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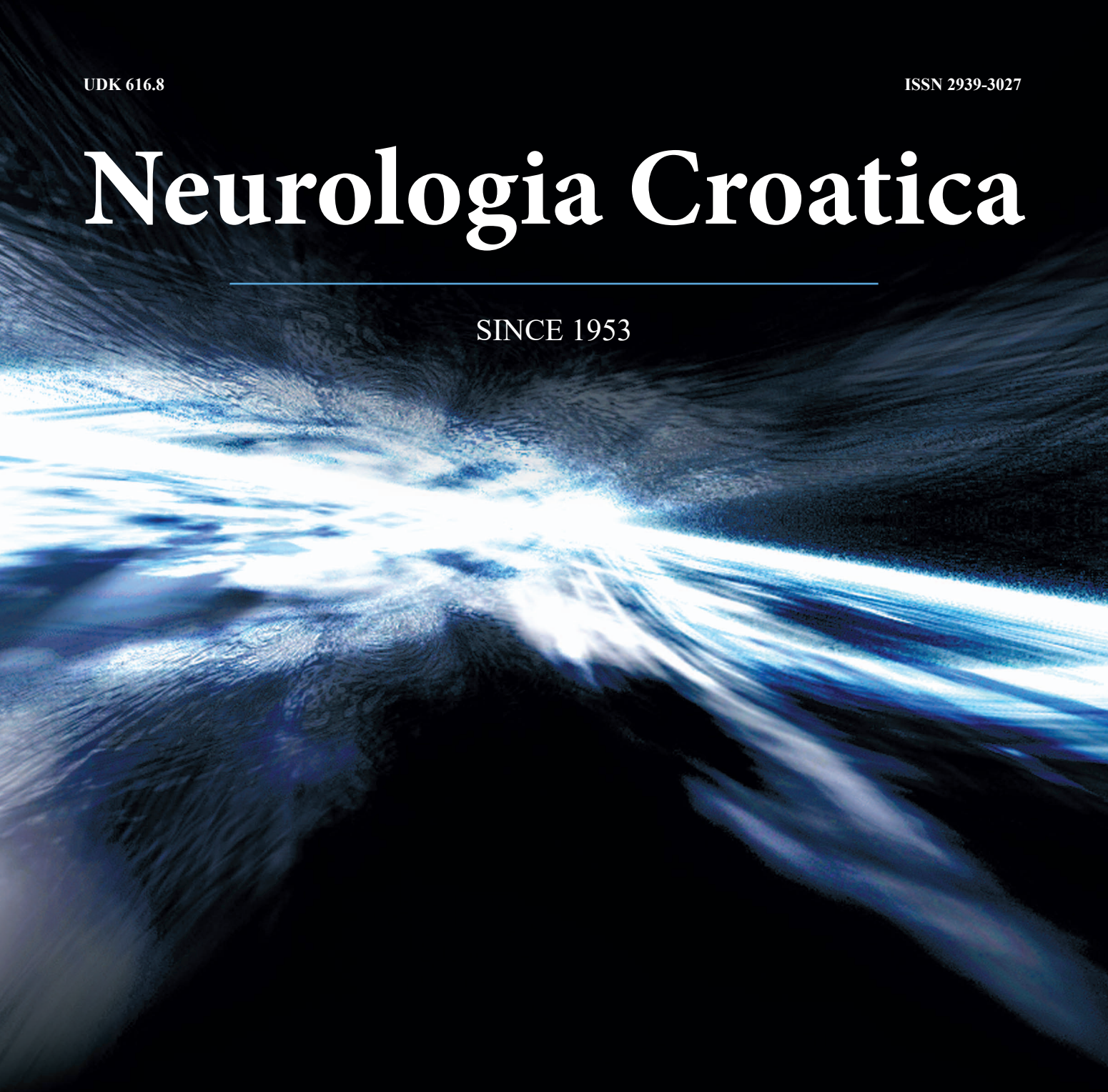

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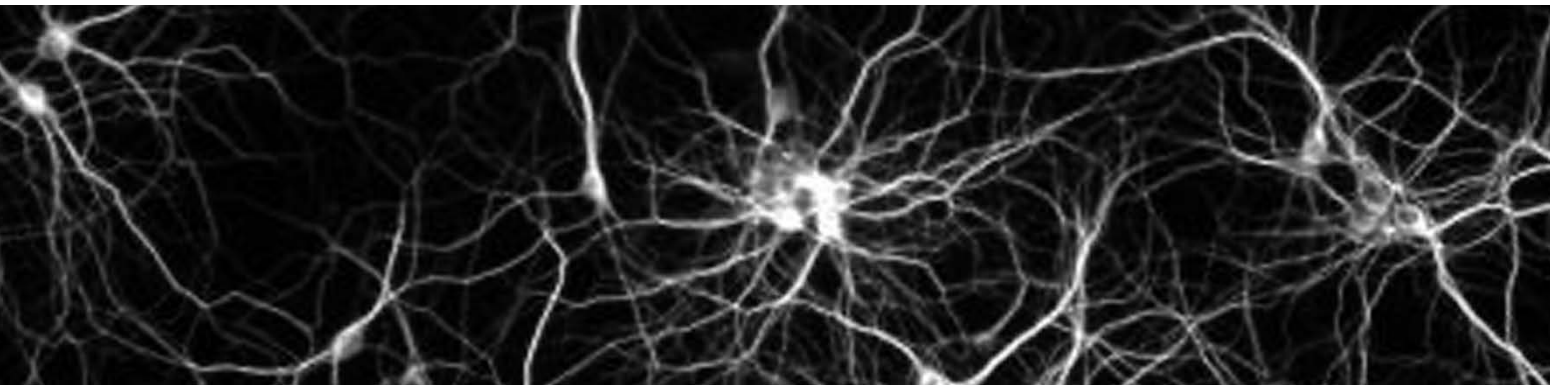


Editorial

Neurological practice continues to evolve at the intersection of expanding diagnostic capabilities and a growing awareness of diverse disease mechanisms that may compromise the nervous system. The contributions presented in this issue of *Neurologia Croatica* highlight this dynamic landscape through four thematically distinct yet conceptually connected case-based investigations. Together, they underscore the heterogeneity of neurological disorders and the importance of refined diagnostic approaches capable of capturing early or atypical manifestations.

The first paper examines the diagnostic challenge of acute sensory polyradiculoneuropathy, emphasizing the limitations of conventional electrophysiological techniques in the early stages of immune-mediated root pathology. In the presented case, standard electromyoneurography failed to confirm the clinical suspicion during the acute phase, whereas targeted assessment of lumbosacral dorsal roots through transcutaneous electrical stimulation identified distinct abnormalities. The subsequent detection of anti-GD1a antibodies and eventual evolution into chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) further supports the immune basis of the condition. This work underscores the relevance of advanced reflex-based electrophysiological methods for the timely identification of selective sensory root involvement–an approach that may significantly influence early therapeutic decisions.

A second contribution expands the clinical spectrum of SMART (Stroke-like Migraine Attacks after Radiation Therapy) syndrome, a rare delayed complication of cranial irradiation. The authors describe an 18-year-old patient with prior treatment for glioblastoma who developed migraine-like symptoms, hemiparesis, and seizures. Notably, MRI revealed not only the characteristic unilateral cortical enhancement but also subcortical grey matter involvement, a feature not traditionally associated with SMART syndrome. The presence of cerebrospinal fluid leukocytosis further challenges existing diagnostic assumptions, illustrating that inflammatory CSF profiles do not preclude this diagnosis. The possible role of alcohol consumption as a precipitating factor broadens the discussion about triggers and pathophysiological mechanisms. This case highlights the need for ongoing refinement of diagnostic criteria and improved recognition of atypical radiological and clinical patterns in post-radiation neurological syndromes.

The third article provides novel insights into diabetic striatopathy (DS) from a cognitive-behavioral perspective. Traditionally characterized by hyperkinetic movement disorders, DS has rarely been investigated for its impact on cognition. Through systematic neuropsychological assessment of five patients, the authors demonstrate that DS may involve variable deficits in attention, executive function, memory, and language, alongside behavioral symptoms such as apathy, depression, and obsessive tendencies. Importantly, visuospatial functions remained preserved, suggesting selective vulnerability of specific corticostriatal circuits. By synthesizing their findings with existing literature, the authors propose that the cognitive-behavioral profile of DS–typically milder than in other striatal disorders–reflects the acute and potentially reversible nature of the underlying metabolic insult. This work expands the clinical understanding of DS beyond its classical motor

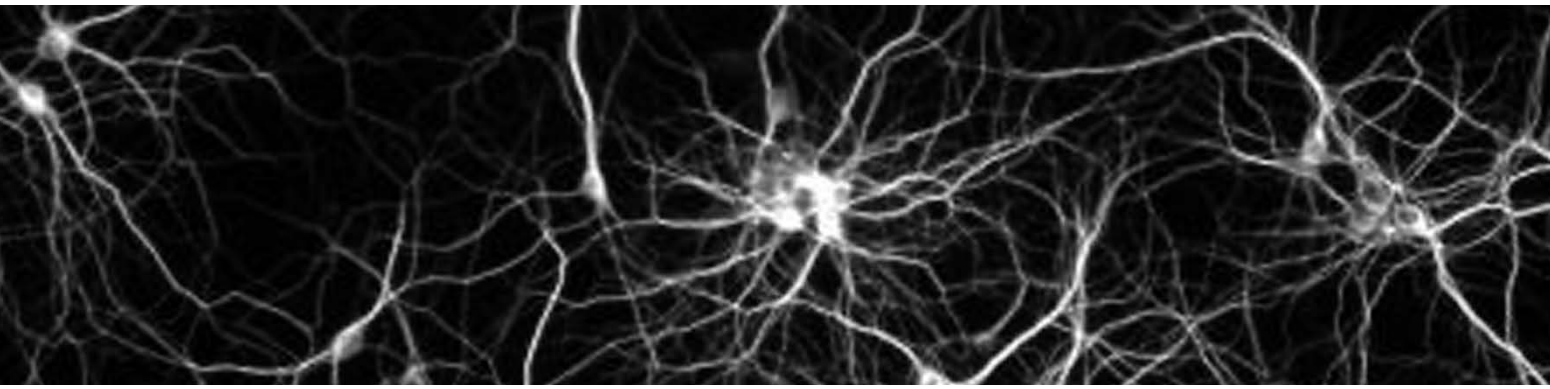
manifestations and highlights the importance of comprehensive neuropsychological evaluation in metabolic movement disorders.

The final contribution describes post-infectious small fiber neuropathy (SFN) following laboratory-confirmed influenza B infection. In the reported patient, the close temporal relationship between infection and symptom onset, combined with preserved large fiber function, strongly suggests an immune-mediated mechanism. The case reinforces the need for clinical vigilance in identifying post-viral neuropathic complications, especially given the chronicity of symptoms and impact on quality of life despite symptomatic pharmacologic therapy. As viral infections remain a common trigger of immune-mediated neurological disorders, this report contributes to the expanding recognition of SFN as a significant and often prolonged post-infectious entity requiring multidisciplinary management.

Across these four papers, several unifying themes emerge. First, the importance of early and targeted diagnostic strategies is evident–from advanced electrophysiological techniques in radiculopathies to refined neuroimaging interpretation in SMART syndrome. Second, the cases highlight the complex interplay of immune-mediated, metabolic, and post-therapeutic mechanisms, illustrating how diverse etiologies can produce overlapping or evolving neurological phenotypes. Finally, the studies reaffirm the value of detailed clinical observation, comprehensive assessment, and interdisciplinary collaboration in characterizing rare or under-recognized neurological conditions.

We hope that the contributions in this issue will stimulate further discussion and research into the diagnostic and pathophysiological nuances of these disorders, ultimately enhancing patient care through earlier recognition and more targeted intervention strategies.

Magdalena Krbot Skorić
Deputy Editor



Early electrophysiological confirmation of acute sensory polyradiculoneuropathy: a case report

Julija Rimac[1], Biserka Kovač[2,3], Aleksandra Šimić[1], Tihana Gilman Kuric[2,4]

ABSTRACT – *Objectives*: Sensory polyradiculoneuropathy is an immune-mediated disorder affecting the peripheral nervous system. Conventional electrophysiological methods often lack the specificity and sensitivity required for definitive diagnosis. However, evaluating muscle reflexes mediated by the lumbosacral roots enables assessment of the functional integrity of both dorsal and ventral spinal roots, as well as the corresponding spinal cord segments. *Case description:* We report the case of a 76-year-old female patient with a history of sensory axonal polyneuropathy and lumbar spinal canal stenosis. She presented with an acute onset of ataxia and severe paresthesia in the lower extremities, without motor weakness. Clinical findings were suggestive of polyradiculoneuropathy. Standard electromyoneurography (EMNG) performed during the acute phase failed to confirm the diagnosis. However, evaluation of dorsal lumbar root function upon admission revealed impaired excitability and conduction in multiple sensory spinal roots, while stimulation of the ventral roots produced responses within expected parameters. The patient received symptomatic treatment and showed good recovery. Subsequent testing revealed positive anti-GD1a antibodies. Ten months later, she was re-admitted with clinical and electrophysiological deterioration consistent with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). She was treated with pulsed corticosteroid therapy, leading to significant clinical improvement and resolution of ataxia. *Conclusion*: Reflex muscle responses elicited via transcutaneous electrical stimulation (TES) of the lumbosacral roots may represent a valuable tool for the early detection of autoimmune polyradiculoneuropathies. This technique has the potential to identify isolated lesions affecting the sensory spinal roots.

Keywords: early detection of disease, electrophysiology, polyradiculoneuropathy, spinal nerve roots, transcutaneous electric nerve stimulation

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INTRODUCTION

Sensory polyradiculoneuropathies are inflammatory disorders of the peripheral nervous system, mediated by immune mechanisms. The primary pathophysiological changes occur in the proximal segments of the spinal nerves and their roots (1,2). Standard electrophysiological testing lacks both the specificity and sensitivity required to reliably detect proximal lesions, especially during the early stages of the disease. Techniques that rely on peripheral nerve stimulation provide only indirect and nonspecific information regarding the functional integrity of the spinal roots (1,2). Diagnostic accuracy is further challenged by the presence of comorbid conditions that can also cause polyneuropathy.

F-waves, which assess the integrity of the monosynaptic reflex arc, evaluate only motor neurons, motor spinal roots, and peripheral motor nerves (2,3). Because they reflect conduction across a broad segment of the peripheral nerve, F-waves are limited in their ability to detect pathology localized to the spinal roots. Similarly, the H-reflex assesses the entire monosynaptic reflex arc via peripheral stimulation, but its clinical utility is restricted due to technical difficulties associated with reliably stimulating sensory nerve fibers (4). Somatosensory evoked potentials (SSEPs) evaluate conduction from the peripheral stimulation site to the sensory cortex; however, the sensory roots constitute only a small portion of the somatosensory pathway, limiting the diagnostic value of SSEPs for root-level lesions.

Transcutaneous electrical stimulation (TES) of the lumbosacral roots at the thoracolumbar junction allows for direct and simultaneous stimulation of both sensory and motor spinal roots (5). This makes TES a more sensitive and specific modality for detecting polyradiculoneuropathy. By analyzing posterior root muscle reflexes (PRMR) and anterior root muscle responses (ARMR), TES provides the means to electrophysiologically confirm polyradiculoneuropathy. Combined interpretation of these reflex responses may offer a reliable indicator of sensory polyradiculoneuropathy.

CASE DESCRIPTION

We present the case of a 76-year-old female patient with a medical history notable for sensory axonal polyneuropathy of unknown etiology and lumbar spinal canal stenosis from L3 to S1. She was admitted to the emergency neurology department due to progressive paresthesia in the lower limbs, gait instability, and recurrent falls. Her symptoms had begun approximately ten days prior to presentation.

Roughly six weeks before admission, the patient had received her second dose of a COVID-19 vaccine. She reported no recent signs or symptoms of infection. Neurological examination revealed normal cranial nerve function and preserved motor strength in the upper extremities. In the lower limbs, gross motor strength was intact; however, patellar reflexes were diminished, and Achilles reflexes were bilaterally absent. Vibration sense was reduced in the lower legs and feet. Romberg's sign was positive, and her gait was ataxic.

Brain MRI showed no structural abnormalities. Laboratory studies ruled out acute infection, and serum protein levels were within normal ranges. Cerebrospinal fluid (CSF) analysis revealed normal cell counts with mildly elevated protein levels (proteinorachia 0.60 g/L). The CSF-to-serum IgG index was elevated. A comprehensive systemic work-up yielded no pathological findings.

Standard electromyoneurography (EMNG), performed on days 10 and 15 following symptom onset, did not support a diagnosis of polyradiculoneuropathy. Findings were consistent with sensory axonal polyneuropathy of the lower extremities and polytopic radiculopathies affecting the lumbar segments. SSEPs of the tibial nerve were within normal limits.

Reflex responses in the lower extremities were further evaluated using TES of the dorsal spinal roots. In all tested muscles (8/8), PRMR demonstrated significantly reduced amplitudes and/or prolonged latencies. In contrast, ARMR elicited via stimulation of the ventral roots displayed latencies comparable to those of healthy controls.

The patient was found to have impaired glucose tolerance, but additional metabolic, paraneoplastic, and autoimmune etiologies were excluded. She was treated with symptomatic therapy, which led to marked improvement in her ataxia.

Subsequent serological testing revealed positivity for anti-GD1a antibodies.

Ten months later, the patient was re-evaluated due to a relapse characterized by worsening sensory symptoms in the lower limbs and acute gait deterioration. Repeat EMNG revealed findings consistent with a sensorimotor demyelinating polyradiculoneuropathy, leading to a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy

(CIDP). She was treated with pulsed corticosteroid therapy, which resulted in clinical improvement and resolution of her ataxia.

DISCUSSION

In a significant proportion of patients with polyradiculoneuropathies, both EMNG and CSF analyses may yield negative results during the early stages of the disease (1,2,6,7). In our patient's case, initial EMNG and CSF findings did not support the clinical diagnosis of polyradiculoneuropathy. However, anti-GD1a antibodies were subsequently detected. Following clinical deterioration ten months later,

EMNG findings became consistent with a chronic sensorimotor demyelinating polyradiculoneuropathy.

During the initial phase, the patient underwent a modified diagnostic approach involving TES of the lumbosacral roots, as described by Professor Minassian (8). PRMR and ARMR were recorded bilaterally in four muscle groups of the lower extremities. The parameters of the muscle responses were compared against reference values for PRMR established in a study of 30 healthy subjects (9). An example of an evoked PRMR exhibiting normal characteristics is shown in Figure 1. In our patient, all eight tested lower limb muscles, PRMRs showed prolonged latencies and/or significantly reduced amplitudes. In contrast, ARMR latencies exhibited expected characteristics when compared with those of healthy controls in a previous study (9).

Due to technical limitations, maximal ARMR amplitudes were not analyzed; however, an increase in amplitude with rising stimulation intensity was observed. The recorded ARMR characteristics were consistent with the expected findings in the study assessing spinal reflex excitability (10).

Direct stimulation at the spinal root level revealed multiple functional lesions affecting the proximal segments of peripheral nerves, allowing a diagnosis independent of the patient's pre-existing chronic sensory polyneuropathy. PRMR analysis enables assessment of the entire reflex arc proximal to the dorsal root ganglion, including sensory roots, spinal gray matter, motor neuron activation, motor roots, and proximal segments of peripheral nerves (11). Simultaneous stimulation of multiple spinal

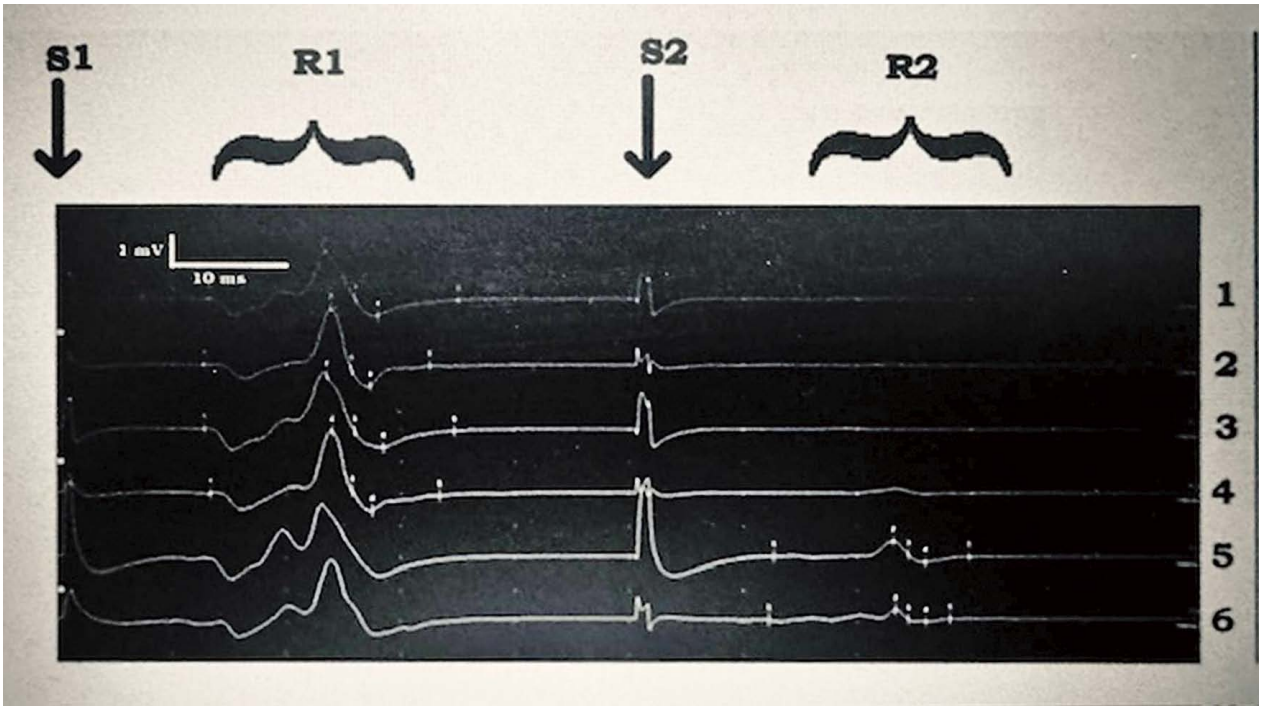

Fig. 1. *Normal finding: Eliciting PRMR (recordings 1, 2, and 3) and ARMR (recordings 4, 5, and 6) by delivering two electric stimuli over the skin of the cauda equina with an interstimulus interval of 50ms. Recordings were done in the hamstring muscles of the right leg (recordings 1, 3, and 5) and left leg (2, 4, and 6). The intensity of stimuli was increased from 90 mA (recordings 1 and 2) to 110 mA (recordings 5 and 6). By increasing stimuli intensity, ARMR appeared (recordings 2, 4, 5, and 6). S1 – first stimulus, S2 – second stimulus, R1 – response after the first stimulus, R2 – response after the second stimulus.*

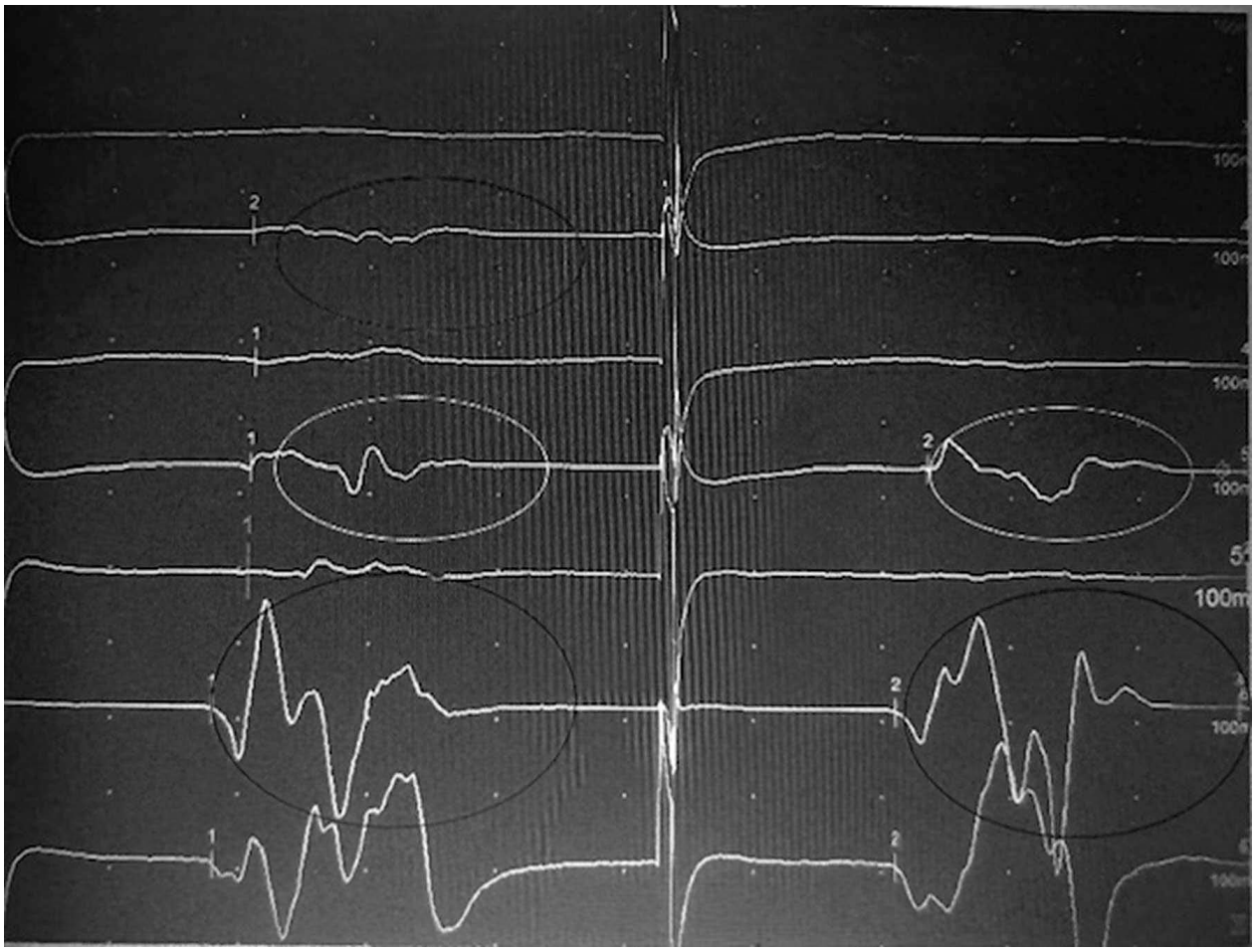

Fig. 2. *Findings in patient's tibialis anterior muscles: PRMR with prolonged latencies and reduced surfaces and ARMR with expected characteristics. Eliciting PRMR (recordings 2 and 3), mixed response (recordings 4 and 5) and ARMR (recordings 6 and 7). Recordings were done in the tibialis anterior muscles of the right leg (recordings 2, 4, and 6) and left leg (3, 5, and 7). The intensity of stimuli was increased from 80mA (recordings 2 and 3) to 100 mA (recordings 6 and 7). By increasing stimuli intensity, ARMR appeared (recordings 6, 7).*

roots likely enhances the sensitivity of this method compared to standard EMNG.

The patient's early clinical presentation, in combination with repeatedly negative EMNG and the PRMR/ARMR findings, supported a diagnosis of sensory polyradiculoneuropathy. Pathological PRMRs in all eight tested muscles, accompanied by ARMRs with normal latency and appropriate amplitude modulation, indicated selective involvement of the sensory spinal roots. PRMR and ARMR findings from the tibialis anterior muscle (TA) are illustrated in Figure 2.

Pathological PRMRs can be expected in cases involving dorsal and/or ventral root lesions, as the method evaluates reflex muscle responses and impulse conduction through the entire monosynaptic reflex arc (12,13). In cases of isolated dorsal root involvement, ARMR findings reflecting direct muscle responses to ventral root stimulation are expected to remain within normal limits, as they assess conduction through the motor component of the peripheral nerve only (14).

In this case, early analysis of PRMR and ARMR contributed significantly to supporting the clinical diagnosis, which could not be confirmed by conventional methods. Given the severity and potential progression of neurological symptoms, timely initiation of treatment is critical, requiring rapid and accurate diagnosis (15). The findings in this patient suggest that spinal root muscle response testing may allow early electrophysiological confirmation of polyradiculoneuropathy. Validation of this method in larger cohorts is warranted, with a comprehensive analysis of all PRMR and ARMR parameters.

CONCLUSION

We present a case in which analysis of posterior and anterior spinal root function indicated a diagnosis of acute sensory polyradiculoneuropathy during the early phase of the disease, despite negative findings on standard electrophysiological tests and cerebrospinal fluid analysis, and in the absence of antiganglioside antibodies.

PRMR and ARMR show promise as early, specific electrophysiological tools for confirming autoimmune polyradiculoneuropathies. Furthermore, they offer potential for the early confirmation of sensory polyradiculoneuropathies.

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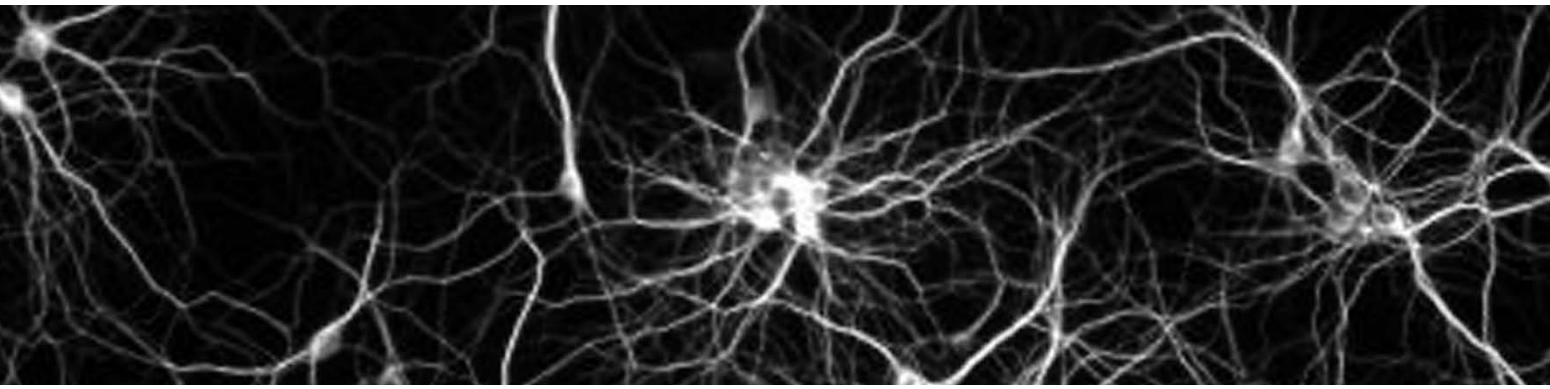

Adding new features to SMART syndrome?

Sarah Gomezelj[1], Matic Ločniškar[2], Tina Vipotnik Vesnaver[3], Gal Granda[1], Gregor Brecl Jakob[1,4]

ABSTRACT – *Background:* Stroke-like migraine attacks after radiation therapy (SMART) syndrome is characterized by severe headache with prolonged and mainly reversible neurological deficits, referable to a unilateral cortical region in patients after cranial irradiation. Magnetic resonance imaging (MRI) usually reveals unilateral cortical enhancement with mild mass effect and no signs of tumor recurrence. Cerebrospinal fluid (CSF) analysis is performed to rule out alternative diagnoses. *Case report:* We report a case of SMART syndrome in an 18-year-old male, diagnosed with right frontal lobe glioblastoma at the age of 10, treated successfully with surgery, chemotherapy, and radiotherapy. He experienced a migraine-like headache with progressive left sided hemiparesis and seizures. Symptom onset was preceded by alcohol consumption. MRI findings were consistent with SMART syndrome, with additional subcortical pathology. CSF analysis yielded leukocytosis. *Conclusions:* CSF leukocytosis does not exclude the diagnosis of SMART syndrome. Subcortical grey matter MRI findings may be present in patients with SMART syndrome. Alcohol consumption might provoke SMART syndrome development.

Keywords: migraine-like headache, cranial irradiation, subcortical grey matter, CSF pleocytosis, blood-brain barrier, SMART syndrome, alcohol-induced neurotoxicity

INTRODUCTION

Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a late complication of brain irradiation. It was first described in 1995 by Shuper *et al.*, and over many cases have been reported since (1,2).

To establish the diagnosis, the following diagnostic criteria have been proposed: (1) Remote history of external beam cranial irradiation without evidence of residual or recurrent neoplasm; (2) Prolonged, reversible or non-reversible signs and symptoms

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referable to a unilateral cortical region, years after irradiation with clinical manifestations including confusion, seizures, visuospatial deficits, hemisensory deficits, hemiparesis, aphasia, antecedent migraine headache with or without aura; (3) Magnetic resonance imaging (MRI) evidence of transient, diffuse, unilateral cortical gadolinium enhancement of the cerebral gyri within the previous irradiation field, sparing the white matter; (4) Not attributable to another disorder (3,4). Recently, two updates of the criteria were proposed (5,6).

The pathophysiology of SMART syndrome remains unclear. A post-radiation vasculopathy, characterized by endothelial dysfunction and increased blood-brain barrier permeability, is suspected (3,7). Other proposed mechanisms include radiation-induced mitochondrial dysfunction and neuronal dysfunction (5).

In order to meet SMART syndrome diagnostic criteria, several diagnostic tests including MRI, electroencephalography (EEG) and cerebrospinal fluid (CSF) analysis should be used to exclude other possible neurological disorders, such as acute infarction, venous sinus thrombosis, infection, mitochondrial disorders, posterior reversible encephalopathy syndrome (PRES), headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL syndrome), as well as rule out neoplasm recurrence (8).

MRI findings typically include reversible, unilateral, gyriform enhancement with T2 and FLAIR hyperintense cortical swelling in the previously irradiated brain region, not following the distribution of vascular territories, as well as leptomeningeal contrast enhancement (1,3).

CSF analysis usually yields normal results (1,3,5,7,9). Some authors report nonspecific abnormalities of CSF studies performed in patients with SMART syndrome, limited to glucose and protein abnormalities (1,8).

CASE REPORT

An 18-year-old male was admitted to the neurology department after his second episode of headache with associated left-hand weakness.

He had been treated for frontal lobe glioblastoma, 8 years earlier, with gross tumor resection, chemotherapy, and right hemisphere irradiation (full dose 59.4 Gy). He had recovered fully, with no neurologic deficits.

The patient presented after a night of heavy alcohol consumption, with a severe throbbing headache *(rated 10/10)* and associated left upper limb weakness. Neurological examination upon admission revealed distal left upper limb weakness associated with numbness of the dorsum of the left hand. In the following 10 days, he progressively developed left hemiplegia with left hemispatial neglect and left homonymous hemianopsia. He suffered several generalized tonic-clonic seizures.

Two weeks prior to admission, he had experienced a migraine-like headache accompanied with left upper limb numbness and weakness, resolving spontaneously in 15 minutes.

MRI revealed a hyperintense T2 signal and thick gyriform postcontrast enhancement over the majority of the right hemisphere cortical grey matter, sparing parts of the parietooccipital cortex (Figure 1A). Small areas of the affected cortex showed restricted diffusion. Focal areas of T2 and fluid attenuated inversion recovery (FLAIR) hyperintense signal with subtle contrast enhancement were also noticed in the ventral lentiform nucleus and pulvinar (Figure 1B). Diffuse hypointense signal of the right hemispheric subcortical white matter was present on T2, FLAIR and susceptibility weighted imaging (SWI) sequences. (Figure 1C). Time of flight MR angiography (TOF MRA) showed irregular narrowing of the proximal M2 segments of the right middle cerebral artery (MCA). There was no evidence of tumor recurrence.

Two separate CSF studies revealed similar leukocytic pleocytosis (results of the first analysis: white blood cell count of $12x10^6$/L (normal range $<5x10^6$/L) with $6x10^6$ neutrophils, $4x10^6$ lymphocytes and $2x10^6$ monocytes) with a slightly elevated protein level – 0.58g/L (normal range 0.15-0.45g/L) and normal glucose. Blood tests revealed an elevated blood leukocyte count of 17,6 x 10^9/L (normal range 4-11 x 10^9/L) and a CRP value of 16 mg/L (normal range <5 mg/L)

Extensive investigations were undertaken to exclude an infectious etiology. A complete panel of polymerase chain reaction (PCR) tests, including HSV1, HSV2, VZV, CMV, HHV6, Enterovirus, Parechovirus, Tick-borne encephalitis (TBE) virus RNA, as well as serologic tests for Lyme disease and TBE, were negative. Blood cultures were also negative. No focus of infectious disease could be found clinically. Serological screening for autoimmune encephalopathies from blood and CSF was negative.

Three EEG studies were performed. The first EEG study, right after the first generalized tonic clonic

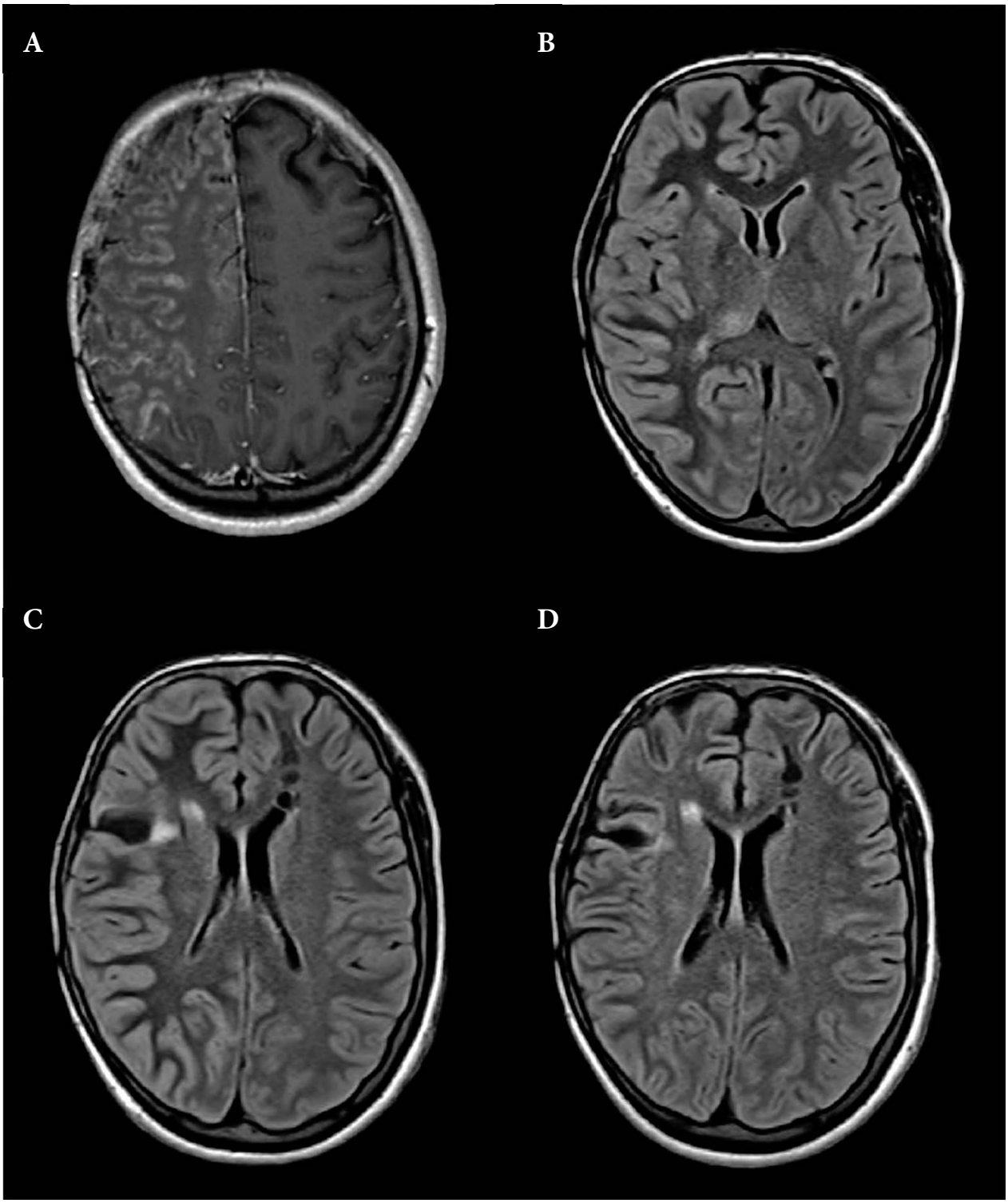

Fig. 1. *A: T1 MPRAGE contrast-enhanced sequence in the axial plane; thick gyriform cortical enhancement of the right hemisphere, sparing a part of the parietal lobe. B: FLAIR image in the axial plane through the basal ganglia with small hyperintense lesions in the right pulvinar and anterior putamen. C: FLAIR image in the axial plane through the postoperative defect in the right frontal region. Note the hypointense signal of the subcortical and partly deep white matter of the right hemisphere. D: resolution of the white matter changes on control MRI*

seizure, was done to exclude the possibility of non-convulsive status epilepticus and showed diffuse delta waves (0.5-1Hz) over the right hemisphere with near normal activity over the left hemisphere. No ictal or interictal epileptiform activity was found, and status epilepticus was excluded. The

other two EEG studies were done during the third week of hospitalization and showed a reduction of asymmetry with regional slow waves and interictal sharp waves right fronto-temporal, which correlated well with the patient's clinical improvement.

Epileptic seizures were treated with lorazepam and levetiracetam. We introduced antiepileptic therapy with carbamazepine and switched to lacosamide due to liver enzyme elevation. The headache was partially relieved using tramadol and metamizole. After exclusion of an infectious etiology, we treated with dexamethasone for 10 days (12mg/day), which was gradually tapered and discontinued.

The patient recovered completely in 14 days. His paresis improved substantially after corticosteroid treatment, and only minor weakness was present upon his discharge from hospital care. No neurological deficits were found at two-year follow-up. Follow-up MRI scans after 6 and 24 months showed resolution of all SMART-related cortical and subcortical changes (Figure 1D).

DISCUSSION

The presented case fulfills all the original and updated proposed diagnostic criteria for SMART syndrome (1,3); however, a few characteristics not described until now, can be identified. Abnormal CSF glucose and protein levels have been reported in cases of SMART syndrome by some authors; however, none reported leukocytosis (1,8). HaNDL syndrome represents one of the important differential diagnostic considerations when SMART syndrome is suspected. Pleocytosis is a hallmark of the HaNDL, and intracranial arterial narrowing can often be observed. On the other hand, CSF pleocytosis has not been reported in SMART syndrome, whereas diffuse gyriform enhancement observed in the presented case is typical. Friedenberg and Dodick propose that the MRI changes observed in SMART syndrome result from meningeal and parenchymal hyperperfusion, edema, or protein extravasation due to blood-brain barrier (BBB) disruption (10). Such pathology could lead to leucocyte migration across the BBB and subsequently to transient CSF leukocytosis. Accordingly, the leukocytosis observed in our patient might be attributable to a specific disease stage, when endothelial dysfunction is at its greatest. SMART syndrome has been reported to occur between 1 and 35 years following radiotherapy(1). Why the interval of disease manifestation is so broad, or what the precipitating factors are, is still unknown. Alcohol can cause vascular endothelial dysfunction through BBB disruption related to oxidative stress. It can thus serve as an aggravating factor in neuroinflammatory disorders. Increased leukocyte migration across the BBB in such conditions has been observed previously (in in vitro studies of samples of human BBB, where ethanol was used to alter the intercellular tight-junction integrity through oxidative stress-related phosphorylation of myosin light chains) (11). In the presented case, excessive alcohol intake occurred approximately 12 hours prior to symptom onset and might thus have triggered SMART syndrome onset. To our knowledge, some radiological changes observed in this case were not yet described. We were not able to find any published cases of subcortical grey matter involvement in SMART syndrome. In the presented case, the patient also had predominant involvement of the frontal and temporal cortical regions, while usually, predominant involvement of the occipitoparietal and temporal cortex with relative sparing of the frontal lobe is observed. We believe that the history of radiation, MRI findings, negative extensive diagnostic workup to exclude other possible etiologies and clinical course of the presented case speak for SMART syndrome and not for other possible diagnoses such as HaNDL. The presented case is, to the best of our knowledge, the first case of SMART syndrome with CSF pleocytosis and subcortical grey matter MRI pathology. We additionally identified ethanol as a potential agent that possibly provokes SMART syndrome development. Due to an increase in patients treated with brain irradiation and better survival of such patients, an increase in SMART syndrome incidence should be expected (9). It is therefore crucial to be aware of all possible disease manifestations. Consequently, we encourage clinicians not to exclude SMART syndrome diagnosis due to CSF leukocytosis or atypical distribution of imaging findings, and encourage patients after irradiation for brain tumors, to avoid excessive ethanol consumption.

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Clinical Implications

CSF leukocytosis does not exclude the diagnosis of SMART syndrome.

Subcortical MRI findings may be present in patients with SMART syndrome.

Alcohol consumption might provoke SMART syndrome development.

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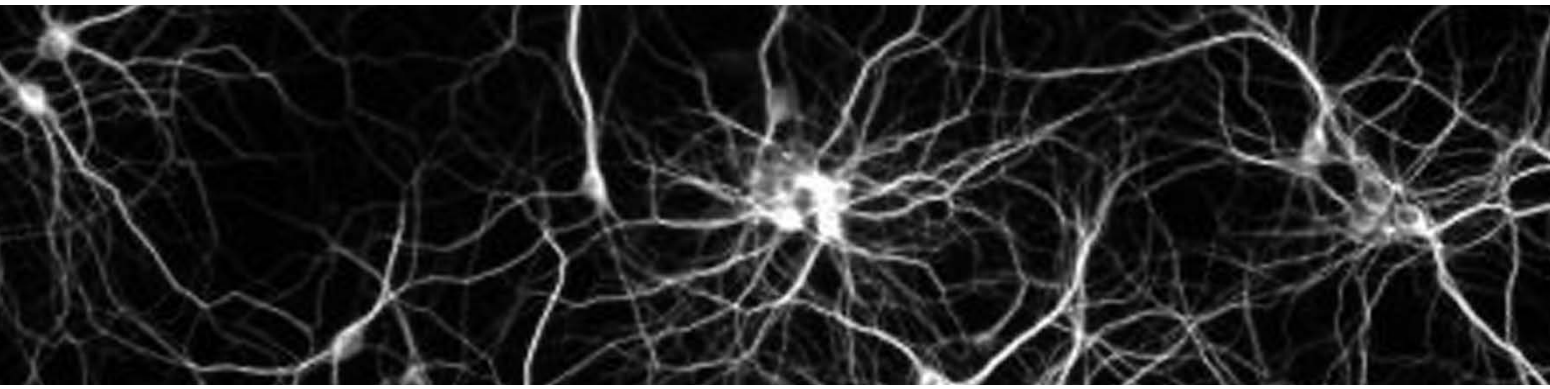

Diabetic striatopathy: cognitive and behavioral insights from case series and literature synthesis

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ABSTRACT – *Objective:* Neurological disorders affecting the striatum are often associated with cognitive impairments and movement abnormalities. Diabetic striatopathy (DS), a rare complication of diabetes mellitus, has been traditionally associated with hyperkinetic movement disorders. However, comprehensive studies exploring the cognitive-behavioral aspects of this condition remain limited. We aimed to examine the cognitive and behavioral profiles of DS patients and explore mechanisms underlying the differential impact on motor versus cognitive-behavioral functions. *Methods:* Five consecutive Bengali patients with DS presenting with hemichorea, all without reported cognitive complaints prior to disease onset, underwent comprehensive neuropsychological assessments. These evaluations, conducted three months after the onset of movement disorders, included the Montreal Cognitive Assessment, Addenbrooke's Cognitive Examination-III, and Frontal Assessment Battery. Behavioral changes were assessed using the Neuropsychiatric Inventory. *Results:* The series included three women and two men (69.7 ± 5.6 years) with poorly controlled diabetes. The cognitive evaluation revealed variable impairments: attention deficits in two patients, executive dysfunction in one, recent memory impairment in two, and language deficits in two patients. Visuospatial and visuoper-

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ceptual functions were preserved, while behavioral manifestations included depression, apathy, and obsessive behavior, notably without psychotic features. A literature review identified five previously reported cases of DS with cognitive-behavioral manifestations. *Conclusions:* DS may produce less severe cognitive-behavioral impairments than other striatal disorders, likely due to selective circuit involvement and preserved compensatory mechanisms. This unique profile may reflect the acute nature of DS pathology, the potential reversibility of striatal changes, and preserved cortical-subcortical connectivity. These findings expand our understanding of DS beyond its classical motor manifestations.

Keywords: diabetic striatopathy, hyperglycemia, basal ganglia, cognitive impairment, psychiatric disturbances, MRI hyperintensity

INTRODUCTION

Diabetic striatopathy (DS) is a rare neurological complication of poorly controlled diabetes mellitus, often presenting with hyperglycemia and movement disorders such as hemichorea and hemiballismus. It is characterized by distinctive neuroimaging findings, including striatal hyperdensity on non-contrast computed tomography (NCCT) and hyperintensity on T1-weighted magnetic resonance imaging (MRI) (1-3). Predominantly affecting older individuals, particularly Asian women, DS is closely associated with chronic hyperglycemia and elevated glycated hemoglobin (HbA1c) levels (1-3). Although its pathophysiology remains incompletely understood, metabolic and vascular alterations, such as obliterative vasculopathy and microhemorrhages, are thought to play a significant role (1-3). Timely glycemic control, typically achieved with insulin therapy, is crucial for symptom resolution and the prevention of recurrence (1-3). Despite its rarity, DS highlights the importance of recognizing neurological manifestations in diabetes mellitus for prompt diagnosis and management (1-3).

The striatum is widely recognized not only as a motor hub but also as a crucial component of the cognitive network, playing a significant role in memory, executive function, and overall cognitive resilience. Its involvement in neurological disorders (including stroke, deposition disorders, and neurodegenerative conditions such as Wilson's disease, neurodegeneration with brain iron accumulation, basal ganglia calcifications, and Huntington's disease) is frequently associated with cognitive impairment, often resulting from disruptions in the frontostriatal network (4-9). This network plays a pivotal role in maintaining attention, executive function, and information processing speed while also influencing language and praxis. Additionally, it governs emotion, motivation, and thought processes, contributing significantly to behavioral constructs (8,9). Within this framework, the ventral striatum governs reward processing, emotional regulation, and affective anticipation. In contrast, the dorsal striatum facilitates the translation of motor plans from the praxicon or supplementary motor area into actions, additionally playing a pivotal role in cognitive functioning (9).

Neurological diseases affecting the entire striatum, whether due to deposition or degeneration, often result in a combination of movement abnormalities and cognitive, emotional, and behavioral impairments. Conversely, selective involvement of the dorsal or ventral striatum tends to disrupt specific functions associated with the respective regions. Recent research has highlighted the diverse spectrum of movement disorders linked to DS (1-3,10). However, despite sporadic reports documenting cognitive impairments in DS (11-15), comprehensive studies exploring its cognitive-behavioral dimensions remain scarce. This study aims to address this gap by examining the cognitive and behavioral profiles of five DS patients, shedding light on the underlying mechanisms and clinical implications of these manifestations.

METHODS

Five consecutive Bengali patients, each with at least four years of formal education, diagnosed with DS in the outpatient departments of Neuromedicine at Bangur Institute of Neurosciences, IPGMER & SSKM Hospital, Kolkata, and Endocrinology at Medical College & Hospital, Kolkata (India), between July 2024 and November 2024,

were evaluated for cognitive dysfunction. DS was defined as a "hyperglycemic condition associated with either or both of the following: (i) acute onset choreoballism and (ii) striatal hyperdensity on NCCT or striatal hyperintensity on T1-weighted MRI" (1,2). Other potential etiologies capable of producing similar clinical or radiological features were excluded through appropriate investigations.

Cognitive assessments were jointly conducted by two investigators, SDubey and SC, using the Bengali versions of the Montreal Cognitive Assessment (MoCA) (16) and Addenbrooke's Cognitive Examination-III (ACE-III) (17) three months after the onset of movement disorders. Frontal executive function was assessed using the Frontal Assessment Battery (FAB), where scores below 12 indicated dysfunction (18). Behavioral and psychiatric symptoms were evaluated using the Neuropsychiatric Inventory (19).

Relevant metabolic and biochemical parameters (fasting and post-prandial plasma glucose, HbA1c, serum urea, creatinine, urine albumin-creatinine ratio, liver function tests, and lipid profile) were documented. Screening for diabetic microvascular and macrovascular complications was also performed on the day of the cognitive assessment.

Cases were analyzed for age, sex, education level, duration of diabetes, semiology of movement disorders, random blood glucose and HbA1c levels at the time of DS diagnosis, the time interval between the onset of involuntary movements and DS diagnosis at our center, NCCT scan and MRI findings, treatments received (anti-hyperglycemic and neuroleptic medications, if any), and other relevant factors. The results were summarized descriptively due to the small sample size, precluding statistical comparisons.

Written informed consent was obtained from each patient for publication. As no study-specific procedures were conducted, ethics committee approval was not required.

A literature search was conducted on PubMed and Google Scholar until December 15, 2024, using the keywords "diabetic striatopathy" OR "hyperglycemic non-ketotic hemichorea hemiballism" OR "chorea hemichorea associated with non-ketotic hyperglycemia" OR "diabetic hemiballism hemichorea" OR "chorea, hyperglycemia, basal ganglia syndrome" AND "cognition" OR "cognitive impairment" OR "dementia" OR "behavior."

RESULTS

Demographic and clinical characteristics

The series consisted of five patients, including three women and two men, with a mean (± standard deviation) age of 69.7 ± 5.6 years, with no reported cognitive complaints or known cognitive impairment prior to DS onset. Educational background averaged 7.0 ± 3.3 years of formal schooling, and the mean duration of diabetes was 2.2 ± 2.6 years, with two patients having previously undiagnosed diabetes mellitus. At initial DS diagnosis, patients presented with markedly elevated mean random blood glucose (517 ± 131.6 mg/dL) and HbA1c (14.4% ± 3.3) levels. The average time from symptom onset to diagnosis at our center was 28.2 (± 46.0) days.

Movement disorders manifested as hemichorea in all patients (Supplementary Video 1), with two patients showing right-sided involvement and three showing left-sided involvement. One patient with left hemichorea additionally displayed facial dyskinesias. Neuroimaging consistently revealed contralateral striatal hyperdensity on NCCT scan and contralateral hyperintensity on T1-weighted MRI (Figure 1), except for one patient who showed clin-

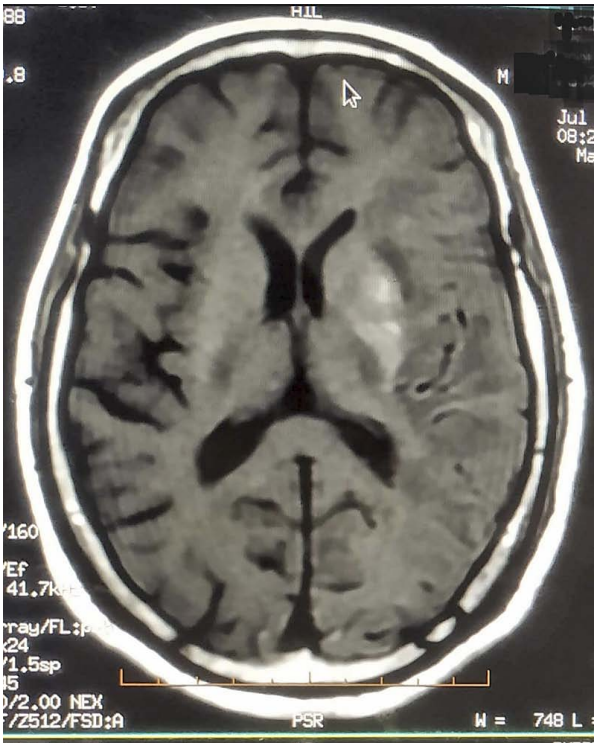

Fig. 1. *An axial T1-weighted MRI image demonstrates hyperintense lesions involving bilateral putamina (left more than right), characteristic of diabetic striatopathy.*

ico-radiological discordance with ipsilateral striatal T1 hyperintensity.

Treatment approaches varied among patients, with three managed solely through oral antidiabetic medications, while two initially required insulin therapy before transitioning to oral antidiabetic drugs. Two patients needed additional neuroleptic medications for movement disorder control. After three months of follow-up, all except one patient achieved complete resolution of involuntary movements, with the non-resolving case showing residual striatal changes on repeat MRI.

Diabetic complications were prevalent in the series. Microangiopathic manifestations included sensorimotor neuropathy in two patients, nephropathy in four, and retinopathy in one. Macrovascular disease affected three patients, comprising two cases of previous ischemic stroke and one myocardial infarction. Small vessel disease was evident on MRI in four patients.

Cognitive and Behavioral Profile

Cognitive evaluations were conducted three months after the onset of movement disorders. By the time of assessment, glycemic parameters had improved significantly, with a mean random blood glucose of 175.0 ± 81.3 mg/dL and an HbA1c of 7.2% ± 1.5%. Cognitive performance measured through the MoCA and ACE-III revealed mean total scores of 23.0 ± 0.82 and 81.7 ± 5.3, respectively.

The evaluations revealed a complex pattern of deficits and preserved functions across various cognitive domains. Two patients demonstrated attention impairment, particularly in backward digit span tasks. Language function showed variable involvement, with one patient experiencing difficulties in complex syntax comprehension and two showing decreased word fluency, though paraphasia was absent and reading remained intact. One patient exhibited mild writing impairment attributed to a persistent movement disorder.

Information processing speed deficits were observed in two patients, manifesting as prolonged Trail B test completion times. Memory assessment revealed intact semantic memory and preserved registration and immediate recall. However, recent memory impairments emerged in two patients during 10-word list testing, suggesting difficulties with new learning or sustained attention. While two patients showed impaired delayed free recall, their recall abilities improved with cueing.

Visuospatial and visuoperceptual functions remained intact across all patients. Similarly, praxis evaluation through TULIA testing showed no evidence of upper limb apraxia, and no patient demonstrated agnosia. Frontal lobe function assessment revealed preserved performance in most areas, with FAB scores exceeding 12 in all patients, though one patient showed executive function impairments. While one patient struggled with Trail B performance, other frontal lobe functions, including inhibitory control, abstraction, proverb interpretation, decision-making, and judgment, remained intact in all.

The behavioral evaluation revealed a spectrum of manifestations, including single cases of depression, apathy, and obsessive behavior. Two patients exhibited impulsivity with intermittent aggression and anger outbursts, though these symptoms likely predated their movement disorders. Hoarding behaviors, psychotic symptoms (delusions or hallucinations), and eating disorders were notably absent.

Literature review

A literature search identified five papers reporting cognitive, behavioral, or psychiatric manifestations in DS (Table 1) (11-15). The earliest report by Kincses *et al.* (11) described a case of hyperglycemic hemiballismus with frontal executive dysfunction, particularly impairing phonemic verbal fluency tasks. Through tractography, they demonstrated altered connectivity between striatal lesions and the frontal cortex, highlighting that DS can affect cognitive networks beyond motor pathways.

Sato *et al.* (12) presented a significant departure from classical DS presentations by describing a case manifesting solely as severe consciousness disturbance without involuntary movements. Their patient achieved marked cognitive improvement following glycemic control, demonstrating that DS can present with neurocognitive impairments even in the absence of typical motor symptoms.

A more recent report by Miyauchi *et al.* (13) documented a case of treatment-resistant diabetic hemichorea accompanied by psychiatric symptoms, including irritability and violent behavior. The patient's symptoms improved with tiapride, suggesting dopamine D2 receptor involvement in both motor and behavioral aspects of DS.

Li *et al.* (14) further expanded the understanding of DS by describing a case of subacute cognitive decline as the primary manifestation without in-

Table 1. *Comparative Analysis of Cognitive and Behavioral Manifestations in Diabetic Striatopathy: Literature Review and Current Series.*

Study Characteristics	**Kincses et al. (2015)[11]**	**Sato et al. (2017)[12]**	**Miyauchi et al. (2022)[13]**	**Li et al. (2023)[14]**	**Ersöz et al. (2024)[15]**	Ersöz **et al. (2024)[15]**	**Current Series (n=5)**
Demographics							
Age/Sex	43 years / Male	58 years / Male	69 years / Male	73 years / Male	82 years / Female	47 years / Female	69.7±5.6 years (three females, two males)
Clinical Presentation							
Primary Manifestation	Right hemiballismus with cognitive impairment	Consciousness disturbance	Treatment-resistant chorea with psychiatric symptoms	Cognitive decline	Altered consciousness and cognitive decline	Altered consciousness and cognitive decline	Hemichorea
Involuntary Movements	Right hemiballismus	None	Present	None	None	None	Hemichorea in all (two right, three left). One patient also presented with facial dyskinesias
Metabolic Parameters							
Initial Glucose (mg/dL)	367	549	252	218	232	550	517±131.6
HbA1c (%)	16.6	16.1	14.6	13.8	>14	16.2	14.4±3.3
Neuroimaging	T1 hyperintensity in the right caudate nucleus and putamen	CT showed faint hyperattenuation in the left striatum. MRI revealed hyperintense signals in the left caudate nucleus and putamen on T1 and T2-weighted images. MRA indicated oozing around the left basal ganglia, suggesting microhemorrhage	T1-weighted MRI showed a high-intensity lesion in the left putamen that later spread to the entire left striatum	High-density lesions in the bilateral lateral caudate nucleus and the region of the nucleus accumbens on CT. MRI showed high signal-intensity lesions in the right caudate and lenticular nuclei on T1-weighted images and low signal-intensity lesions in the corresponding regions on T2-weighted images. SWI indicated a low signal lesion in the right caudate nucleus	CT scan showed hyperdense areas in the left putamen and caudate nucleus; MRI revealed hypointensity in the basal ganglia on FLAIR and hyperintensity on diffusion-weighted imaging.	CT showed hyperdense signals in the left striatum; T1-weighted MRI revealed hyperintense lesions in the left caudate nucleus and putamen	Contralateral striatal hyperdensity on non-contrast CT scan and contralateral hyperintensity on T1-weighted MRI, except for one patient who showed clinico-radiological discordance with ipsilateral striatal T1 hyperintensity

Cognitive Features							
Attention	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	2/5 impaired
Language	Impaired (phonemic fluency)	Impaired (non-fluent aphasia)	Not specified	Not specified (slurred speech)	Not specified	Not specified	2/5 impaired word fluency
Information processing speed	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	2/5 impaired
Memory	Mildly impaired (short-term)	Impaired (amnesia)	Not specified	Recent memory impaired	Not specified	Not specified	2/5 impaired (recent memory)
Visuospatial and visuoperceptual functions	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Preserved
Praxis and Gnosis	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Preserved
Executive Function	Impaired (phonemic fluency)	Not specified	Not specified	Not specified	Not specified	Not specified	1/5 impaired
Behavioral Features							
Psychiatric Symptoms	None reported	None reported	Violent acts, verbal threats	None reported	None reported	None reported	Depression (1), apathy (1), obsessive behavior (1), impulsivity (2)
Treatment Response							
Glycemic Control	Improved (delayed resolution of symptoms)	Improved	Partial improvement with adjunctive tiapride	Improved	Improved	Improved	Complete resolution in 3/5
Other Treatments	Tiapride and tetrabenazine were attempted but ineffective. Spontaneous improvement was observed	None needed	Tiapride effective	None needed	None needed	None needed	Neuroleptics in 2/5
Outcome							
Motor Symptoms	Right hemiballismus, resolved over 2 months with mild residual chorea	Not applicable	Improved with tiapride	Not applicable	Not applicable	Not applicable	Resolved in 4/5
Cognitive Symptoms	Improved	Improved	Not applicable	Improved	Improved	Improved	Not applicable

voluntary movements. The patient demonstrated significant improvement in cognitive function with glycemic control. MRI findings revealed bilateral caudate nucleus involvement, providing additional evidence for the role of striatal circuits in cognitive regulation.

The most recent report by Ersöz *et al.* (15) described two cases of cognitive decline as the primary presentation of DS, both without hyperkinetic movement disorders. Both patients recovered fully with glycemic control, further supporting the emerging concept that DS can primarily present with cognitive impairments rather than motor symptoms.

DISCUSSION

This study integrates our findings with prior evidence to provide a comprehensive understanding of the cognitive and behavioral manifestations of DS. While traditionally viewed as a movement disorder, DS presents a broader spectrum of neurological involvement. Our results reveal selective neural network vulnerabilities alongside compensatory mechanisms, contributing to variable patterns of cognitive preservation and impairment. These findings expand on previous reports, highlighting both commonalities and distinctions in DS presentations.

Analysis of attention and executive functions revealed impairments in a subset of patients, consistent with disruptions in the fronto-parietal network and its subcortical contributions (20,21). These findings align with those of Kincses et al. (11), who reported a single case of DS presenting with hemiballismus and executive dysfunction, specifically impairments in phonemic verbal fluency. Their tractography study identified the involvement of frontostriatal pathways, suggesting that lesions in these circuits could account for the observed cognitive deficits. Nevertheless, the preservation of executive functions in most patients indicates robust compensatory mechanisms within the frontal cortex and its white matter connections (22,23).

Recent memory functions are mediated by a distributed network involving the temporal cortex, including the hippocampus, parahippocampal gyrus, and the Papez circuit (24). In our series, the variable pattern of impairment–preserved in some patients but deficient in others–suggests that DS differentially affects this network. Semantic memory, anchored in anteromedial temporal structures (25), remained largely intact, while deficits in recent memory and delayed recall were observed in some instances. This selective dysfunction likely reflects the involvement of striatal-temporal connections rather than direct temporal lobe damage. Furthermore, the preservation of categorical memory, which relies on temporal cortical regions, along with variability in letter fluency tasks dependent on frontal cortical function (26), underscores the distinct cognitive profile of DS. These findings support the hypothesis that DS disrupts specific striatal circuits without causing widespread memory network dysfunction.

The preservation of visuospatial and visuoperceptual functions in our series aligns with the anatomical basis of these processes, which primarily rely on an integrated network of posterior cortical regions, including the parietal, temporal, and occipital lobes (27). Intact performance on tasks such as dot counting and fragmented letter tests suggests that, despite striatal dysfunction, DS does not significantly impair these posterior cortical networks. This preservation corresponds to the anatomical distribution of pathology in DS, which predominantly affects striatal structures while sparing posterior cortical regions essential for complex visual processing and spatial integration.

The striatum also plays a critical role in language production and speech expression through its intricate connections with Broca's area. Our findings suggest that striatal dysfunction in DS may partially affect but not entirely disrupt language networks, as evidenced by variable language preservation in DS patients; some demonstrated intact function, while others exhibited mild deficits in word fluency and complex syntax comprehension. This stands in contrast to the more severe language impairments typically seen in stroke affecting these circuits. The pattern observed in our series indicates that DS may cause partial rather than complete disruption of striatal-language networks, allowing for the preservation of essential language functions while affecting more complex linguistic processes.

Information processing speed, while reliant on frontal-subcortical circuits, appears to be more influenced by the integrity of white matter connections than by subcortical nodes. In our DS patients, the relative preservation of information processing speed contrasts with the marked impairment observed in conditions predominantly affecting white matter, such as multiple sclerosis (28). This differential pattern suggests that intact white matter pathways may play a more critical role in maintaining processing speed, compensating for disruptions in subcortical structures caused by DS.

The behavioral manifestations observed in our series, including depression, apathy, and obsessive behavior, warrant careful interpretation within the broader context of diabetes mellitus and movement disorders. These symptoms contribute to the growing body of evidence that DS can present with significant psychiatric manifestations. However, it is important to recognize that depression, anxiety, and obsessive behaviors are generally more prevalent among patients with diabetes (29). The interplay between movement disorders and psychiatric symptoms in DS appears complex, as abnormal motor movements may exacerbate low mood and impulsivity (30). Our observations, coupled with Miyauchi *et al.*'s (13) report of treatment-resistant DS associated with psychiatric symptoms, highlight that the emotional-behavioral aspects of DS may be more common than previously acknowledged. Notably, across our series and in the literature, psychotic features such as delusions and hallucinations were consistently absent, suggesting that DS may selectively impact specific limbic circuits while sparing those involved in psychosis.

The dissociation between motor and cognitive-behavioral manifestations in DS reflects a distinct pattern of striatal involvement that contrasts with other basal ganglia disorders. Conditions such as Wilson's disease, neurodegeneration with brain iron accumulation, and Huntington's disease typically cause severe cognitive impairment due to extensive bilateral basal ganglia involvement (4,5,7). In contrast, DS appears to selectively affect specific striatal circuits, leading to more significant disruption of dorsal striatal regions controlling motor functions while relatively sparing substrates responsible for cognitive and behavioral processes. This relative preservation likely arises from multiple factors, including the acute nature of DS pathology, the potential reversibility of striatal changes, and the integrity of cortical structures and white matter connections, which may compensate for striatal dysfunction. Moreover, the inherent resilience of multimodal cognitive-behavioral networks, with their redundant pathways, offers further protection against dysfunction. The architectural redundancy of these networks, compared to the more focused organization of motor circuits, helps explain the differential impact on motor versus cognitive functions.

Current evidence increasingly supports the concept of DS as a spectrum disorder rather than a uniform condition. Ersöz *et al.* (15) demonstrated that cognitive decline could be the primary manifestation of DS, even in the absence of movement disorders, aligning with our findings of variable clinical presentations. Similarly, Li *et al.* (14) described a case of subacute cognitive decline as the predominant symptom, highlighting the variability in DS manifestations. Sato *et al.* (12) reported a presentation limited to severe consciousness disturbance, while Miyauchi *et al.* (13) detailed a case with psychiatric symptoms accompanying movement abnormalities. Collectively, these reports, along with our findings, underscore the diverse clinical spectrum of DS, ranging from motor symptoms to cognitive and behavioral impairments, and emphasize the need for broader diagnostic considerations beyond the classical motor-dominant paradigm.

The cognitive and behavioral impairments observed in DS, though less severe than anticipated given the extent of striatal involvement, likely result from a combination of mechanisms. Selective striatal involvement, with more pronounced disruption of motor circuits in the dorsal striatum while relatively sparing cognitive-behavioral substrates, provides an anatomical explanation for this phenomenon. Additionally, the acute and potentially reversible nature of DS pathology, coupled with preserved functionality of cognitive-behavioral circuits despite structural changes visible on imaging, may account for this relative preservation. The integrity of cortical structures and white matter connections appears to play a crucial role in compensating for striatal dysfunction and maintaining cognitive-behavioral functions. Furthermore, the resilience of cognitive-behavioral networks, supported by their multimodal nature and redundancy, enhances their ability to withstand damage. This hypothesis is further supported by the general improvement in both cognitive and motor symptoms observed with glycemic control (11-15). However, it is noteworthy that in our patients, cognitive deficits persisted for at least three months from symptom onset, contrasting with previous reports of faster recovery. This discrepancy may stem from the more detailed cognitive evaluation performed in our study, which may have captured subtle deficits that could otherwise remain undetected.

This study has several limitations. A major limitation is that the cognitive status of patients who eventually developed DS was not known prior to the diagnosis. While participants had no cognitive complaints, impairments were only recognized after a detailed battery of assessments. Thus, it is possible that such deficits were already present before DS onset and were only revealed during evalua-

tion. In addition, the small sample size and absence of control groups (such as diabetic patients without striatopathy, individuals with other striatal disorders, and age-, sex-, and education-matched healthy controls) limit the generalizability of our findings. The lack of functional imaging prevented exploration of network-level mechanisms underlying the observed deficits, and the cross-sectional design precludes conclusions about their temporal evolution. Longitudinal investigations will therefore be crucial to clarify the progression of cognitive and behavioral manifestations in DS and their relationship to glycemic control and treatment response.

In summary, our findings indicate that DS exhibits relatively mild cognitive-behavioral impairments compared to what might be anticipated, given the degree of striatal involvement. Similarly, behavioral manifestations were less prominent compared to those that are usually observed in other striatal pathologies (4-9). Notwithstanding, these insights hold significant implications for clinical practice. Clinicians should remain vigilant for DS, even in the absence of classical movement disorders, particularly in diabetic patients presenting with acute cognitive or behavioral changes. Comprehensive cognitive and behavioral evaluations should be routinely included in the assessment of these patients, and treatment strategies must address both motor and non-motor symptoms, with glycemic control serving as the cornerstone of management.

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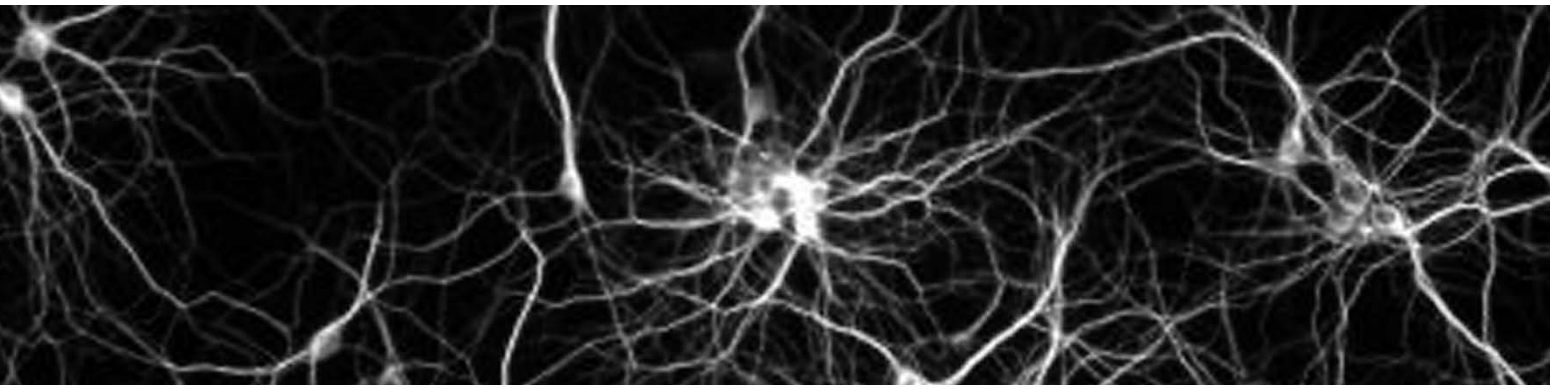

Small fiber neuropathy after influenza B infection

Ivan Martinez[1], Mirea Hančević[1], Rujana Šprljan Alfirev[1], Branimir Ivan Šepec[1], Gabrijela Pejkić[2], Tomislav Bečejac[3]

ABSTRACT – *Objectives*: Small fiber neuropathy (SFN) is a peripheral nervous system disorder due to affection of small nerve fibers, which include Aδ-fibers and C-fibers. Clinically, it frequently manifests with intense pain, sensory disturbances, or autonomic dysfunction. *Case description*: We present a case of a 43-year-old female who developed acute, progressive small fiber neuropathy following laboratory-confirmed influenza B infection. *Results*: The temporal relationship between the patient's influenza B infection and the onset of symptoms, coupled with the absence of other identifiable etiologies and normal large fiber studies, suggests an immune-mediated mechanism triggered by viral infection. *Conclusion*: Management of SFN is primarily symptomatic, with pharmacologic options such as duloxetine providing partial relief in this case. The persistence of symptoms despite treatment underscores the potential for chronicity and impact on quality of life, highlighting the need for early recognition and multidisciplinary management of post-infectious SFN.

Keywords: influenza B, small fiber neuropathy

INTRODUCTION

Small fiber neuropathy (SFN) is a disorder of the peripheral nervous system (PNS) due to affection of small nerve fibers, which include Aδ-fibers and C-fibers (1). SFN frequently manifests with intense pain, sensory disturbances, or autonomic dysfunction. In addition to sensory and autonomic symptoms, patients with SFN may experience fatigue, cognitive disturbances, headache, and widespread musculoskeletal pain, all of which can negatively affect quality of life. SFN can occur in association with various systemic diseases but can also present as idiopathic (2). Small fibers build up to 80–90%

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of the peripheral nerves (3). They originate from pseudo-unipolar neurons and can both conduct pain signals and sequester antigen-specific antibodies. This dual functionality allows them to act as both sensory receptors and antigen-presenting cells, potentially leading to immune-mediated hyperalgesia (4).

CASE DESCRIPTION

We present a case of a 43-year-old female who developed acute, progressive SFN following laboratory-confirmed influenza B infection. The patient initially presented with fever and cough. At her primary care consultation, a combined antigen test for SARS-CoV-2, influenza A/B, and respiratory syncytial virus yielded a positive result for influenza B. On the fifth day of illness, she reported a sudden onset of diffuse cutaneous pain described as a burning or "sunburn-like" sensation involving the entire body. Concurrently, she experienced bilateral loss of thermal sensation, both hot and cold, below the knees. Approximately three weeks after the initial influenza diagnosis, the patient reported worsening of cutaneous pain localized to the lower extremities, without back pain, which progressively intensified over the subsequent two weeks. This prompted her to seek care at the Emergency Department, where she was referred to the Neurology Department. In addition to the described sensory disturbances, including paresthesia ("pins and needles"), impaired thermal sensation, and hyperalgesia, the patient reported generalized fatigue and occasional tingling in her feet provoked by neck flexion as well as an increase in pain during ambulation. She had no dizziness, loss of consciousness, constipation, urinary retention, or lack of sweating. Neurological examination revealed symmetrical dysesthesia in both lower legs, but no sensory level or hypoesthesia was reported. Tendon reflexes on both upper and lower extremities were symmetrical, without hyperreflexia, and the plantar reflex was normal. Cranial nerve testing, pupil function, motor function testing, as well as balance and walking, were unremarkable. Lasegue sign was negative.

RESULTS

As part of the diagnostic evaluation, a lumbar puncture was performed, which revealed mildly elevated cerebrospinal fluid protein levels, normal oligoclonal bands type I and normal kappa-free light chain index. Serological testing for neurotropic viruses and *Borrelia burgdorferi* was negative, and laboratory investigations demonstrated normal vitamin B12, folic acid, and trace element levels. Enzyme Immunoassay (EIA) test for the influenza B antibody IgG titer EIA was > 200 RU/ml. Electromyography (EMG) and nerve conduction studies were unremarkable, revealing no evidence of large fiber neuropathy or myopathy. However, findings were suggestive of mild to moderate chronic bilateral Th1 and L5, and left S1 radiculopathies. Magnetic resonance imaging (MRI) of the neuroaxis excluded ischemia, demyelination, or neoplastic lesions and did not reveal significant neuroforaminal conflict requiring surgical intervention. Temperature threshold testing (TTT) demonstrated findings consistent with small fiber neuropathy, specifically involving C-fibers, while Aδ-fiber function remained within normal limits (Fig.1). Bedside autonomic nervous system testing (active standing test) showed normal findings. In view of history and examination results, the patient was diagnosed with small fiber neuropathy according to NEURODIAB criteria and the revised Besta criteria (5, 6). After exclusion of other possible etiologies (Table 1, adapted from 7,8,9) either through history and examination or through laboratory testing, it was concluded that small fiber neuropathy was most likely a consequence of influenza B infection. Symptomatic management was initiated. Due to intolerance of pregabalin and gabapentin, duloxetine was prescribed. At follow-up one month later, the patient reported partial symptom resolution, with intermittent lancinating pain and thermal dysesthesia persisting in the lower extremities.

DISCUSSION

This case highlights a rare complication of influenza B infection, acute SFN. SFN primarily affects thinly myelinated Aδ-fibers and unmyelinated C-fibers, which are responsible for nociceptive, thermal, and autonomic functions. The temporal relationship between the patient's influenza B infection and the onset of symptoms, coupled with the absence of other identifiable etiologies and normal large-fiber studies, suggests an immune-mediated mechanism triggered by viral infection. This pathophysiological process likely involves the generation of autoantibodies or pro-inflammatory cytokines targeting small fibers, resulting in sensory disturbances and hyperalgesia (10,11). The patient did not experience widespread severe autonomic dysfunction, which would suggest autoimmune autonomic ganglionopathy. Although lumbar

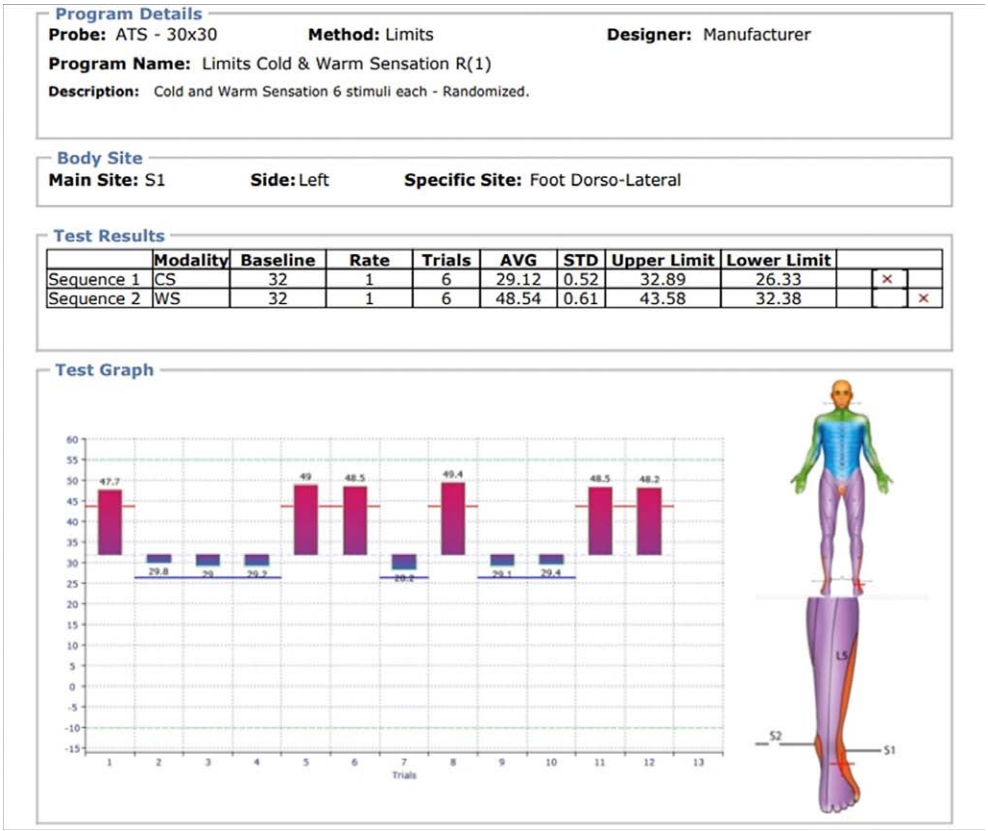

Fig. 1. *Temperature threshold testing result showing selective involvement of C-fibers*

Table 1. *SFN causes and testing (adapted from 7,8,9)*

Metabolic	
Diabetes mellitus	Hemoglobin A1c
Impaired glucose intolerance	2-h oral glucose tolerance test
Vitamin B12 deficiency	Vitamin B 12, methylmalonic acid, homocysteine
Copper deficiency	Cu
Abnormal thyroid function	TSH, T4
Infectious	
HIV	Serologic testing
Lyme	
Hepatitis	
Immune-mediated	
Sarcoidosis	ACE level
Rheumatic diseases, Sjogren syndrome, Lupus,	ESR, CRP, ANA, SS-A, SS-B
Connective tissue disease	Free light chains
Primary systemic amyloidosis	Serum (and/or urine) immunofixation electrophoresis
Monoclonal gammopathy	Neve conduction studies
Chronic inflammatory demyelinating polyneuropathy	
Drug induced and toxic	
Alcohol	GGT
Chemotherapy	
Neurotoxic drugs	
Vaccine-associated	
Genetic	
Fabry's disease	Alpha-galactosidase assay or gene sequencing
Mutation in sodium channels	SCN9A, SCN10A gene sequencing
Familial amyloidosis	TTR gene sequencing
Ehlers-Danlos	

puncture revealed mildly elevated protein levels, a finding often associated with inflammatory neuropathies, serological testing for neurotropic infections and common metabolic causes was negative. Multiple sclerosis was excluded based on normal MRI findings, while serum AQP4-IgG and MOG-IgG antibodies returned negative. These antibodies were obtained as part of the initial laboratory workup prior to neuroimaging. Notably, the patient's EMG and nerve conduction studies were normal, consistent with the selective involvement of small fibers in SFN. The TTT findings further supported this diagnosis, showing selective C-fiber dysfunction. These findings, in correlation with the clinical presentation, were consistent for SFN, and additional testing, such as skin biopsy or somatosensory evoked potentials, was not considered at the time. The associated radiculopathies identified on electrophysiological studies were chronic and did not correlate with the severity or distribution of her symptoms, suggesting these findings were incidental rather than causative.

CONCLUSION

Management of SFN remains primarily symptomatic, with pharmacologic options such as duloxetine providing partial relief from neuropathic pain in this case. The persistence of symptoms despite treatment underscores the potential for chronicity and impact on quality of life, highlighting the need for early recognition and multidisciplinary management of post-infectious SFN. Timely recognition of SFN and appropriate symptomatic treatment can mitigate its impact on patients' quality of life.

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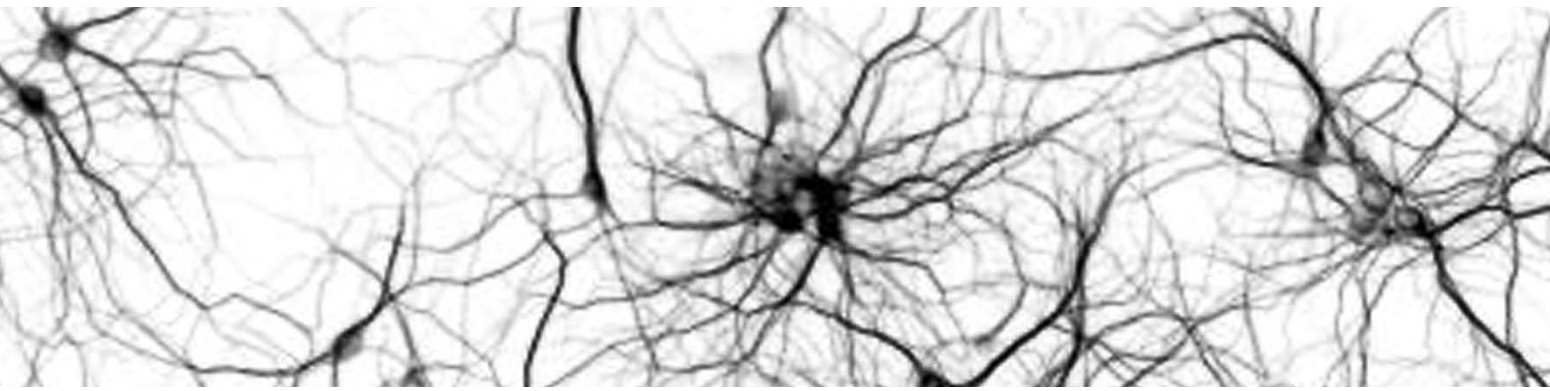

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