

Methotrexate-Induced Stroke-Like Syndrome in Pediatric Acute Lymphoblastic Leukemia: A Case Series from a Resource-Limited Center in Mexico

Edgar Selem¹⁻³, Alejandro Torres^{1,2}, Joseph Varon^{3,4}, Pablo González Montalvo^{1,2}

Abstract

Methotrexate (MTX)-induced stroke-like syndrome (SLS) is a very rare complication that presents up to three weeks after chemotherapy treatment with a constellation of nonspecific neurological signs and symptoms that may suggest alternative pathologies. During the consolidation phase, methotrexate is a key antimetabolite drug that reduces the synthesis of DNA and RNA. It occasionally causes transient neurotoxicity by damaging white matter. Three patients with ALL without prior central nervous system (CNS) involvement were studied; they developed focal neurological deficits within the first 8 days following intrathecal (MTX-IT) and high-dose MTX (HDMTX) administration. Imaging studies showed focal frontotemporal hyperintensity with

self-limitation within 48 to 72 hours without sequelae; two of the three patients received specific pharmacological treatment. A relevant methodological limitation is that homocysteine levels (the central biomarker in pathophysiology) were not measured in any of the three patients, as the necessary reagent was not available at the institutional laboratory. The purpose of this case series is to document the signs and symptoms, their clinical course and resolution, and to report the chemotherapy protocol followed by each patient for comparison with the existing literature. Early recognition of signs and symptoms, neuroimaging findings, and laboratory characteristics is essential for adequate management and to ensure continuity of oncological treatment.

Keywords: Acute lymphoblastic leukemia, methotrexate, stroke, pediatrics

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer worldwide, with a cure rate of 80–90%. However, its management is complex, requiring up to three years of chemotherapy. (1) Among the drugs used in chemotherapy regi-

mens is MTX, an antimetabolite widely used in oncology and other medical fields for its immunosuppressive and antineoplastic effects. It acts by competitively inhibiting the enzyme dihydrofolate reductase, which allows the conversion of folic acid into dihydrofolate and finally into its active form, tetrahydrofolate. In this way, it blocks the synthesis of purine and pyrimidine nucleotides, directly affecting DNA and RNA. Some toxic effects of MTX include myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, and neurotoxicity with acute or chronic encephalopathy. (2) Subacute neurotoxicity secondary to intrathecal treatment or high intravenous doses (>500 mg) of MTX-IT or HDMTX has been documented within the first 21 days of administration. (3) This is known as stroke-like syndrome (SLS) and presents symptoms such as hemiplegia, aphasia, dysarthria, diplopia, and, occasionally, seizures. This clinical spectrum is self-limited, with a duration of approximately 15 minutes to 72 hours, without short-term sequelae. (4) It is a very rare

¹ Hospital General Dr. Agustín O'Horán, Mérida, Yucatán, México

² Universidad Autónoma de Yucatán, Yucatán, México

³ Dorrington Medical Associates, Houston, Texas, USA

⁴ Independent Medical Alliance, Washington, DC, USA

Corresponding author:

Edgar Selem
Itzáez Av. # 498, Centro, 97000 Mérida, Yucatán, México
Email: edgar.mdk@gmail.com

complication of MTX treatment, with an incidence of 0.8% to 3.8%, although more recent literature suggests it may be as low as 0.2%. In a retrospective review of 1,251 Australian children with ALL, Mateos et al. reported an incidence of MTX-related central neurotoxicity of 7.6%, with a median presentation at 8 days following intravenous or intrathecal drug administration, which is consistent with the risk period observed in our series. (5)

Neurotoxicity secondary to intravenous or intrathecal administration of MTX must fulfill three characteristics:

1. Recent onset of ≥ 1 of the following symptoms: paresis or paralysis, movement disorder or bilateral weakness, aphasia or dysarthria, altered mental status, and/or seizures.
2. White matter abnormalities indicating leukoencephalopathy on magnetic resonance imaging (MRI), or a characteristic clinical course with fluctuating symptoms with complete or partial resolution within one week.
3. Absence of any other identifiable cause. (6)

The pathophysiology is not yet fully understood; however, it is associated with demyelination, white matter necrosis, loss of oligodendroglia, axonal edema, and deep cerebral white matter atrophy secondary to direct antimetabolite damage, which causes accumulation of homocysteine and its metabolites in plasma and cerebrospinal fluid, which are toxic to the vascular endothelium. (1) Homocysteine acts as an agonist at the N-methyl-D-aspartate (NMDA) receptor, and dextromethorphan is a non-competitive NMDA receptor antagonist, which is why it is used as a therapeutic option in neurological disorders associated with transient MTX CNS toxicity. (7) From a genomic perspective, genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms in genes related to neuronal growth, neuronal differentiation, and cytoskeletal organization that may confer individual susceptibility to this complication, opening the possibility of prospectively identifying high-risk patients before the start of chemotherapy. (5)

Some risk factors associated with SLS include age >10 years, Hispanic ethnicity, and elevated aspartate transaminase (AST) levels during the induction/consolidation phase. (2) From a neuroimaging standpoint, López-De Suso et al. reviewed 8 years of institutional experience in the diagnosis and management of pediatric MTX-induced SLS, confirming that MRI (particularly diffusion sequences with characteristic restricted diffusion and T2/FLAIR

hyperintensities in the white matter of the centrum semiovale) is the modality of choice, given that computed tomography typically shows no abnormalities in the acute phase. (8)

López-De Suso et al. reported that the risk of SLS recurrence upon restarting MTX as part of the chemotherapy protocol was low, as the majority of patients re-exposed to MTX after an SLS episode did not experience recurrence of neurotoxicity, supporting the safety of continuing the oncological protocol after full clinical recovery. (8) This is consistent with the data of Mateos et al., who documented a recurrence rate of only 12.9% in patients who continued with MTX-IT after a first episode of neurotoxicity. (5) It should be noted that other series have reported higher recurrence estimates (up to 20-37%) when broader SLS definitions or different re-exposure intervals are applied, highlighting the variability in published rates and the importance of close neurological monitoring in subsequent cycles, regardless of the figure cited. (4) These data reinforce that permanent discontinuation of MTX is not justified following an SLS episode.

Case Presentations

Case 1

A 17-year-old female patient, originally from and residing in Temozón, Yucatán. Diagnosed with intermediate-risk acute lymphoblastic leukemia on February 20, 2025. Molecular profile: FISH negative, IDNA 1.14, MRD15 0.06%, B immunophenotype, karyotype SNG PAX5:ZCCHC7 (9p13). White blood cell count at diagnosis: 37,200 cells/ μ L. CSF at diagnosis: negative. Renal function at diagnosis within normal parameters.

The patient began her first consolidation cycle with HDMTX 2.5 g/m² over 24 hours, 6-mercaptopurine (6-MP) 50 mg/m²/day, and asparaginase (ASP) 15,000 IU/m² on days 3 and 10, plus intrathecal chemotherapy (MTX-IT). Leucovorin rescue was administered according to the institutional protocol. She progressed without documented neurological complications during this cycle. She received her second consolidation cycle with the same regimen; during this admission, the development of an intragastric abscess was documented, requiring surgical management with completion of the antimicrobial regimen with cefepime and doxycycline for 10 days. No neurological events were recorded during this cycle.

During her admission for her third consolidation cycle in April 2025, following high-dose MTX admin-

istration, serum MTX levels of 0.7 $\mu\text{mol/L}$ were recorded, with a subsequent control reporting less than 0.3 $\mu\text{mol/L}$. Homocysteine levels were not measured in this or any other case in this series, as the required laboratory reagent was not available at the institutional laboratory. This constitutes a recognized limitation, particularly given the central role of homocysteine in the pathophysiology of MTX-induced neurotoxicity. During this admission, she developed the first episode of subacute MTX neurotoxicity, manifested as aphasia and sialorrhea without fever, leading to the decision to discharge her on April 28, 2025, with partial improvement after steroid management. That same night, she again developed aphasia and sialorrhea and returned to the pediatric emergency department, where she presented mild sialorrhea and swallowing difficulties.

A cranial CT scan showed no alterations. MRI was not performed during the acute episode, as this imaging modality is not available at the Hospital General "Agustín O'Horán". The diagnosis was established based on the clinical criteria of Schmiegelow et al. She was subsequently evaluated by pediatric neurology, who confirmed the presentation as SLS, and treatment with methylprednisolone was initiated. Three days later, she was admitted to the Pediatric Oncology ward with recovered speech and no sialorrhea, no motor deficit, and no other abnormalities. The structured neurological examination at the time of the second admission revealed normal muscle strength with no alterations in deep tendon reflexes or meningeal signs.

Management was continued with methylprednisolone and dextromethorphan, with close monitoring of neurological status. The following day, the patient reported general improvement, although mild dysphagia and left facial palsy persisted. Twenty-four hours later, she was asymptomatic, with no difficulties speaking or moving, no pareses or paresthesias, moving all four limbs normally, and without swallowing alterations. Dexamethasone and mercaptopurine continued, and the patient was encouraged to learn a new language and play a musical instrument as a cognitive neurological rehabilitation strategy.

During this same admission, her fourth consolidation cycle was administered with complete SLS remission; prophylactic dextromethorphan was initiated, and MTX levels of 0.18 $\mu\text{mol/L}$ were documented.

Case 2

A 16-year-old female patient with a diagnosis of in-

termediate-risk acute lymphoblastic leukemia by age, IDNA 1.00, MRD15 <0.01%, established on November 1, 2024. History of asparaginase allergy from the second consolidation cycle. One month before her February 2025 admission, the patient experienced a transient episode of labial commissure deviation with spontaneous recovery, without hospitalization and without formal evaluation at the time. In retrospect, this episode is highly suggestive of an undiagnosed first SLS event, as it occurred within the post-MTX risk period and resolved spontaneously, fulfilling the characteristic clinical course criterion described by Schmiegelow et al. The exact timing of that episode in relation to MTX administration was not formally documented at the time.

She was admitted to the Pediatric Emergency Department in February 2025 with a 10-hour history of aphasia, labial commissure deviation, decreased muscle strength in the left upper and lower extremities with gait difficulties, followed by headache, nausea, and vomiting on four occasions. MTX serum levels at the time of the episode were not measured, and homocysteine levels were not measured, because the required reagent was unavailable at the institutional laboratory.

On admission, she was found to be hypoactive, reactive to stimuli, pale, with dry mucous membranes, right-deviated labial commissure, right upper limb Daniels strength 3/4, left upper limb 1/4, right lower limb 3/4, and left lower limb 1/4. No meningeal signs were documented. Vital signs at admission: 66 bpm, 24 breaths/min, 107/61 mmHg, and 36.8°C.

The following day, cranial CT showed no ischemic or hemorrhagic zones and no space-occupying lesions. CSF showed no characteristics of an infectious process. Simple and gadolinium-enhanced MRI was performed using T1, T2, and FLAIR sequences and showed subcortical frontotemporal hyperintensity without contrast enhancement, suggesting drug-induced leukoencephalopathy and small vessel hypoperfusion. Following evaluation by pediatric neurology, neuroprotection with citicoline 500 mg every 12 hours for 6 weeks was initiated. No follow-up MRI was performed at discharge.

On February 10, she was admitted to the Pediatric Oncology ward, regaining facial mobility and strength in the left hemibody. She was discharged on February 13 with muscle strength in the left upper limb 4/5 and left lower limb 4/5, with the remainder normal.

Case 3

An 11-year-old male patient with a diagnosis of

high-risk T-cell acute lymphoblastic leukemia, SNG negative, MRD28 <0.01%, established on December 2, 2024. History of asparaginase allergy from the second consolidation cycle. He received the first consolidation cycles according to protocol with HDMTX 5 g/m² over 24 hours, 6-MP 50 mg/m²/day, ASP 15,000 IU/m², and intrathecal chemotherapy. Serum MTX levels during prior cycles and at the time of the episode were not documented. Homocysteine levels were likewise not determined.

On February 25, 2025, the day after completing his fourth consolidation cycle, the patient experienced a gradual, progressive loss of strength in the left arm, progressing to complete inability to move the left hand and arm, accompanied by dysarthria and dysesthesia of the left hemiface. The mother reported partial spontaneous improvement in mobility in the half hour before admission.

He was admitted to the Pediatric Oncology ward on February 25, where it was determined that he met the clinical characteristics of SLS according to the criteria of Schmiegelow et al. Vital signs at admission: 91 bpm, 20 breaths/min, 107/71 mmHg, and 36.5°C. CNS infiltration was considered unlikely given the recent acellular CSF result and the partial spontaneous recovery. No lumbar puncture was performed during the SLS episode.

During his stay, he reported improvement in symptoms, but with persistence of decreased strength in the left hemibody and left facial palsy. Physical examination revealed discrete dysarthria, dysesthesia of the left hemiface with mild asymmetry, and impaired mobility. Cranial CT showed no alterations, and dextromethorphan 1 mg/kg/dose was prescribed. MRI showed an ovoid lesion in the right frontotemporal white matter without vascular compromise. In this case, MRI was accessible through referral to an external center, in contrast to Case 1, in which the patient's clinical stability and the institutional absence of on-site MRI precluded its performance during the acute episode. No follow-up MRI was performed after clinical recovery.

In the following days, the patient showed progressive symptom improvement, although residual decreased strength in the left hemibody was noted at discharge.

Discussion

All three patients developed focal neurological deficits during the consolidation phase of ALL treatment, with an onset interval between 24 hours and

8 days following HDMTX or MTX-IT administration (**Table 1**). This range is consistent with the risk period described in the literature, which establishes the subacute transient neurotoxicity window within the first 21 days after drug administration. (3,4)

The constellation of observed symptoms: aphasia, limb paresis, dysarthria, facial palsy, dysphagia, and sialorrhea, is consistent with the phenomenology reported in previous multicenter series. Santangelo et al. described, in their Italian series of 43 pediatric SLS episodes, that hemiparesis and aphasia were the most frequent manifestations, with spontaneous resolution being the norm in the majority of cases. (4) In our series, all three patients fulfilled the three diagnostic criteria of the consensus definition by Schmiegelow et al.: acute onset of focal neurological symptoms, absence of any other identifiable cause, and a self-limited clinical course compatible with transient leukoencephalopathy. (5)

A particularly relevant clinical finding is the history of Case 2, who experienced a transient episode of labial commissure deviation with spontaneous recovery approximately one month before her hospitalization, without formal evaluation at the time. In retrospect, this episode is highly suggestive of an undiagnosed first SLS event, which would imply that this patient experienced two episodes of subacute neurotoxicity. The risk of SLS recurrence after MTX- re-exposure has been documented across published series with considerable variability: Mateos et al. reported a rate of 12.9% in patients who continued MTX-IT, (5) while broader estimates from Santangelo et al. range up to 20-37% depending on the SLS definition and re-exposure interval applied. (4) This discordance reflects the heterogeneity of study designs and re-exposure protocols, and reinforces the need for individualized neurological monitoring rather than a single universal threshold for clinical decision-making.

All three patients share the most widely recognized risk factors for MTX-induced SLS development: age greater than 10 years and Hispanic ethnicity. Leitão Santos et al. highlight that Hispanic ethnicity constitutes an independent risk factor for this complication, which has been attributed to possible pharmacogenomic differences in folate metabolism and individual susceptibility to antimetabolite neurotoxicity. (3) Additionally, two of the three patients had a history of asparaginase allergy, a finding that, while not formally established as a risk factor for SLS, may reflect a broader pharmacological hypersensitivity that deserves investigation in larger series.

It is worth noting that all three cases involved adolescent patients (11, 16, and 17 years old) with heterogeneous molecular and risk profiles: intermediate-risk B-cell in Cases 1 and 2 and high-risk T-cell in Case 3, suggesting that SLS can occur regardless of ALL subtype when HDMTX is administered in patients with relevant demographic risk factors. The HDMTX dose in Case 3 (5 g/m²) was double that used in Case 1 (2.5 g/m²), consistent with the higher-intensity protocol for high-risk ALL; however, the small sample size precludes establishing a dose-response correlation in this series.

The pathophysiology of MTX-induced SLS has not been completely elucidated. The most accepted mechanism involves inhibition of dihydrofolate reductase with a consequent reduction in tetrahydrofolate levels, leading to accumulation of homocysteine in plasma and CSF. Homocysteine exerts neurotoxic effects through two complementary pathways: direct toxicity to the vascular endothelium, compromising white matter perfusion, and excitotoxic activation of NMDA receptors, triggering an anomalous neuronal depolarization cascade.

This latter pathway is of particular clinical relevance in the context of this series, as it supports the use of dextromethorphan as a neuroprotective agent by blocking the ion channel activated by homocysteine, thereby reducing excitotoxicity. In Case 3, administration of dextromethorphan at 1 mg/kg/dose was associated with progressive clinical improvement in a patient with persistent symptoms, supporting the pharmacodynamic rationale for its use. In Case 1, its prophylactic use during the fourth consolidation cycle was associated with the absence of recurrence and MTX levels within the safe range (0.18 µmol/L), although the observational nature of this report does not allow causality to be established. (1,7)

It is important to note that the use of dextromethorphan for this indication is reported primarily in case series and individual case reports; to date, no controlled clinical trials have evaluated its efficacy in MTX-induced SLS. Santangelo et al. reported its use in some of their participating centers with favorable results. (4) This series contributes additional clinical evidence in a pediatric Hispanic population that may guide therapeutic decisions while higher-level prospective studies are generated.

The therapeutic approach in this series was heterogeneous, reflecting both the variability described in the literature and the differences in clinical severity across cases. The treatment decision in each case was guided by a combination of clinical presenta-

tion severity, the neurologist's assessment, and institutional availability of agents. In Case 1, corticosteroids (methylprednisolone, subsequently transitioned to dexamethasone) were initiated empirically given the prolonged, fluctuating, and recurrent course of the neurological deficit, as steroids have been used in the literature for their anti-inflammatory and edema-reducing effects in MTX leukoencephalopathy. Dextromethorphan was added given its NMDA antagonist mechanism and was later continued prophylactically for the subsequent consolidation cycle. In Case 2, dextromethorphan was not available at the time of management; citicoline was selected as an alternative neuroprotective agent due to its known role in supporting membrane phospholipid synthesis, promoting neuronal repair, and its documented safety in pediatric populations with acute neurological conditions. In Case 3, dextromethorphan was available and was prescribed as the primary intervention based on the established pathophysiological rationale for NMDA blockade, with a favorable clinical response. While this variability reflects real-world resource constraints and evolving clinical judgment rather than a standardized protocol, it also underscores the need for consensus-based treatment guidelines for MTX-induced SLS. In all cases, permanent discontinuation of MTX treatment was avoided.

This point is of critical importance from an oncological perspective: high-dose MTX is an essential component of consolidation protocols for pediatric ALL, and its omission or substitution significantly compromises treatment efficacy and patient prognosis. (1,7) The self-limited nature of SLS, with resolution in hours to days without permanent sequelae in the vast majority of cases, justifies continuation of the chemotherapy protocol after complete clinical recovery, with close neurological monitoring in subsequent cycles. Monitoring serum MTX levels and, where possible, homocysteine levels, may contribute to identifying patients at higher risk of recurrence.

In all three cases, cranial CT showed no alterations, while MRI demonstrated focal hyperintensities in the frontotemporal white matter in Cases 2 and 3. In Case 1, an MRI was not performed during the acute episode because the Hospital General Dr. Agustín O'Horán does not have an on-site MRI unit. In this resource-limited setting, the clinical diagnosis of SLS was established exclusively based on the Schmiegelow et al. consensus criteria, which explicitly allow for diagnosis in the absence of imaging when the clinical course is characteristic. This approach is consistent with the recommendations of

López-De Suso et al., who emphasize that SLS is primarily a clinical diagnosis and that neuroimaging, while ideal, should not delay initiation of supportive management. (8) MRI findings included T2/FLAIR hyperintense lesions in the subcortical frontotemporal white matter without gadolinium enhancement in Case 2, and an ovoid lesion in the right frontotemporal white matter in Case 3, both without evidence of vascular compromise.

These findings are consistent with the characteristic radiological description of SLS, which consists of areas of transient vasogenic edema in the white matter without diffusion restriction (allowing differentiation from true ischemic stroke) and without contrast enhancement, distinguishing it from infectious or neoplastic processes. (2,4) The systematic normalcy of CT in all three cases underscores that this modality has insufficient sensitivity to detect the acute and transient white matter abnormalities associated with SLS, and that MRI is the modality of choice when this complication is clinically suspected. (8) When an MRI is not immediately available, the diagnosis can and should be based on clinical criteria, as occurred in Case 1.

Notably, all three cases are presented within four months at a single center, with two occurring in the same month (February 2025). Given that all patients received similar chemotherapy protocols, with comparable HDMTX doses and at equivalent treatment phases, this clustering warrants analysis. No changes in the institutional therapeutic protocol or in drug preparation and administration were identified during this period that could explain the cluster.

As a hypothesis-generating observation, the possibility that a physicochemical alteration in the methotrexate batch used during this period may have contributed to the clustering of cases cannot be entirely excluded. A concentration deviation, instability at reconstitution, or suboptimal cold-chain storage could theoretically result in higher effective plasma levels than expected, amplifying the dihydrofolate reductase inhibition cascade; however, batch identity, reconstitution records, and storage conditions were not systematically documented, and this hypothesis remains speculative without pharmacovigilance data. Future institutional clusters of chemotherapy-related neurotoxicity should prompt formal engagement of the pharmacovigilance committee for batch-level review.

An alternative hypothesis is that the true prevalence of SLS in pediatric Hispanic ALL patients may be underestimated in the reference literature, whose published rates (0.2%–3.8%) come predominantly

from European and North American cohorts of different ethnic composition (3,4). Hispanic ethnicity has been identified as an independent risk factor, and it is possible that in a population such as that of Hospital O'Horán, the observed frequency is intrinsically higher. Prospective epidemiological studies in Latin American populations are needed to characterize the true incidence of this complication in this demographic group.

This series has several limitations that must be explicitly acknowledged. First, the sample size of three cases precludes statistical or generalizable conclusions; the value of this report lies in the detailed clinical description and its contribution to the case literature on this complication in a Spanish-speaking population. Second, homocysteine levels were not determined in any of the three patients due to the unavailability of the required laboratory reagent at the institutional level — a structural constraint of regional centers with limited diagnostic resources. This is a relevant gap given that homocysteine accumulation is the central pathophysiological substrate of MTX-induced neurotoxicity; its measurement would have allowed correlation between biomarker levels and clinical severity and could have guided monitoring in subsequent cycles. We strongly recommend that this measurement be incorporated into the diagnostic workup at centers treating ALL patients with HDMTX, as its absence limits the interpretation of these cases.

Conclusion

SLS is a complication secondary to MTX treatment as part of the chemotherapy protocol in ALL patients; in these cases, it was observed to occur during the consolidation phase. This study demonstrates the importance of always maintaining a high index of suspicion for any focal neurological deficit in pediatric post-chemotherapy patients. It is essential to recognize that the course of this condition is self-limited and transient, which justifies not suspending oncological treatment or adding interventions that may compromise and prolong the patient's hospital stay.

This series of three MTX-induced SLS cases in pediatric ALL patients concretely illustrates the clinical presentation, risk profile, neuroimaging findings, and therapeutic options for this complication in the context of pediatric oncology at a regional center in Mexico. The cases reinforce that SLS is a real and recognizable complication in the daily clinical practice of units caring for childhood ALL with HDMTX-based consolidation regimens.

The main clinical messages derived from this series are as follows. First, SLS should be considered in the differential diagnosis of any acute focal neurological deficit in a pediatric ALL patient who has received MTX in the preceding weeks, especially if they meet the demographic risk factors (age greater than 10 years and Hispanic ethnicity). Second, CT has limited utility in this context; MRI with T2/FLAIR and diffusion sequences is the modality of choice and should be requested when clinical suspicion arises. Third, early recognition of the condition and understanding of its self-limited nature are essential to avoid unnecessary interruption of oncological treatment, whose continuity is determinant for ALL prognosis.

Fourth, dextromethorphan constitutes a therapeutic option with solid pathophysiological rationale both in the management of the acute episode and in the prevention of recurrence in subsequent MTX cycles, although the available evidence is limited to case reports and small series that do not yet allow

formal clinical practice recommendations to be issued.

From a regional public health perspective, the clustering of three cases within four months in a predominantly Hispanic population invites reflection on the possible underestimation of the true incidence of SLS in Latin American populations, and on the need to establish multicenter prospective registries in Mexico and Latin America that would allow characterization of the local epidemiology of this complication, identification of risk biomarkers, and systematic evaluation of available therapeutic interventions.

In summary, MTX-induced SLS is a rare but clinically impactful complication of pediatric ALL chemotherapy protocols. Its timely diagnosis, based on a high index of clinical suspicion and appropriate use of neuroimaging, allows effective management that preserves both the patient's neurological integrity and the continuity of the oncological treatment that determines their survival.

Table 1. Comparative summary of three pediatric patients with methotrexate-induced stroke-like syndrome

Variable	Case 1	Case 2	Case 3
Age	17 years	16 years	11 years
Sex	Female	Female	Male
LLA risk group	Intermediate risk (B-cell, SNG PAX5:ZCCHC7)	Intermediate risk (B-cell, IDNA 1.00)	High risk (T-cell, SNG negative)
MTX dose / route	HDMTX 2.5 g/m ² IV (24 h) + IT MTX	HDMTX 2.5 g/m ² IV (24 h) + IT MTX	HDMTX 5 g/m ² IV (24 h) + IT MTX
Cycle number at SLS onset	3rd consolidation	4th consolidation	Day after 4th consolidation
Days post-MTX to symptom onset	6–8 days	10 hours after admission	Day after completion (24 hours)
Neurological signs	Aphasia, sialorrhea, facial palsy (left), dysphagia	Aphasia, facial deviation (right), left hemiparesis (upper + lower), headache, nausea, vomiting	Left arm paresis (progressive), dysarthria, dysesthesia (left hemiface), left facial palsy
MTX level at event (μmol/L)	0.7 μmol/L (follow-up: <0.3 μmol/L)	Not reported	Not reported
Homocysteine level	Not reported, reagent unavailable at the institutional laboratory	Not reported, reagent unavailable at the institutional laboratory	Not reported, reagent unavailable at the institutional laboratory
CT findings	No alterations	No ischemic or hemorrhagic zones; no space-occupying lesions	No alterations
MRI findings	Not performed, MRI not available at the institution; diagnosis established by clinical criteria (Schmiegelow et al.)	Frontotemporal subcortical hyperintensity (T2); no contrast enhancement; suggests drug-induced leukoencephalopathy	Ovoid lesion in right frontotemporal white matter; no vascular compromise
Treatment	Methylprednisolone → Dexamethasone + Dextromethorphan (prophylactic for 4th cycle)	Citicoline 500 mg every 12 h × 6 weeks (neuroprotection)	Dextromethorphan 1 mg/kg/dose
Time to resolution	48–72 hours (full resolution by day 4 of admission)	3–4 days (partial at discharge: muscle strength 4/5 left limbs)	Days (residual mild left-sided weakness at discharge)

Abbreviations: LLA = acute lymphoblastic leukemia; MTX = methotrexate; HDMTX = high-dose MTX intravenous; IT = intrathecal; SLS = stroke-like syndrome; SNG = single nucleotide genotyping; IDNA = DNA index; MRI = magnetic resonance imaging; CT = computed tomography. * Homocysteine levels were not measured in any of the three cases.

References

1. Kantarjian H, Pui CH, Jabbour E. Acute lymphocytic leukaemia. *The Lancet*. agosto de 2025;406(10506):950-62. doi:10.1016/S0140-6736(25)00864-5
2. Inaba H, Khan RB, Laningham FH, Crews KR, Pui CH, Daw NC. Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. *Ann Oncol*. enero de 2008;19(1):178-84. doi:10.1093/annonc/mdm466
3. Leitão Santos M, Silva S, Moreira A, Ribeiro A. Methotrexate-Induced Stroke-Like Syndrome: A Typical Presentation of a Rare Complication. *Cureus*. 5 de junio de 2023. doi:10.7759/cureus.40004
4. Santangelo A, Bartolini E, Nuzzi G, Foiadelli T, Michev A, Mina T, et al. The Clinical Impact of Methotrexate-Induced Stroke-Like Neurotoxicity in Paediatric Departments: An Italian Multi-Centre Case-Series. *Front Neurol*. 10 de junio de 2022;13:920214. doi:10.3389/fneur.2022.920214
5. Mateos M, Marshal G, Barbaro P, Quinn M, George C, Mayoh C. Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. 2022. 107:635-43. doi:10.3324/haematol.2020.268565
6. Schmiegelow K, Attarbaschi A, Barzilai S, Escherich G, Frandsen TL, Halsey C, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. *Lancet Oncol*. junio de 2016;17(6):e231-9. doi:10.1016/S1470-2045(16)30035-3
7. Afshar M, Birnbaum D, Golden C. Review of Dextromethorphan Administration in 18 Patients With Subacute Methotrexate Central Nervous System Toxicity. *Pediatr Neurol*. junio de 2014;50(6):625-9. doi:10.1016/j.pediatrneurol.2014.01.048
8. López-De Suso D, García-Salido A, Andiñ-Catalán M, Leoz-Gordillo I, Lassaleta-Atienza Á, Sirvent-Cerdá S. Methotrexate-induced stroke-like neurotoxicity: Case report, 8 years of experience, and literature review. *Pediatr Blood Cancer*. septiembre de 2022;69(9):e29627. doi:10.1002/pbc.29627.

This page is intentionally left blank

