results must be viewed strictly as outcomes within a resource-constrained neurocritical care framework, where differences in monitoring levels significantly dictate both mortality and short-term functional recovery.

Ultimately, while our cohort was statistically grounded by initial power calculations, a much larger patient cohort would be highly preferable to control for subtle baseline imbalances and to confidently rule out chance variations in mortality trends within this population.

Our results also showed no significant difference in the mean length of ICU stay between the two groups (p=0.401). This finding is partially supported by some studies that indicated conflicting results regarding ICU length of stay.[23,24] However, other studies have reported significant reductions in ICU length of stay with probiotic use.[25,26] The inconsistency across studies underscores the heterogeneity in study designs, patient populations, and probiotic products used in current research, making direct comparisons challenging.

Regarding general complications during admission, the proportion of patients who developed complications was lower in the probiotic group (51.9%) compared to the non-probiotic group (66.7%); even though this difference did not reach statistical significance (p=0.268). Some other authors reported a similar pattern of complications.[27,28] Ultimately, optimizing overall clinical outcomes and mitigating such systemic complications relies heavily on structured intensive care unit frameworks and standardized neuroprotection protocols for severe TBI patients.[29,30]

Limitations

A major limitation influencing the interpretation and generalizability of our results relates to adherence to standard of care. Standard neuro-critical care guidelines mandate ICU admission for all severe TBI patients for continuous monitoring and mechanical ventilation. However, due to resource constraints and bed availability within our setting, only 68.5% of the total cohort was admitted to the ICU (77.8% in the probiotic group and 59.3% in the control group).

This variation in the location of care introduces potential confounding factors related to the level of monitoring and specialized care received by the participants. Most importantly, because a significant portion of our cohort had to be managed on general wards rather than in a dedicated ICU due to local resource limitations, our findings cannot be directly generalized to healthcare settings with universal ICU admission and standard mechanical ventilation protocols for all severe TBI cases.

Regarding our study population, the single-center nature of our trial restricts immediate external generalizability. While our sample size was calculated a priori using defined assumptions for the primary dichotomized 3-month GOSE endpoint, the relatively compact scale of this single-center cohort limits its statistical power to detect smaller, localized subgroup variations or to confidently resolve secondary safety endpoints such as mortality trends.

Additionally, due to socio-economic constraints and the resource-limited nature of our setting, patients were fed using relative-sourced fortified pap rather than standardized commercial enteral formulas. The inability to quantify the exact daily caloric and protein intake for each participant represents an additional limitation to our nutritional protocol execution.

CONCLUSION

As a result, this randomized, placebo-controlled trial demonstrated no statistically significant functional recovery benefit from combining enteral feeding with this specific probiotic regimen in patients with severe traumatic brain injury.

Although 30-day mortality was numerically higher in the probiotic cohort, this change was not statistically significant, and the lack of distinct functional benefits indicates that routine probiotic supplementation provides no clear efficacy in this framework. Rather than indicating definitive danger, this numerical trend suggests that a cautious approach should be maintained regarding routine probiotic use in severe TBI until larger, adequately powered multicenter trials can thoroughly evaluate its safety and utility profiles.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Research Committee of the University Teaching Hospital in Ilorin (Date: 10.05.2021, Decision No: ERC PAN/2021/10/020).

Informed Consent

Written informed consent was obtained from relatives and caregivers of all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Conceptualization: OOA; Data Curation: OOA; Formal analysis: OOA; Writing-Original Draft: OOA; Writing-Review and Editing: OTO, NAA, OMA, OE, HAY, SAAİ; Supervision: OTO, SAAİ.

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Review

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Restless legs syndrome: linking neuroanatomical mechanisms to clinical management

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ABSTRACT

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder that can markedly disturb sleep, daytime functioning, and quality of life. Patients usually describe an urge to move the legs, often with unpleasant sensations that are hard to localize or put into words. Symptoms arise or worsen during rest, ease with movement, and tend to be most prominent in the evening or at night. Diagnosis is clinical; it depends on recognizing this pattern and considering disorders that can mimic RLS, in line with the International RLS Study Group criteria. RLS is not readily explained by a single pathway. Current evidence links the disorder to altered brain iron regulation, dopaminergic signaling, genetic susceptibility, basal ganglia circuitry, thalamocortical-somatosensory processing, and spinal sensorimotor pathways. These mechanisms provide a biological context for the sensorimotor features of the disorder. The management plan should be personalized, taking into account the symptom load, iron levels, co-morbidities, any secondary contributing factors, and other drugs that might aggravate the symptoms. Conservative measures may be sufficient for mild or intermittent symptoms, whereas persistent or disabling symptoms require tailored treatment. RLS is therefore better understood as a clinically important sensorimotor network disorder than as a simple sleep-related complaint.

Keywords: Restless legs syndrome, Willis-Ekbom disease, basal ganglia, brain iron metabolism, dopaminergic system, alpha-2-delta ligands

INTRODUCTION

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological sensorimotor disorder in which patients experience an urge to move their legs, usually together with unpleasant sensations that appear or become worse during rest. Patients may use words such as tingling, crawling, pulling, aching, tension, or inner restlessness. Despite this variability, the clinical pattern is usually clear: symptoms worsen during inactivity, improve at least temporarily with movement, and become more prominent in the evening or at night.[1]

The burden of RLS is often underestimated. What may first seem like a minor complaint of leg discomfort can interfere with sleep initiation and sleep maintenance, leading to daytime fatigue, impaired concentration, and reduced quality of life.[2] Epidemiological studies suggest that RLS affects approximately 5-10% of the general population, although clinically significant symptoms requiring medical attention occur in a smaller proportion of individuals.[2,3]

Current evidence indicates that RLS is not simply a peripheral disorder of the legs. Rather, it appears to arise from interactions between brain iron regulation, dopaminergic neurotransmission, genetic susceptibility, basal ganglia circuits, thalamocortical sensory processing, and spinal sensorimotor pathways.[4-6] This network-based view helps explain the characteristic sensory discomfort, urge to move, circadian symptom pattern, temporary relief with movement, and frequent association with periodic limb movements during sleep.

This review brings together the historical background, epidemiology, pathophysiology, neuroanatomical mechanisms, clinical features, diagnostic approach, and current treatment strategies of RLS, with particular emphasis on the relationship between neuroanatomical mechanisms and clinical decision-making.

TERMINOLOGY AND HISTORY

Clinical observations resembling what is now known as RLS can be traced back to the 17th century. Thomas Willis described patients with marked restlessness of the limbs, particularly at night, in a clinical picture that is now regarded as one of the earliest recognizable descriptions of RLS.[7] Although his terminology reflected the medical language of his time, the central features of nocturnal restlessness and disturbed sleep remain closely aligned with the modern understanding of the disorder.

The modern clinical identity of RLS was shaped mainly by Karl-Axel Ekbom in the mid-20th century. In his 1945 monograph, Ekbom outlined the symptom pattern that remains central to RLS today.[8] He described unpleasant sensations in the legs, an urge to move, relief with movement, and worsening of symptoms in the evening or at night. This careful clinical description helped separate RLS from nonspecific leg discomfort, peripheral pain syndromes, and general sleep complaints. It also supported the recognition of RLS as a distinct clinical entity.

'Restless legs syndrome' remains the most widely used term in clinical practice and research, whereas 'Willis-Ekbom disease' is also used to acknowledge both Willis's early observations and Ekbom's systematic clinical description.1 This historical development helped establish RLS as a defined neurological sensorimotor disorder rather than a nonspecific complaint of leg restlessness.[9]

DEFINITION AND DIAGNOSTIC CRITERIA

RLS is a neurological sensorimotor disorder defined by an urge to move the legs, usually accompanied by unpleasant sensations that appear or worsen during rest, improve with movement, and become more prominent in the evening or at night.[1] Patients may describe these sensations as tingling, pulling, aching, crawling, tension, or inner restlessness; however, the overall clinical pattern is often more important than the exact wording of the symptom.

No laboratory test, imaging finding, or polysomnographic marker can independently confirm the disorder. In practice, RLS is diagnosed by recognizing a characteristic symptom pattern in the patient's history. The International Restless Legs Syndrome Study Group criteria provide the main clinical framework for this assessment.[1]

The updated criteria require five key features. Patients have an urge to move their legs, often but not always accompanied by unpleasant sensations. Symptoms begin or worsen during rest or inactivity, improve partially or completely with movement, and show a clear evening or nighttime predominance. The same symptom pattern should not be more plausibly explained by another clinical condition.[1]

This last criterion deserves particular attention. Several disorders can resemble RLS, including peripheral neuropathy, nocturnal leg cramps, akathisia, positional discomfort, chronic venous insufficiency, arthritis, leg edema, and nonspecific musculoskeletal pain.[1,10] These disorders often lack the typical combination of rest-induced worsening, movement-related relief, and evening or nighttime predominance.

Clinical assessment should also document symptom severity, disease course, and the effect of RLS on sleep, daytime functioning, and quality of life.[1,2,11] This information helps determine clinical significance and treatment need, and provides a consistent framework for clinical follow-up and research.[1,10,11]

PREVALENCE, EPIDEMIOLOGY, AND RISK FACTORS

RLS is a relatively common neurological sensorimotor disorder, yet it is still easily missed in everyday clinical practice. Population-based studies suggest that RLS affects approximately 5-10% of the general population, although clinically significant symptoms requiring medical attention are less frequent, usually affecting about 2-3% of individuals.[2,3,12] Mild or occasional symptoms may not require treatment, whereas persistent symptoms that interfere with sleep, daytime functioning, or quality of life warrant clinical attention.

Prevalence estimates for RLS also vary across populations. Higher rates have generally been reported in Europe and North America, while several Asian studies have described lower rates.[2,3] These differences probably reflect a combination of genetic background, environmental influences, cultural differences in symptom reporting, and diagnostic awareness. In routine practice, RLS may remain unrecognized when patients present with insomnia, leg discomfort, fatigue, or nonspecific restlessness rather than clearly describing an urge to move.

Several demographic and clinical factors influence the expression of RLS. The disorder becomes more common with advancing age and is reported more often in female than in male.[12] It may also occur in children and adolescents, although symptoms in these age groups can be mistaken for growing pains, behavioral restlessness, attention-related problems, or nonspecific sleep disturbance.[13] Pregnancy is also a recognized period of increased vulnerability to RLS, particularly during the third trimester. Changes in iron metabolism, hormonal factors, and the increased physiological demands of late pregnancy are thought to contribute.[14] A positive family history is also common, particularly in patients with earlier symptom onset, supporting the role of inherited susceptibility.[15]

Secondary or exacerbated RLS should be considered when symptoms occur in association with iron deficiency, chronic kidney disease, neuropathy, pregnancy, or relevant medication exposure.[16,17] A medication review is particularly useful because antidopaminergic agents, some antidepressants, sedating antihistamines, and other centrally acting drugs may worsen symptoms in susceptible patients.[10] Identifying these factors is clinically relevant, as some are modifiable and may influence both evaluation and treatment planning.

ETIOLOGY AND PATHOPHYSIOLOGY

RLS has a multifactorial etiology and cannot be reduced to a single anatomical structure, neurotransmitter

system, or peripheral process. Rather, current evidence supports a network-based model in which altered brain iron homeostasis, dopaminergic dysfunction, genetic susceptibility, thalamocortical sensory processing, and spinal sensorimotor mechanisms interact.[4-6,18,19] Primary RLS is often associated with familial predisposition and earlier symptom onset, whereas secondary or exacerbated forms may occur in relation to iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[6,14,16] These factors, they appear to converge on shared pathways, particularly iron-dependent dopaminergic regulation and altered sensorimotor network excitability.

In this model, abnormal sensory processing generates discomfort, while motor circuits respond with an urge to move. The temporary relief produced by movement suggests that motor activity can transiently modify this abnormal sensorimotor state.[1,6]

Brain Iron Homeostasis and Iron-Dopamine Interaction

Altered brain iron regulation has been one of the most consistent biological findings in RLS. This link is biologically meaningful because iron is involved in several key neural processes, including dopamine synthesis, myelination, mitochondrial function, and cellular energy metabolism. In dopaminergic neurons, iron also serves as a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine production.[4,20]

An important feature of RLS is that central iron deficiency may occur even when peripheral iron measures are not markedly abnormal. Evidence from neuropathological and neuroimaging studies points to altered brain iron handling in RLS. In the substantia nigra, impaired iron acquisition and reduced iron-related staining have been described in affected individuals.[21] Lower regional brain iron measures have been reported most consistently in the substantia nigra, with less prominent changes in the putamen.[22] This pattern is more consistent with a functional deficiency of iron within the central nervous system than with systemic iron deficiency alone.

Disturbed iron regulation may affect dopamine synthesis, receptor function, and circadian dopaminergic activity, which may contribute to evening worsening, the urge to move, and partial response to dopaminergic therapies. However, RLS should not be interpreted as a straightforward dopamine-deficiency state. Current evidence suggests a more complex disturbance involving iron-dependent modulation of dopaminergic and sensorimotor networks.[4,20]

Assessment of iron status is an important part of the evaluation of patients with clinically significant RLS, and iron replacement may reduce symptoms in selected patients. This makes iron metabolism one of the most clinically relevant mechanisms in RLS, linking biological vulnerability with diagnostic work-up and treatment planning.[17]

Dopaminergic Function and Basal Ganglia Circuits

Dopamine contributes to motor regulation and sensorimotor integration, largely through basal ganglia circuits. Within these circuits, the striatum, globus pallidus, substantia nigra, and subthalamic nucleus interact with motor and premotor cortical areas to shape movement initiation, inhibition, and control.[4]

Although treatment response does not make dopamine dysfunction the sole explanation for the disorder, the improvement seen with dopaminergic agents supports a role for dopamine-related pathways in its clinical expression.[23] Imaging studies have also reported changes in dopaminergic markers, including D2-receptor binding and striatal dopamine transporter availability.[24,25] The available evidence points instead to a more complex disturbance of dopaminergic regulation, shaped in part by brain iron metabolism and circadian variation in dopamine-related activity.[4]

Altered dopaminergic modulation within these circuits may contribute to the urge to move, difficulty remaining still, evening worsening, and temporary relief after movement. In this sense, basal ganglia dysfunction provides a link between the iron-dopamine interaction described above and the characteristic sensorimotor phenotype of RLS.[4,24]

Genetic Susceptibility and Neurodevelopmental Factors

Genetic susceptibility is an important part of the pathophysiology of restless legs syndrome, especially in patients with earlier symptom onset or a positive family history. Familial clustering has long suggested that inherited factors contribute to disease risk. However, RLS usually does not follow a simple monogenic pattern. Instead, available evidence supports a complex genetic background in which several variants contribute modestly to overall susceptibility.[26]

Genome-wide association studies have identified several loci associated with RLS, including regions near or within MEIS1, BTBD9, MAP2K5/SKOR1, and PTPRD.[15,18] These findings suggest that genetic factors may influence neural systems involved in sensory processing, motor regulation, and sensorimotor integration. Their main value is to help explain why some individuals may be biologically more vulnerable to developing RLS.[26]

Risk variants have been associated with neuronal differentiation, axonal guidance, synaptic organization, and circuit maturation. These changes may create a persistent vulnerability within central nervous system pathways, even if symptoms appear only later in life or after additional triggers such as iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[18,27]

A 2024 genome-wide meta-analysis expanded the number of reported risk loci and linked RLS risk to biological pathways involved in neurodevelopment, neurotransmission, and neuronal connectivity.[27] These findings support the broader concept of RLS as a distributed sensorimotor network disorder rather than a disease of a single anatomical structure or one neurotransmitter system.

From a clinical perspective, genetic information is most useful for recognizing disease patterns rather than for routine genetic testing. A positive family history, early symptom onset, and similar complaints across generations may support the diagnosis and help distinguish primary RLS from symptoms mainly related to secondary conditions.

Thalamocortical and Somatosensory Network Involvement

The sensory component of RLS suggests that the disorder involves more than abnormal motor control. Many patients describe their symptoms as deep, unpleasant, and difficult to localize, which points toward altered central sensory processing rather than a purely peripheral source of discomfort.[1,28] Thalamocortical and somatosensory networks are therefore relevant because they participate in the transmission, interpretation, and integration of sensory input from the lower extremities.[19,29-31]

Early imaging work identified cerebral activation patterns associated with sensory leg discomfort and periodic limb movements, including regions involved in sensorimotor processing.[19] More recent resting-state studies have emphasized altered thalamic connectivity and reduced connectivity within dopaminergic networks, supporting the view that RLS reflects distributed network dysfunction rather than a single focal abnormality.[30]

In patients with severe RLS, reduced cortical thickness has been reported in the bilateral postcentral gyrus, together with changes in corpus callosum regions connected with somatosensory pathways.[31] These findings may help explain why symptoms are experienced as deep, uncomfortable sensations closely linked to the urge to move.

Taken together, thalamocortical and somatosensory network findings provide a useful framework for understanding the sensory burden of RLS, particularly the deep and unpleasant sensations that are closely linked to motor restlessness.[19,30,31] These findings should not be interpreted as making neuroimaging a routine diagnostic tool, because RLS remains a clinical diagnosis based on established IRLSSG criteria.[1]

Spinal Sensorimotor Mechanisms and the A11 Dopaminergic System

Spinal sensorimotor mechanisms may help explain the close relationship between sensory discomfort, the urge to move, and periodic limb movements in restless legs syndrome. Sensory input from the lower limbs converges on interneuronal networks, reflex pathways, and motor neurons within the lumbosacral spinal cord. Changes in descending modulation may increase spinal excitability. This could lower the threshold for sensory discomfort and facilitate repetitive motor activity.[5,32]

The A11 dopaminergic system offers a possible anatomical link between central dopaminergic dysfunction and spinal involvement. Descending projections from the A11 region to the spinal cord are thought to influence sensory transmission, reflex activity, and motor excitability. Disturbance in this pathway may therefore contribute not only to the urge to move, but also to the motor phenomena seen in RLS.[5]

These stereotyped movements commonly involve flexion at the ankle, knee, or hip. Neurophysiological findings suggest that they may reflect state-dependent changes in spinal flexor reflex excitability.[33] Although PLMS are not specific to RLS, their frequent association with the disorder supports the view that spinal sensorimotor circuits form part of a wider network. This network includes brain iron regulation, basal ganglia circuits, thalamocortical sensory processing, and descending spinal modulation.[5,32,33]

Integrated Pathophysiological Model

RLS is best understood as a disorder of distributed sensorimotor network regulation rather than the result of a single anatomical lesion or isolated neurotransmitter abnormality. Brain iron dysregulation may influence dopamine synthesis and receptor function, while dopaminergic alterations within basal ganglia circuits may affect motor control, sensorimotor integration, and circadian symptom expression.[4,21,24] Genetic susceptibility may create a background vulnerability in these networks, which can be unmasked or worsened by factors such as iron deficiency, pregnancy, chronic kidney disease, neuropathy, or medication exposure.[18,27]

The sensory and motor features of RLS appear to arise from the interaction of supraspinal and spinal mechanisms. Altered thalamocortical and somatosensory processing may contribute to the deep, unpleasant, and difficult-to-localize sensations described by patients, whereas spinal sensorimotor excitability and A11-mediated descending modulation may help explain the urge to move and periodic limb movements during sleep.[5,19,30-33]

Altered brain iron regulation and dopaminergic transmission, together with changes in sensory processing and spinal excitability, may explain why symptoms worsen during rest, become more prominent in the evening or at night, and improve temporarily with movement. Clinically, this approach is valuable because it supports a structured evaluation of iron status, secondary contributors, aggravating medications, and treatment options tailored to the individual patient (**Figure**).[1,17]

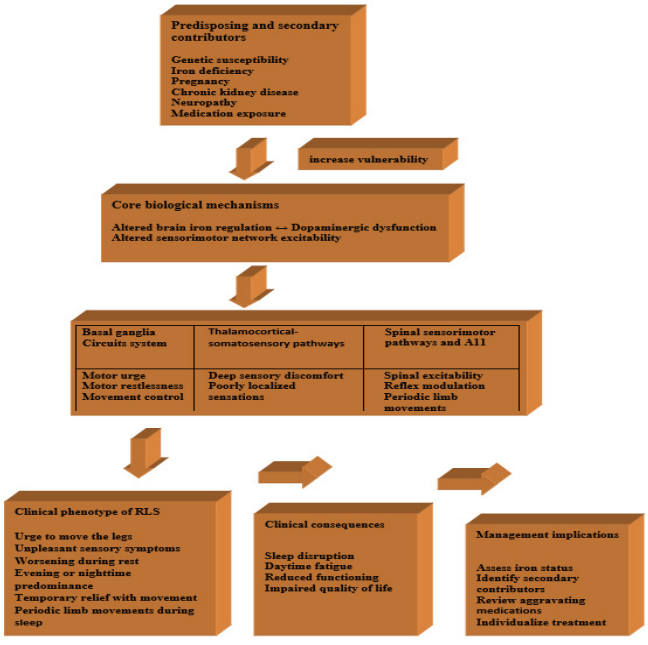

Figure. Integrated neuroanatomical and clinical model of restless legs syndrome

Genetic susceptibility and secondary contributors may interact with altered brain iron regulation, dopaminergic dysfunction, and sensorimotor network excitability. These mechanisms involve basal ganglia circuits, thalamocortical-somatosensory pathways, and spinal sensorimotor pathways, including the A11 dopaminergic system. Their interaction may explain the sensory, motor, circadian, and sleep-related features of RLS and supports individualized clinical management. RLS: Restless legs syndrome

NEUROANATOMICAL AND CLINICAL CORRELATES

The clinical manifestations of RLS are best understood as the result of altered communication within sensorimotor

networks rather than dysfunction of a single anatomical structure. Although symptoms are felt mainly in the legs, the characteristic combination of sensory discomfort, urge to move, relief with movement, circadian worsening, and periodic limb movements points to the interaction of central and spinal pathways[6,19,30,31] (Table).

Table. Neuroanatomical mechanisms and clinical correlates in RLS

Mechanism/network	Main anatomical-functional correlate	Clinical expression
Brain iron dysregulation	Substantia nigra, putamen, CNS iron handling	Dopaminergic modulation, symptom vulnerability
Dopaminergic-basal ganglia circuits	Striatum, globus pallidus, substantia nigra, subthalamic nucleus	Urge to move, motor restlessness
Thalamocortical-somatosensory processing	Thalamic networks, postcentral gyrus	Deep, unpleasant, poorly localized sensations
Spinal sensorimotor pathways	Lumbosacral spinal circuits, flexor reflex pathways	Periodic limb movements, movement-related relief
A11 dopaminergic system	Descending dopaminergic modulation	Link between central dopamine and spinal excitability

RLS: Restless legs syndrome

Basal ganglia circuits are likely to be most relevant to the motor dimension of RLS. Through striatal pathways and dopaminergic modulation, these circuits help regulate whether movement is initiated, suppressed, or adjusted in response to sensory input. In RLS, altered dopaminergic signaling within these pathways may contribute to motor restlessness and to the compelling urge to move that emerges during periods of rest.[4,24,25]

The sensory component of RLS points more strongly to thalamocortical and somatosensory processing. Patients often describe their symptoms as deep, diffuse, unpleasant, and difficult to localize, rather than as ordinary pain or numbness. Neuroimaging findings are consistent with this view, showing functional and structural changes in regions involved in sensory integration, including thalamic networks and the postcentral gyrus.[19,30,31]

Descending dopaminergic projections from the A11 system are thought to modulate spinal sensory transmission, reflex activity, and motor excitability, while state-dependent changes in spinal flexor reflex excitability may contribute to periodic limb movements during sleep.[5,33] Thus, the clinical pattern of RLS can be understood as the expression of interacting central and spinal mechanisms, although diagnosis remains based on clinical criteria rather than routine neuroimaging or neurophysiological testing.[1,6]

CLINICAL FINDINGS AND SYMPTOMATOLOGY

The clinical picture of RLS is usually built from the patient's own description. Most patients report an urge to move the legs, but the sensation that accompanies this urge is often difficult to define precisely. It may be described as pulling, tingling, crawling, tension, discomfort, or a deep inner restlessness in the legs. Although these descriptions vary, the pattern is typically consistent: symptoms appear or become worse during rest, improve for a short time with movement, and are most troublesome in the evening or at night.[1,28,29]

In some patients, symptoms remain mild and intermittent. In others, they become persistent enough to disturb sleep, limit daily activities, and make prolonged sitting or lying still difficult. Symptoms are usually bilateral and most commonly involve the calves or thighs. However, unilateral onset, asymmetry, or spread to the arms or trunk may also occur in some patients.[34]

Periodic limb movements during sleep can accompany RLS and add to sleep fragmentation. When frequent, these movements may cause repeated nocturnal awakenings, non-restorative sleep, and daytime fatigue.[34,35]

In clinically significant cases, sleep disruption, daytime fatigue, reduced concentration, and impaired quality of life may become the main reasons for seeking medical care.[2] Symptom severity can be assessed with the International RLS Rating Scale, which is useful for grading disease severity and monitoring treatment response.[11]

DIAGNOSTIC EVALUATION

RLS remains a clinical diagnosis, grounded principally in the patient's history. Ancillary tests such as laboratory studies, neuroimaging, or polysomnography may be considered when clinically indicated, but they do not establish the diagnosis in most patients. What matters is the presence of a consistent symptom pattern: an urge to move the legs that appears or worsens during rest, is relieved by movement, and is most prominent in the evening or at night. Importantly, common RLS mimics should be considered, and the diagnosis should be made only when this symptom pattern is not more plausibly explained by another clinical condition. This pattern forms the basis of the updated International Restless Legs Syndrome Study Group diagnostic criteria.[1]

Polysomnography is not routinely required. It may be helpful when the history is unclear, when periodic limb movements during sleep need objective documentation, or when another sleep disorder is suspected. Periodic limb movements are common in RLS, but they are not diagnostic on their own. For this reason, PLMS should always be interpreted together with the patient's clinical symptoms rather than used as an isolated diagnostic marker.[1,34,35]

Laboratory testing does not confirm RLS directly, but it is useful for identifying factors that may contribute to symptoms or influence management. Serum ferritin and transferrin saturation should be assessed in patients with clinically significant RLS, because iron deficiency or reduced iron availability may affect both symptom expression and treatment planning.[17]

Peripheral neuropathy, nocturnal leg cramps, akathisia, positional discomfort, chronic venous insufficiency, arthritis, leg edema, and nonspecific musculoskeletal pain may resemble RLS. In most cases, RLS can be distinguished from these mimics by its typical pattern: symptoms worsen during rest, improve with movement, and become more prominent in the evening or at night.[1,10]

MANAGEMENT AND TREATMENT

Management of RLS should be guided by the patient's overall symptom burden, including symptom frequency, severity, sleep disruption, daytime impairment, and impact on quality of life, rather than by the diagnosis alone. Initial treatment planning should include a review of comorbid conditions, iron status, and medications that may aggravate RLS symptoms, as these factors can influence both treatment need and therapy selection.[36,37] These may include regular sleep routines, limiting prolonged inactivity when possible, reducing caffeine, alcohol, and nicotine intake, and adjusting medications that may worsen symptoms. Moderate exercise, stretching, or massage may also be considered when patients report benefit.[10,37,38]

Serum ferritin and transferrin saturation should be evaluated in patients with clinically significant RLS, because iron deficiency is a modifiable factor. In adults, iron supplementation is generally considered when ferritin is low or when transferrin saturation is reduced; intravenous iron may be appropriate in selected patients, particularly when oral iron is ineffective, poorly tolerated, or insufficient for more severe symptoms. Treatment thresholds in RLS may differ from those used for general iron deficiency.[17,36,37]

For patients requiring pharmacological treatment, alpha-2-delta ligands such as gabapentin, gabapentin enacarbil, and pregabalin are now preferred options for many adults with chronic persistent RLS, especially when sleep disturbance, pain, or prominent sensory symptoms are present.[36,37,39] Sedation, dizziness, gait instability, edema, weight gain, and renal function should be considered when selecting and dosing these agents.

Dopamine agonists, including pramipexole, ropinirole, and rotigotine, may reduce RLS symptoms in the short term, but their long-term use is limited by the risk of augmentation and impulse-control disorders.[36,40] Therefore, they should be reserved for selected patients, used at the lowest effective dose, and monitored carefully rather than presented as routine first-line long-term therapy.

Refractory RLS should prompt reassessment of the diagnosis, iron status, comorbid sleep disorders, and exacerbating medications. In selected severe cases that remain symptomatic despite standard treatment, combination therapy or low-dose opioid therapy may be considered under specialist supervision, with careful attention to adverse effects and dependence risk.[37,41]

CONCLUSION

RLS is not merely a complaint of uncomfortable legs at night. For many patients, it is a persistent sensorimotor disorder that interferes with sleep, daytime alertness, daily activities, and overall quality of life. The available evidence suggests that no single mechanism is sufficient to explain the disorder. Altered brain iron regulation, dopaminergic modulation, genetic susceptibility, basal ganglia circuitry, thalamocortical-somatosensory processing, and spinal sensorimotor excitability probably contribute to RLS in different proportions across patients. This may explain why clinical presentation varies between individuals, while the core symptom pattern remains recognizable.

Evaluation should include iron status, possible secondary causes, comorbid conditions, and medications that may worsen symptoms. Treatment should then be individualized rather than based on a single routine approach.[17,36,37] Future studies should clarify whether different biological profiles of RLS can be identified and whether these profiles can lead to more targeted diagnostic and therapeutic strategies.

Recent publications further support this individualized approach. Diagnostic accuracy data indicate that RLS screening instruments vary in performance and should be interpreted within the full clinical context.[42] Contemporary epidemiological and burden studies emphasize the global prevalence, regional variation, quality-of-life impact, psychiatric burden, and secondary comorbidity patterns of RLS.[43-47] Updated guideline/review literature and recent intravenous ferric carboxymaltose data also support systematic assessment of iron status, secondary contributors, and careful long-term treatment selection, including cautious use of dopamine agonists because of augmentation risk.[48-50]

ETHICAL DECLARATIONS

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Letter to the Editor

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The invisible burden of multiple sclerosis: neuropsychiatric presentations and clinical pharmacology challenges

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Dear Editor,

Multiple sclerosis (MS) is a chronic central nervous system disease in which inflammation, demyelination, and neurodegeneration play interconnected roles. Thanks to significant advancements in disease-modifying therapies (DMTs) over the last two decades, relapse rates have been reduced and the progression of physical disability has been slowed.[1] Traditionally, MS has been evaluated primarily through its motor, sensory, and neuro-ophthalmological manifestations. However, a reality increasingly drawing attention is that neuropsychiatric presentations such as cognitive dysfunction, depression, and anxiety frequently emerge in early disease stages, sometimes even preceding physical symptoms.[2,3] In this context, I wish to highlight this often-overlooked neuropsychiatric burden and its associated clinical pharmacology challenges.

Neuropsychiatric symptoms including depression, anxiety, cognitive impairment, fatigue, sleep disturbances, and, rarely, psychosis are among the most significant yet underrecognized MS components.[2,3] In my clinical practice, I encountered a patient with MS who initially presented with acute psychosis, highlighting the profound impact of demyelination and neuroinflammation on cortical and limbic networks.[2] Cortical demyelination, gray matter atrophy, disruption of limbic connectivity, and chronic neuroinflammation are increasingly recognized as biological contributors to these psychiatric and cognitive manifestations rather than merely psychological reactions to chronic illness.[2,3]

Clinical management becomes highly complex at the intersection of neurological and psychiatric treatments. High-dose corticosteroids used in acute relapse treatment can cause significant psychiatric side effects such as insomnia, mania, and steroid-induced psychosis.[4] These manifestations can sometimes be confused with true disease activity. Similarly, interferon-beta's association with depression and the cardiac interaction risks of sphingosine-1-phosphate (S1P) receptor modulators with specific psychotropics demand careful monitoring.[4] Conversely, sedative psychotropics (e.g., benzodiazepines) can mimic MS progression by inducing cognitive slowing and balance impairment. For this reason, both neurologists and psychiatrists should exercise caution when prescribing medications to patients with MS.

From a clinical pharmacology perspective, the concomitant use of high-efficacy DMTs and psychotropic medications deserves particular attention.[4,5] In one of my patients receiving ocrelizumab (anti-CD20) therapy, leukopenia developed shortly after clobazam was initiated for psychiatric symptoms. Although a causal relationship cannot be established based on a single observation, this case underscores the importance of close hematological monitoring and multidisciplinary pharmacovigilance when psychotropic agents are introduced in patients receiving potent immunomodulatory therapies. It should not be forgotten that these observations are based on individual clinical cases and therefore should be interpreted with caution.

In conclusion, successful MS management is not limited solely to suppressing inflammation. Early recognition of psychiatric presentations and meticulous planning of psychopharmacological interventions are essential. A strong multidisciplinary collaboration among neurologists, psychiatrists, and pharmacologists will alleviate the mental burden of the disease and minimize pharmacological morbidity. To enhance quality of life and long-term treatment success, there is an urgent need for comprehensive clinical guidelines that address this intersection.

Sincerely,

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

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Author Contributions

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