

Clinical Characteristics, and current perspectives of Kernicterus Spectrum Disorder in Palestine

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Abstract

Background:

Kernicterus spectrum disorder (KSD) includes a spectrum of acute bilirubin encephalopathy (ABE) and its long-lasting effects caused by the neurotoxicity of unconjugated bilirubin on brain areas that are particularly sensitive. The 2022 guideline from the American Academy of Pediatrics sets hour-specific risk criteria for intervention, educates parents, and sets up structured transfer plans to avoid missing or delayed therapy that can cause ABE.

This study aims to determine the neonatal presentation and treatment modalities and characterize long-term neurodevelopmental and auditory outcomes to inform prevention and resource allocation in babies diagnosed with KSD in west bank.

Methods:

We conducted a retrospective case series from 2015-2024. 10 children (≤ 10 years) were met the criteria for KSD. All available medical records were reviewed, perinatal risk factors, neonatal presentation, bilirubin levels, treatment, neurology follow up and investigations, were recorded. Ethical approval and data confidentiality were guaranteed for the descriptive analysis, which was conducted using SPSS version 29.

Results:

This case series involved 10 neonates diagnosed with KSD. The average peak TSB for hazardous jaundice was 34.7 mg/dL. Immune mediated Hemolysis was the most prevalent etiology. Global Developmental delay was the most frequent diagnosis upon diagnosis. Brain MRI, ABR was most useful conclusive ancillary modalities.

Conclusion:

KSD is still diagnosed in the west bank despite applying the updated neonatal hyperbilirubinemia screening and treatment protocols. This study highlights the importance of medical awareness and early referrals of suspected hyperbilirubinemia cases with create adequate reporting system for cases of KSD.

Introduction and literature review

Kernicterus spectrum disorder (KSD) encompasses the continuum of acute bilirubin encephalopathy (ABE) and its long-term sequelae resulting from neurotoxic effect of unconjugated bilirubin on selectively vulnerable brain structures, particularly, the basal ganglia, cerebellum and auditory pathways. The clinical presentation of KSD is highly variable and range from subtle motor, behavioral abnormalities or auditory neuropathy to classic dystonic cerebral palsy, impaired upward gaze, feeding difficulties and enamel

hypoplasia. These manifestations reflect not only the timing and severity of bilirubin exposure but also the coexisting vulnerabilities such as prematurity, hemolysis and infection. [1–3]

Although prevention strategies have reduced kernicterus in many high-resource settings, severe neonatal jaundice and KSD remain a major, unevenly distributed global health problem. The burden is disproportionally concentrated in low- and lower-middle-income countries, where delayed presentation, limited bilirubin testing, inadequate phototherapy resources, and higher prevalence of risk factors such as G6PD deficiency increase progression to ABE and KSD. These global data provide the public-health rationale for locally driven studies assessing incidence and outcome. [4–5]

Advances in prevention and early-detection strategies had refined the management of neonatal hyperbilirubinemia. The 2022 American Academy of Pediatrics guidelines emphasize universal pre-discharge bilirubin assessment, hour-specific treatment thresholds, risk-based follow-up, caregiver education, and structured handoffs to reduce delayed recognition and progression to ABE.[6] Implementation studies show these guidelines changes can substantially influence phototherapy and readmission rates. However, they also highlight the ongoing challenges of guidelines application, particularly in resource-limited settings. [6, 9]

Peak total serum bilirubin (TSB) alone is an incomplete predictor of subsequent KSD diagnosis. Evidence from prospective and systematic reviews showed improved accuracy when TSB is interpreted alongside clinical risk factors (prematurity, hemolysis and sepsis), bedside neurologic assessment, and early auditory testing. Brain MRI has limited early sensitivity in the neonatal period but remains valuable for later confirmation. These findings support multimodal diagnostic approach and follow-up rather than reliance on single biomarker. [1–2, 10–12]

G6PD deficiency remains one of the most important risk factors for severe hyperbilirubinemia and KSD worldwide, with recent reviews demonstrating markedly increased odds of severe jaundice in affected neonates, supporting targeted newborn screening in at-risk populations. Other modifiable contributors include delayed recognition of jaundice, breastfeeding, weight loss, and limited access to effective phototherapy or timely exchange transfusion. [13–16]

Emerging evidence of selective auditory and white-matter vulnerability following severe neonatal hyperbilirubinemia supports early audiologic follow up and neurodevelopmental assessment and rehabilitation for affected infants and justifies local prospective studies to determine the incidence of KSD in our setting, validate multimodal predictive algorithms, and assess long-term neurodevelopmental outcomes [12, 17–18].

Methodology

Study Design

This study is a retrospective case series describing all children diagnosed with kernicterus spectrum disorder (KSD) in Palestine over a ten-year period. The study aimed to characterize epidemiological features, neonatal risk factors, acute clinical presentation, management of hazardous hyperbilirubinemia, neurodevelopmental outcomes, and neurodiagnostic findings.

Study Period

Medical records were reviewed for the period from January 2015 to December 2024, ensuring inclusion of all eligible cases diagnosed with KSD in participating centers and neurology clinics.

Study Setting

Data were collected from three major tertiary pediatric and neurology centers in West Bank and Jerusalem, including; Makassed Charitable Hospital in Jerusalem, Palestine Red Crescent Society Hospital in Hebron and Palestine Medical Complex in Ramallah. These institutions serve as national referral centers for pediatric neurology and receive patients from multiple cities across Palestine.

Study Population

All children equal or less than 10 years of age who presented to pediatric wards or neurology outpatient clinics with neurological symptoms warranting evaluation for KSD and subsequently diagnosed with KSD. Ten infants met the final inclusion criteria and had sufficient documentation for analysis (N = 10).

Eligibility Criteria

Inclusion Criteria

Children were included if they met at least one of the following criteria: (1) a history of severe neonatal hyperbilirubinemia, defined as a peak total serum bilirubin (TSB) > 20 mg/dL or the need for exchange transfusion; (2) clinical features suggestive of bilirubin-induced neurologic dysfunction, with two or more manifestations such as extrapyramidal symptoms (e.g., dystonia or athetosis), other movement abnormalities (spasticity or hypotonia), gaze abnormalities, sensorineural hearing loss, intellectual disability, or enamel dysplasia of the deciduous teeth; or (3) a neuroimaging-based diagnosis, specifically MRI findings showing bilateral globus pallidus and/or subthalamic nucleus abnormalities in the context of severe neonatal hyperbilirubinemia.

Exclusion Criteria

Children were excluded if they: (1) were born at < 35 weeks' gestational age; (2) had a neurological disorder known to affect the basal ganglia (e.g., glutaric acidemia type II, pyruvate dehydrogenase deficiency, Hallervorden–Spatz disease, neurofibromatosis type I or carbon monoxide poisoning).

Sampling Method and Case Identification

Cases were identified through: electronic medical record searches, neurology clinic registries and discharge coding for kernicterus, bilirubin encephalopathy, or cerebral palsy associated with hyperbilirubinemia. All available and complete records meeting inclusion criteria were included (total sample = 10). No sampling or case selection beyond eligibility criteria was performed.

Data Collection and Variables

Data were collected retrospectively using a structured abstraction form and included demographic characteristics (gestational age, birth weight, sex, mode of delivery, maternal age, and place of origin), neonatal hyperbilirubinemia details (peak bilirubin level, age at peak TSB, etiology of hemolysis, and associated non-hemolytic risk factors), acute neurological signs during neonatal admission, and management of severe jaundice, including phototherapy, exchange transfusion, IVIG, and PRBC transfusion. Follow-up data included long-term neurological, developmental, and sensory outcomes, as well as neurodiagnostic evaluations such as brain MRI, CT scans, and auditory brainstem response (ABR) assessments. Because documentation varied across cases, denominators differ between variables in the Results.

Statistical Analysis

Statistical analysis was performed using SPSS version 29 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the cohort. Categorical variables were reported as frequencies and percentages, while continuous variables were summarized using mean $\pm$ standard deviation (SD) and median with interquartile range (IQR), depending on their distribution. Given the small sample size ($n = 10$) and variability in data completeness, no inferential statistical tests were conducted.

Ethical Considerations

Ethical approval

for this study was granted by the Al-Quds University Research Ethics Committee and the institutional review boards of Makassed Charitable Hospital, the Palestine Red Crescent Society Hospital, and the Palestine Medical Complex. All data were fully anonymized before analysis, and no identifiable patient information was collected or stored.

Results

Cohort Demographics and Baseline Characteristics

This case series included 10 neonates diagnosed with kernicterus, of whom 6 (60%) were males and 4 (40%) were females. The mean gestational age (GA) at birth was 37.4 ± 1.5 weeks (range 35–40 weeks), and the mean birth weight was 2577 ± 462.8 grams. Delivery mode was evenly distributed, with 5 infants (50%) born vaginally and 5 (50%) delivered by caesarean section. Detailed demographic and clinical characteristics for the cohort are shown in **Table 1**.

Patients originated from five cities across West Bank. The highest proportion was from Hebron (3 infants, 30%), followed by Tulkarem (2 infants, 20%), Jenin (2 infants, 20%), Jericho (2 infants, 20%), and Ramallah (1 infant, 10%).

All infants had hazardous hyperbilirubinemia, with a mean peak total serum bilirubin (TSB) of 34.7 mg/dL (range 21.8–48 mg/dL) reached at a median age of 5 days (IQR: 3.0–7.5). The median age at readmission was around 6 ± 2.3 days ($n = 8$). Readmission from home was documented in eight of nine infants (88.9%).

The diagnosis of kernicterus was confirmed at a median age of 6 months (IQR: 2.5–33), though the timing varied widely (range: 2–36 months; mean: 16.1 ± 15.1 months), indicating a skewed distribution and reflecting variability in timing of recognition and referral.

Hemolytic disease was identified in 8 of 10 infants (80%) with hazardous hyperbilirubinemia. Among these, 3 infants (30%) had ABO incompatibility with a positive direct anti-globulin (Coombs) test, 3 infants (30%) had Rh isoimmunization, and 2 infants (20%), both from the same monozygotic twin pair, were diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In 2 infants (20%), no underlying etiology or contributing factor could be identified based on available records. All infants (100%, 10/10) received phototherapy, nine (90%, 9/10) underwent exchange transfusion and two (28.6%, 2/7) received Intravenous immunoglobulin (IVIG). Only 2 infants (33.3%, 2/6) required packed red blood cell (PRBC) transfusions.

Among infants with available clinical data, the most frequently observed acute neurologic signs on admission were poor sucking (66.7%, 6/9), lethargy (62.5%, 5/8), and seizure (55.9%, 5/9). Infants with seizures reached peak bilirubin levels earlier (median: 4 days vs. 7 days) and had higher median birth weights (3000 g vs. 2275 g) than those without. Other features, such as hemolysis, infection, and dehydration, were also noted in subgroups.

A summary of etiologies, clinical manifestations during neonatal admission, and management modalities is provided in Table 2. Additional analyses comparing peak bilirubin levels, age at peak bilirubin, and birthweight stratified by clinical signs are available in **Supplementary Table 1**.

Table 2
Acute Clinical Presentation, and Neonatal Management of Infants with Kernicterus (N = 10)

Category	Variable	n / N	%
Etiology	ABO Incompatibility (DAT +)	3 / 10	30
	Rh Isoimmunisation	3 / 10	30
	G6PD Deficiency	2 / 10	30
	Not identified	2 / 10	30
Clinical picture during neonatal admission	Poor Sucking	6 / 9	66.7
	Absent Moro reflex	2 / 8	25
	Seizure	5 / 9	55.9
	Lethargy	5 / 8	62.5
	Opisthotonus	2 / 8	25
	Hypertonia	2 / 8	25
	Hypotonia	3 / 8	37.5
	Shrill cry	3 / 6	50
	Infection	3 / 8	37.5
	Dehydration	2 / 8	25
Modality of treatment	Phototherapy	10 / 10	100
	Exchange Transfusion	9 / 10	90
	IVIG	2 / 7	28.6
	PRBC transfusion	2 / 6	33.3

Values are presented as n/N available (%). Percentages were calculated using the number of infants with documented data for each variable. Denominators vary because of missing information in the medical records. Abbreviations: DAT, direct anti-globulin test; IVIG, intravenous immunoglobulin; PRBC, packed red blood cells.

Neurological and developmental follow-up findings revealed a broad spectrum of long-term impairments among affected infants. The distribution of these findings and manifestations is summarized in Table 3.

Follow-up data were available for most infants, revealing a high prevalence of long-term impairment. Global developmental delay (including motor, intellectual, and/or language) affected eight infants (88.9%, 8/9). Extrapyramidal symptoms were prominent and presented in 5 of 9 infants (55.6%). The most common manifestation was dystonia, observed in 4 infants (44.4%). Chorea and athetosis were each

documented in 1 infant (11.1%), occurring together in the same patient. Hypo- and hypertonia were also prominent findings and represented a 50% of cases with disturbance in tone. Sensorineural hearing loss was observed in four cases (44.4%, 4/9). Both vision impairment and upward gaze palsy were observed in only one case (11.1%, 1/9). Persistent seizure disorder was evident in 1 case (11.1%).

Additional findings including enamel dysplasia was documented in 2 of 9 infants (22.2%). Oral motor abnormalities including swallowing difficulties and dysarthria were observed in 12.5% and 11.1% respectively.

Table 3
Neurological, Developmental, and Investigative Findings Among Infants with Kernicterus

Outcome Category	Variable	n / N	%
Developmental outcome	Global developmental delay	8 / 9	88.9
	SNHL	4 / 9	44.4
	Vision impairment	1 / 9	11.1
	Dysarthria	1 / 9	11.1
Extrapyramidal findings	Any extrapyramidal sign	5 / 9	55.6
	Dystonia	4 / 9	44.4
	Chorea	1 / 9	11.1*
	Athetosis	1 / 9	11.1*
Seizure disorder	----	1 / 9	11.1
Motor tone abnormalities	Hypertonia	4 / 8	50
	Hypotonia	5 / 10	50
Cranial nerves / Brainstem findings	Paralysis of upward gaze	1 / 9	11.1
	Swallowing difficulties	1 / 8	12.5
Other criteria	Enamel dysplasia	2 / 7	22.2
Investigations (Neuroimaging and hearing assessment)			
	Abnormal brain MRI	4 / 8	50
	Abnormal brain CT scan	0 / 3	0
	Abnormal ABR	4 / 6	66.7

Values are expressed as n/N available (%). Denominators vary due to missing documentation in follow-up records. Abbreviations: ABR, Auditory brainstem response; CT, Computed tomography; MRI, Magnetic

resonance imaging, SNHL, Sensorineural hearing loss.

** Chorea and athetosis occurred in the same infant.*

Neuroimaging was performed for most infants and provided key diagnostic insights as abnormalities were common. Brain MRI was available for 8 children and was abnormal in 40%, with reported findings including classic globus pallidus signal abnormalities and additional white matter changes when reported. This subgroup had higher median peak TSB levels (38.0 mg/dL vs. 30.0 mg/dL) compared with others. Cranial CT scan was performed in 3 infants, all of whom had normal scans.

Hearing evaluation using Auditory Brainstem Response (ABR) was completed in 6 infants, among whom 4 (66.7%) had evidence of sensorineural hearing loss, ranging from unilateral involvement to profound bilateral loss. The remaining infants had normal or inconclusive auditory responses.

Discussion

This study represents the detailed characteristics, early neonatal course, etiologies, neurodevelopmental outcomes, and findings on investigations in infants diagnosed of KSD in Palestine over a ten-year period. Findings revealed gaps in early recognition of severe neonatal jaundice and post-discharge follow up, which leads to the known long-term morbidity. Being the first organized assessment of KSD across West Bank, it sets the need for a structured surveillance and reporting system to address this preventable condition. Results in this study underscores that kernicterus continues to occur in Palestine despite advances in neonatal care and established neonatal guidelines.

The geographical clustering of cases - especially in Hebron and northern West Bank - likely reflects the differences in access to early jaundice screening, parental awareness and follow-up. Studies from low- and middle-income countries with limited resources had reported similar data, where disparities in access to healthcare system remain a key determinant of developing kernicterus. [11, 23]

The median age of diagnosis in our cohort was 6 months, this aligns with reports from resource-limited settings, where KSD is often recognized only after developmental delay, motor abnormalities, or auditory deficits become clinically evident. [1, 24] This underscores the ongoing gap in early recognition of acute bilirubin encephalopathy during the neonatal period and timely neurodevelopmental surveillance after discharge.

Neonatal History and Morbidity

The extremely elevated peak bilirubin levels observed in this cohort (mean 34.7 mg/dL) are consistent with most reports indicating that hazardous hyperbilirubinemia continues to occur despite advances in screening and early postnatal care [19, 26–27] Very high bilirubin levels, particularly values higher than 25 mg/dL are strongly linked to acute bilirubin encephalopathy (ABE) and long-term neurodevelopmental problems, especially when diagnosis or treatment is delayed [19]. High rate of readmissions seen in this

cohort reflects a broad global pattern where early discharge without reliable follow-up leads to delayed detection of rapidly rising bilirubin levels. [5–6]

Around half of infants (55.9%) presented with seizures, often alongside sepsis, supporting the existing evidence that systemic infection exacerbates bilirubin neurotoxicity, which emphasize the ongoing susceptibility of newborns where early discharge and missed or unsteady follow-up are common, leading to significant neurological injury before timely intervention. [27]

Underlying Diagnoses and Contributing Conditions

Hemolytic conditions (e.g., ABO incompatibility, Rh isoimmunization, or enzymatic deficiency) were the predominant underlying cause in this cohort (80%). This finding mirrors global epidemiological patterns in which hemolysis is the leading cause of severe neonatal hyperbilirubinemia worldwide. [25–28]

Reports from middle-income regions showed a resurgence of Rh-mediated disease, reflecting gaps in antenatal maternal screening tests and incomplete anti-D prophylaxis. [29] Identification of G6PD deficiency in two affected infants, both twins, is consistent with its high prevalence in the Middle East and its major role in precipitating rapid bilirubin rise and kernicterus when present. [30–31]

Approximately, 20% of infants had no clear etiologic cause for severe hyperbilirubinemia, this was described in the literature as “idiopathic severe hyperbilirubinemia,” where genetic susceptibility, breastfeeding jaundice, or subclinical hemolysis may contribute. [22]

The universal requirement of phototherapy and the high rates of exchange transfusion (90%) in this cohort reflect the severity of presentation and aligns with global data indicating that late presentation and hemolytic causes necessitate intensive interventions. [6] These findings highlight an urgent need for strengthened antenatal screening, early bilirubin monitoring, and targeted prevention strategies in high-risk populations.

A substantial number of infants presented with clinical features of acute bilirubin encephalopathy (ABE), including lethargy, opisthotonus, abnormal Moro reflex, seizures, and high-pitched cry.[32, 34–35] Many infants were readmitted after early discharge, reflecting inadequate post-discharge follow-up and delayed recognition [5]

The universal need for phototherapy treatment and the high rate of exchange transfusion (90%), reflect the severity at presentation in the neonatal period, this aligns with global data indicating that late presentation and hemolytic causes often require aggressive interventions. These findings emphasize the crucial need for strict antenatal screening, early bilirubin monitoring, and targeted preventive strategies in infants at high risk. The management approach observed is consistent with current recommendations for aggressive management when treatment thresholds are reached or neurologic signs are present.[6, 34] The use of IVIG in immune-mediated hemolysis and PRBC transfusion in anemic patients also aligns with management strategies outlined in most neonatal guidelines.[6, 35]

Neurological and Developmental Outcomes

Neurodevelopmental follow-up in our cohort disclose a high burden of long-term impairment, consistent with evidence that kernicterus remains a major cause of neurodevelopmental disability despite advances in preventive neonatal care and practice [19, 32]

Nearly, all infants demonstrated global developmental delay, in combination with extrapyramidal features, reflecting the characteristic basal ganglia injury associated with chronic bilirubin encephalopathy. [32–33, 36–37] Dystonia, was the most frequent finding, which is widely described as the hallmark motor feature of kernicterus, while choreoathetoid movements occur less frequently and indicate extensive basal ganglia involvement. [33, 38]. Coexistence of different extrapyramidal signs reflects more severe presentation. [32–33]

Sensorineural hearing loss affected more than half of infants with KSD, reinforcing auditory neuropathy spectrum as a sensitive marker of bilirubin neurotoxicity, even when motor findings are vary. [32–33]

Less frequent manifestations (e.g., enamel dysplasia, upward gaze palsy and vision impairment) illustrate multisystem sequelae of severe hyperbilirubinemia. [32, 36, 39] Overall, this pattern underscores the lasting consequences of delayed recognition and inadequate early management of severe neonatal jaundice.

Investigations

Neuroimaging findings in this study are consistent with the known radiologic characteristics of bilirubin-induced neurologic injury. Eight infants underwent MRI, globus pallidus (GP) signal abnormalities were the main finding, aligning with evidence identifying basal ganglia injury as the hallmark of kernicterus. [2, 40–44] Cranial CT scan was uniformly normal, underscoring its limited sensitivity in this context.

Hearing assesment using the Auditory brainstem response (ABR) revealed sensorineural hearing loss (SNHL) in approximately two-thirds of tested infants, consistent with literature demonstrating the increased vulnerability of the auditory pathway to bilirubin toxicity and contributing to the diagnosis of auditory neuropathy spectrum disorder (ANSD) which may precede or occur independently of motor abnormalities defined as auditory-predominant KSD. [3, 32–33, 45] This reinforces the importance of routine auditory screening in infants with significant hyperbilirubinemia, even when neurological examination or neuroimaging findings are inconclusive

Strengths and Limitations

A key strength of this study is its ability to follow the course of infants with kernicterus across the continuum of care - from the neonatal period through long-term neurological follow-up and neuroimaging. This comprehensive approach provides a valuable insight into disease progression, particularly in a resource-limited setting where continuity of care can be challenging. Careful chart review and confirmation of neurodevelopmental assessments further enhanced the accuracy and reliability of the findings. Additionally, it this study focuses on a real-world gap between recommended strategies and their implementation.

Several limitations should be acknowledged. The sample size was small, reflecting the rarity of kernicterus, and inevitably limits the generalizability of the results. Some clinical and follow-up variables were missing, which may have affected certain estimates. As a retrospective study, the work relied heavily on existing documentation, and variability in record completeness - particularly regarding early bilirubin monitoring and hearing assessments - posed challenges.

Despite these constraints, the study offers rare contemporary data from a setting where kernicterus remains under recognized. It highlights the urgent need for stronger systems for neonatal jaundice surveillance, early intervention, and structured long-term follow-up and reporting of suspected case of KSD.

Conclusion and Recommendations

Severe hyperbilirubinemia remains a major and largely preventable cause of mortality and long-term neurodevelopmental disability in low- and middle-income countries. The burden is likely to be exacerbated by delayed recognition and limited access to timely, evidence-based interventions that routinely available in high-resource settings.

Addressing these gaps requires strengthened international collaboration to improve epidemiological surveillance and to support the development of and effective technologies for managing hyperbilirubinemia. At the national level, efforts should focus on enhancing maternal and antenatal education, early identification of high-risk infants, adequate resourcing of neonatal care services and implementation of updated relevant clinical guidelines.

Abbreviations

KSD

Kernicterus Spectrum Disorder

ABE

Acute bilirubin encephalopathy

TSB

Total serum bilirubin

BIND

Bilirubin induced neurologic dysfunction

ANSD

Auditory neuropathy spectrum disorder

Declarations

Clinical Trial: Not Applicable

Consent for publication: Not applicable.

Funding Declaration: This research didn't receive external funding

Ethics Approval: Ethical approval was obtained from the Institutional Review Board of Al-Quds University. This study was conducted in accordance with the Declaration of Helsinki

Due to the retrospective nature of the study and the use of fully anonymized data, the requirement for informed consent was waived by the respective ethics committees. **Ref#: Re1-22-024**

Competing interests: The authors declare that they have no competing interests..

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contribution: Ahmed Khammash and Mohammad Ghannam contributed equally to this work and share first authorship. Ahmed Khammash conceptualized and designed the study, had full access to all data, and takes responsibility for the integrity and accuracy of the data. He supervised data collection, performed data interpretation, and drafted the manuscript. Mohammad Ghannam contributed to study design, case identification and data acquisition, data analysis, and manuscript drafting.

Hatem Khamash served as the corresponding author and contributed to study supervision, clinical oversight, and critical revision of the manuscript.

Motee Abu Awad contributed to overall study supervision and provided clinical guidance throughout the research process.

Motee Ashhab, Hany Abu Eita, Osama Atawneh contributed to case identification and selection from clinical records, participated in data acquisition, and provided neurological interpretation of the cases. They also contributed to critical revision of the manuscript, particularly the discussion section.

Jamal Amireh, Hamza Aboueita, Hamza Sondoqah, and Ahmad Awies contributed to clinical data acquisition, data entry, and literature review.

All authors contributed to manuscript revision, approved the final version, and agree to be accountable for all aspects of the work.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table

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