British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(6): 55135
https://doi.org/10.31083/BJHM55135

Review

Methotrexate Neurological Toxicities: Current State-of-the-Art

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Academic Editor: John Alcolado
Submitted: 29 August 2025 Revised: 9 January 2026 Accepted: 26 January 2026 Published: 22 June 2026

Abstract

Methotrexate is a highly effective anti-folate drug, used for a range of oncological and inflammatory conditions. Toxic effects of methotrexate on the bone marrow, mucosa, liver and kidneys are widely appreciated; however, clinicians may be less familiar with neurotoxic side-effects. Neurotoxicity is primarily reported in those receiving high-dose or intrathecal methotrexate; however, it may occur in patients receiving low-dose treatment. Symptoms range from acute headache/somnolence, sub-acute onset of seizures/stroke-like symptoms, to long-term cognitive and behavioural difficulties. Stroke-like symptoms occur several days after administration when the patient may be out of the hospital, meaning that acute care providers must be able to recognise and appropriately manage these conditions. The mechanism by which methotrexate causes neurotoxicity remains poorly understood, and although some treatments and preventative agents have been identified, they lack robust evidence at present, representing a key area for future research. This article aims to provide a state-of-the-art review of methotrexate neurotoxicity, which will increase physician awareness of this condition, its presentation, and to highlight evidence and research gaps relating to treatment and prevention.

Keywords: leukemia; methotrexate; nervous system diseases; neurotoxicity syndromes; drug-related side effects and adverse reactions

1. Introduction

Folate antagonists such as methotrexate were the first effective anti-cancer therapies for childhood acute lymphoblastic leukaemia (ALL) [1]. Methotrexate is still widely used for malignant and non-malignant disease, including inflammatory arthritis, haematological and solid tumours and medical treatment of ectopic pregnancy [2,3]. Methotrexate is considered an 'essential medication' by the World Health Organization [4].

Methotrexate impedes cell division by inhibiting dihydrofolate reductase, resulting in impaired purine and pyrimidine synthesis, which are required for cell proliferation [5]. This impacts rapidly dividing cancer cells, such as in ALL. However, the pathways involved in the anti-inflammatory effect of low-dose methotrexate are less well understood and may differ from its anti-cancer effect at much higher doses [6].

Intravenous high-dose methotrexate (HD-MTX) and intrathecal methotrexate (IT-MTX) are used almost exclusively in malignant disease. HD-MTX is usually defined as doses of $\geq$500 mg/m^2 intravenously (typically 2–5 g/m^2), with 4–12 mg (according to age) used intrathecally [7]. In ALL, both HD-MTX and IT-MTX are important components of central nervous system (CNS) directed treatment, given to all patients to prevent disease recurrence at this sanctuary site. Low-dose methotrexate (LD-MTX) by the oral, intravenous or subcutaneous route is used in inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease [8,9]. LD-MTX can also play a role in the management of malignant disease, for example, in leukaemia maintenance therapy, low-risk trophoblastic disease or as an adjunct in metastatic breast cancer [10,11].

Scale of the Problem

The effects of methotrexate toxicity on the bone marrow, mucosa, liver and kidneys are widely appreciated; however, clinicians who do not regularly prescribe HD/IT MTX may be less familiar with the potential neurotoxicities [2]. Importantly, stroke-like syndrome and seizures often show delayed presentation 2–10 days after administration, meaning that the patient may be out of the hospital and present to emergency or out-of-hours services [12,13]. Thus, it is vital that emergency providers are aware of this rare but clinically significant condition whose management differs from conventional stroke. While methotrexate neurotoxicity is usually seen with intrathecal or high-dose intravenous (IV) administration associated with oncological uses, cases have rarely been reported with low-dose and oral MTX [14,15].

Estimates of the prevalence of methotrexate neurotoxicity vary; however, a study of almost 500 cancer patients receiving high-dose IV or intrathecal methotrexate found that 3% of adults and 7% of children experienced neurotoxicity [16]. In the UKALL 2003 trial of over 3000 children treated for ALL (of which methotrexate forms a mainstay of treatment), 8% of patients experienced a neurotoxic adverse event [17,18]. These findings were supported by Mateos and colleagues [19], who showed a 7.6% prevalence rate in 1251 children treated for ALL, although rates as high as 14% have been reported [20]. Furthermore, up to

60% of children with ALL treated with methotrexate may have identifiable brain magnetic resonance imaging (MRI) changes of leukoencephalopathy, suggesting an additional burden of sub-clinical neurotoxicity [21]. These studies may suggest that methotrexate neurotoxicity is more common in children compared to adults, of whom around 5–10% may experience acute/sub-acute events and over half may have sub-clinical neurotoxicity.

There is a spectrum of acute, sub-acute and chronic neurological toxicities associated with methotrexate, including somnolence/headache, seizures, methotrexate 'stroke-like syndrome' (SLS), leukoencephalopathy and a long-term impact on cognition and attention as illustrated in Fig. 1 [22]. Chemotherapy-related neurological toxicities are classified in the Ponte Di Legno Toxicity Working Group Consensus on severe acute toxic effects of childhood ALL treatment [23]. There are no established time-based definitions for acute, sub-acute and chronic neurotoxicities; however, for the purposes of this article, we have considered 'acute' effects likely to occur within 48 hours, sub-acute within 48 hours—21 days following treatment and chronic effects lasting months to years. The Ponte Di Legno Toxicity Working Group described methotrexate stroke-like syndrome as occurring within 21 days of treatment [23]. Although the majority of cases of methotrexate-related neurotoxicity resolve and do not recur, they can be life-threatening, and some patients may be left with permanent physical or mental disability [24]. Considering the mechanisms of methotrexate neurotoxicity and strategies to prevent and treat them are therefore crucial in optimising long-term outcomes.

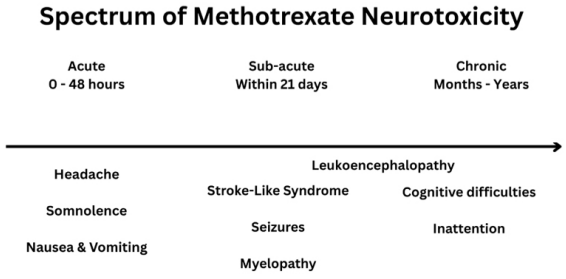

Fig. 1. Spectrum of acute, sub-acute and chronic methotrexate neurotoxicity. Original figure created using Canva (https://www.canva.com/zh_cn/).

2. Clinical Features

2.1 Acute Somnolence/Headache

Headache is a recognised toxicity of intrathecal methotrexate (IT-MTX), although the precise mechanism remains unclear. It has been hypothesised that IT-MTX may cause inflammation of the arachnoid mater (chemical arachnoiditis) [25]. Another proposed mechanism is by adenosine release, resulting in a disturbance in blood flow to the brain and neuronal excitability [26]. Indeed, one of the first attempted treatments for acute methotrexate toxicity (including headache) was an adenosine antagonist, aminophylline [27]. Headache appears to be a relatively common occurrence following IT-MTX administration; however, it is often difficult to delineate whether this is caused by lumbar puncture complications such as cerebrospinal fluid (CSF)-leak, intrathecal methotrexate or a combination of both [28].

A meta-analysis of adverse effects in low-dose methotrexate (LD-MTX) found that 7% of patients with inflammatory conditions on LD-MTX experienced headache [29]. Moreover, issues with both daytime somnolence and insomnia have been reported, which may impact quality of life and well-being [30]. The lack of randomised controlled trials in this area means that it is difficult to fully establish the true causative role of methotrexate from other factors, such as disease-related effects and other medication side effects. Further research is warranted, given the wide use of methotrexate in managing inflammatory arthritis and its potential impact on quality of life.

2.2 Seizures

Seizures are an important sub-acute toxicity of methotrexate, particularly in high-dose and intrathecal administration [31,32]. For instance, Bhojwani and colleagues (2014) [31] found that 3.8% of their patients with ALL treated with MTX experienced neurotoxicity, and that half of these events presented with seizures. Moreover, cases of status epilepticus due to methotrexate administration have been reported, emphasising the potential seriousness of this side-effect [33,34].

Overall, seizures represent a significant proportion of neurotoxicity events in paediatric ALL—for example, seizures accounted for 86 of 300 neurotoxicity events reported in the UKALL 2003 trial [18]. Furthermore, a retrospective analysis of 649 paediatric patients treated for ALL revealed that 13% experienced neurotoxicity, of which seizures represented two-thirds of presentations [35]. These findings were mirrored by Kranjčec et al. (2024) [36], who in addition, reported that of 10 seizure events, 4 progressed to status epilepticus, of which 3 required endotracheal intubation. Of note, seizures are also associated with posterior reversible encephalopathy syndrome (PRES), which may occur in the first few months of ALL therapy. PRES is most commonly caused by vincristine and/or corticosteroids, which are used alongside methotrexate in induction chemotherapy [37]. Therefore, pinpointing the responsible agent can often be difficult. PRES should always be part of the differential diagnosis in a patient presenting with seizures on ALL therapy, and it is often associated with visual disturbance, hypertension and confusion [38]. Early imaging is recommended to distinguish the two conditions and rule out alternative causes such as an intracerebral bleed or cerebral venous sinus thrombosis.

Table 1. Comparison of clinical features of methotrexate stroke-like syndrome compared to classical stroke presentations in patients receiving high-dose or intrathecal methotrexate.

Condition	Clinical presentation	Onset	Aetiology	Imaging	Treatment
Methotrexate stroke-like syndrome (SLS)	Paralysis Cranial nerve palsies Altered mental status Waxing and waning presentation is classic	Within 21 days of methotrexate administration	Methotrexate exposure—numerous proposed mechanisms	CT—usually normal MRI—deep white matter changes/leukoencephalopathy DWI shows restricted water diffusion	Supportive May be a role for dextromethorphan or aminophylline Unlikely to re-occur on re-exposure
Posterior reversible encephalopathy syndrome (PRES)	Seizure Visual disturbance Headache Hypertension Altered mental status	Usually within first 3–4 months of treatment	Vincristine (and steroid) induced endothelial dysfunction leading to vasogenic oedema	CT—often normal MRI shows bilateral subcortical or cortical oedema typically in parieto-occipital regions DWI shows enhanced water diffusion	Treat hypertension, supportive care
Cerebral venous sinus thrombosis (CVST)	Headache Seizures Focal neurological deficit Visual symptoms	Usually within 2 weeks of asparaginase administration	Hypercoagulable state associated with asparaginase (and possibly exacerbated by steroids)	MRI with venography shows thrombus in dural venous sinuses, cerebral veins or both High resolution CT venogram with contrast—may show thrombus however may be less sensitive than MRI	Anticoagulation—close liaison with haematologist especially if significant associated haemorrhage or thrombocytopenia
Haemorrhagic stroke	Depends on site— Paralysis Cranial nerve palsies Headache Reduced conscious level	Most common at initial presentation of leukaemia	May be precipitated by thrombocytopaenia, anticoagulants, coagulopathy	CT—usually reveals intra-parenchymal haemorrhage	Treat underlying cause. Supportive management
Ischaemic stroke	Depends on distribution— Hemiparesis Cranial nerve palsies Dysphasia Altered mental status	Rare in patients with leukaemia—always consider SLS as a more likely diagnosis. Relatively sudden onset	May be underlying cause, e.g., PFO, AF, thrombophilia	CT—may be normal or reveal early ischaemia MRI—ischaemia, usually territorial	Careful consideration of aspirin and/or thrombolysis if clear occlusive thrombus in context of cancer. Close liaison with haematology in patients with low platelet counts
Other important causes to consider: Infection, hypoglycaemia, electrolyte abnormalities, epilepsy, CNS leukaemia, encephalitis					

Abbreviations: AF, atrial fibrillation; CNS, central nervous system; DWI, diffusion-weighted imaging; CT, computed tomography; MRI, magnetic resonance imaging; PFO, patent foramen ovale.

Seizures appear to be exceedingly rare in patients treated with LD-MTX for non-malignant conditions, with only one case (to our knowledge) reported of a patient with rheumatoid arthritis (RA) who experienced new seizures following initiation of LD-MTX [39]. However, a meta-analysis of population-based studies suggested that the risk of epilepsy in patients with RA and of children born to mothers with RA may be significantly increased (relative risk [RR] 1.601, $p = 0.017$) [40]. It is unclear to what degree (if any) methotrexate may contribute to this increased risk.

2.3 Methotrexate Stroke-Like Syndrome

Methotrexate stroke-like syndrome (SLS) is perhaps the most important neurotoxic side effect for the general physician to be aware of. It is defined by the Ponte Di Legno Consortium as new-onset paralysis/weakness, aphasia, dysarthria, altered consciousness (with or without seizures) within 21 days of IV or IT MTX administration, with one of the following: (1) characteristic MRI changes of leukoencephalopathy; or (2) a waxing-and-waning clinical course, with no other identifiable cause [23]. This definition aids in ensuring consistent diagnosis; however, there is still some variation in use in the literature. The rapid appearance and disappearance of rotating physical neurological signs such as cranial nerve palsies and hemiparesis over minutes to hours to days (so-called waxing and waning pattern) is particularly characteristic of SLS and can help distinguish it from other causes of stroke, such as intracranial thrombosis or haemorrhage [23]. Of note, computed tomography (CT) scans are often normal, which may help in excluding haemorrhagic stroke in the first instance [41]. Characteristic MRI findings include deep white matter changes detected on diffusion-weighted imaging (DWI); however, these can be transient, so diagnosis may need to be made on ruling out other important causes and on its characteristic clinical picture [23,32]. An important differential to consider in patients with stroke-like symptoms undergoing ALL treatment includes cerebral venous sinus thrombosis (CVST), which can be associated with asparaginase administration [42]. The features of SLS, PRES, CVST and haemorrhagic/ischaemic strokes are summarised in Table 1. Key differentiating features for SLS include the waxing and waning clinical picture and characteristic MRI findings, albeit that these may be transient. Importantly, although mimicking stroke, the aetiology of SLS is distinct and neither aspirin nor thrombolysis is indicated for SLS, and may be dangerous due to the thrombocytopenia often accompanying methotrexate containing chemotherapy regimens.

MRI diffusion weighted imaging is thought to be useful in distinguishing SLS and PRES. PRES causes capillary leak associated with increased water diffusion, whilst SLS usually displays normal or restricted water diffusion [43]. However, case series of SLS MRI findings often show a mixed picture. This may reflect incorrect classification (i.e., inclusion of some classical PRES cases caused by vincristine/steroids in an MTX-SLS cohort), or may indicate that the underlying pathogenesis of methotrexate stroke-like symptoms can vary.

Apiraksattayakul and colleagues (2024) [16] reported stroke-like syndrome in 7 of 18 patients who experienced methotrexate neurotoxicity (2.9% prevalence in all paediatric cancer patients treated with methotrexate). A retrospective review of 1251 children in Australia treated for ALL revealed 53 cases of SLS using the Ponte Di Legno definition (4.2% prevalence) [19]. This suggests that although uncommon, SLS is perhaps not as rare as initially believed, representing an important and serious toxicity of methotrexate therapy.

Risk factors for SLS are poorly understood, with increasing age as the only robust risk factor identified in multiple studies [18,19,44,45]. Liver function test abnormalities in induction and Latino/Hispanic ethnicity are other potential risk factors [19,20,45]. The relationship with methotrexate dose is unclear, with some studies reporting higher rates of toxicity with higher doses [46] but others failing to find an association between methotrexate pharmacokinetics and neurotoxicity [47].

To our knowledge, there is only one case report in the literature of a stroke-like syndrome in a patient on LD-MTX, suggesting that SLS in low-dose MTX is likely to be extremely rare [48]. Their case describes a patient with systemic lupus erythematosus (SLE) and RA who experienced transient stroke-like symptoms with MRI changes, both of which were reversible on cessation of MTX [48]. More evidence is required to determine the prevalence of SLS in patients on LD-MTX.

2.4 Leukoencephalopathy

Methotrexate-related leukoencephalopathy is an overarching term for brain white-matter changes attributed to methotrexate use [31]. As previously discussed, these changes can be observed in SLS but can also be associated with other MTX-related neurological symptoms such as encephalopathy and seizures, or be completely asymptomatic [21]. Furthermore, severity ranges from asymptomatic to a severe subtype of leukoencephalopathy termed ‘disseminated necrotising leukoencephalopathy’, which appears to be very rare but can be fatal [21,49]. Most reported cases of MTX-related leukoencephalopathy are in patients receiving high-dose/intrathecal MTX; however, there are a limited number of case reports in patients receiving LD-MTX [14,15,50].

Leukoencephalopathy has been described primarily in paediatric patients with ALL and lymphoma receiving IT-MTX, sarcoma receiving IV methotrexate, and in children with brain tumours, delivered via a ventriculocisternal catheter [31,32,51]. A number of studies have shown a high incidence of leukoencephalopathy during methotrex-

ate chemotherapy and up to one year after, with estimates ranging from 23–75%, albeit in relatively small cohorts [46,52,53]. More recently, Bhojwani and colleagues (2014) [31] performed prospective imaging for 369 children with ALL being treated with high-dose and intrathecal methotrexate, which revealed leukoencephalopathy in all patients who experienced neurotoxicity and in 20.6% of asymptomatic patients, suggesting a significant subclinical burden of disease. Moreover, a number of studies have identified increased methotrexate exposure (measured by 42-hour MTX/leucovorin ratio), or as increased dose/number of courses), as a significant risk factor for leukoencephalopathy, supporting a dose-dependent mechanism [21,31,46,54]. Of interest, Reddick and colleagues [21] showed that the prevalence of leukoencephalopathy significantly decreased by 18 months following IV MTX administration. A similar phenomenon was reported by Bhojwani and colleagues (2014) [31] in which the grade of leukoencephalopathy improved over time for 17% of patients and 23% had completely resolved, perhaps suggesting a degree of reversibility.

Leukoencephalopathy is of significant clinical interest in paediatric ALL, given that acute leukoencephalopathy (during treatment) is associated with long-term cognitive problems and structural brain differences, such as reduced white matter integrity [55]. As most children are now cured of their ALL, it is crucial to consider how to maintain excellent treatment response, while aiming to mitigate long-term damage from therapy.

2.5 Long-Term Cognitive Impact

Long-term cognitive dysfunction is reported to affect one-third of childhood cancer survivors in the United States, with reported issues in working memory, organisation and planning [55,56]. Furthermore, childhood cancer survivors are at greater risk of poor academic achievement and are more likely to be unemployed compared to their siblings [57,58]. This illustrates the importance not only of curing children of their cancer but also of minimising potential long-term therapy-related neurotoxicity, which impacts on life chances and wellbeing.

Although the cognitive issues experienced by childhood cancer survivors are likely to be multifactorial, methotrexate chemotherapy has been implicated as a significant risk factor for their development [56,59]. In line with common indications for high-dose/intrathecal methotrexate, long-term cognitive dysfunction related to methotrexate has been reported primarily in survivors of ALL, sarcoma and brain tumours [60–62]. Hustu and Aur (1978) [63] showed that intrathecal methotrexate and cranial irradiation vastly reduced relapse rates for ALL, leading to its adoption in clinical practice in the 1980s. However, concerns regarding the long-term cognitive impact of whole-brain irradiation, in addition to evidence that chemotherapy-only CNS-directed treatment was sufficient to prevent relapse, caused a change in practice towards intensive intrathecal therapy for CNS prophylaxis [64,65]. Given that many children with ALL received both radiotherapy and IT-MTX, it can be challenging to delineate the long-term effects of MTX alone. However, a meta-analysis of the neuropsychological sequelae of paediatric ALL patients receiving chemotherapy-only showed that even after omitting radiotherapy, children still experienced significant cognitive deficits and reduced academic attainment [66]. Of interest, two randomised controlled trials have shown similar levels of neuropsychological problems between children with ALL treated with cranial irradiation or HD-MTX, suggesting that HD-MTX may lead to greater long-term neurotoxicity than previously thought [67,68].

It has been suggested that episodes of acute neurotoxicity (such as seizure and leukoencephalopathy) are associated with increased risk of neurocognitive problems in the longer-term. For instance, the St Jude's Lifetime Cohort Study of over 2000 childhood cancer survivors reported that seizures in patients treated for CNS tumour were associated with reduced executive function and processing speed ($p < 0.02$), and in patients with non-CNS tumours, seizures were associated with poorer cognitive functioning in all domains [69]. Harris and colleagues [70] showed that children with ALL who had experienced acute neurotoxicity had reduced performance in most cognition domains, including fine motor and attention, over 1 year following treatment ($p = 0.02$). Furthermore, children with leukoencephalopathy during treatment are at greater risk of neurocognitive issues and reduced quality of life, emphasising the wide-ranging effect that MTX-related cognitive issues can have for survivors of childhood cancer [55,62,71]. It is therefore paramount to consider the underlying pathophysiology of MTX-related neurotoxicity, and strategies to minimise the long-term effects of cancer treatment, especially in children and young people.

A systematic review of long-term cognitive outcomes suggested that attention and executive functioning appeared to be most commonly affected [60]. Moreover, a study of neurocognitive outcomes of 34 patients who had received IV-MTX for childhood sarcoma reported significantly reduced processing speed compared to controls [62]. Although methotrexate neurotoxicity has been reported to affect almost all domains of cognition, attention and executive functioning appear to be major challenges, which is crucial for planning effective treatments and interventions.

As with other forms of methotrexate-related neurotoxicity, greater MTX exposure appears to correlate with poorer neurocognitive outcomes, possibly suggesting a dose-dependent relationship [72,73]. Reports of cognitive problems caused by LD-MTX appear to be rare, with only one case report of reversible MTX-induced dementia found [74]. More research is required to determine whether low-dose MTX has any effect on cognition.

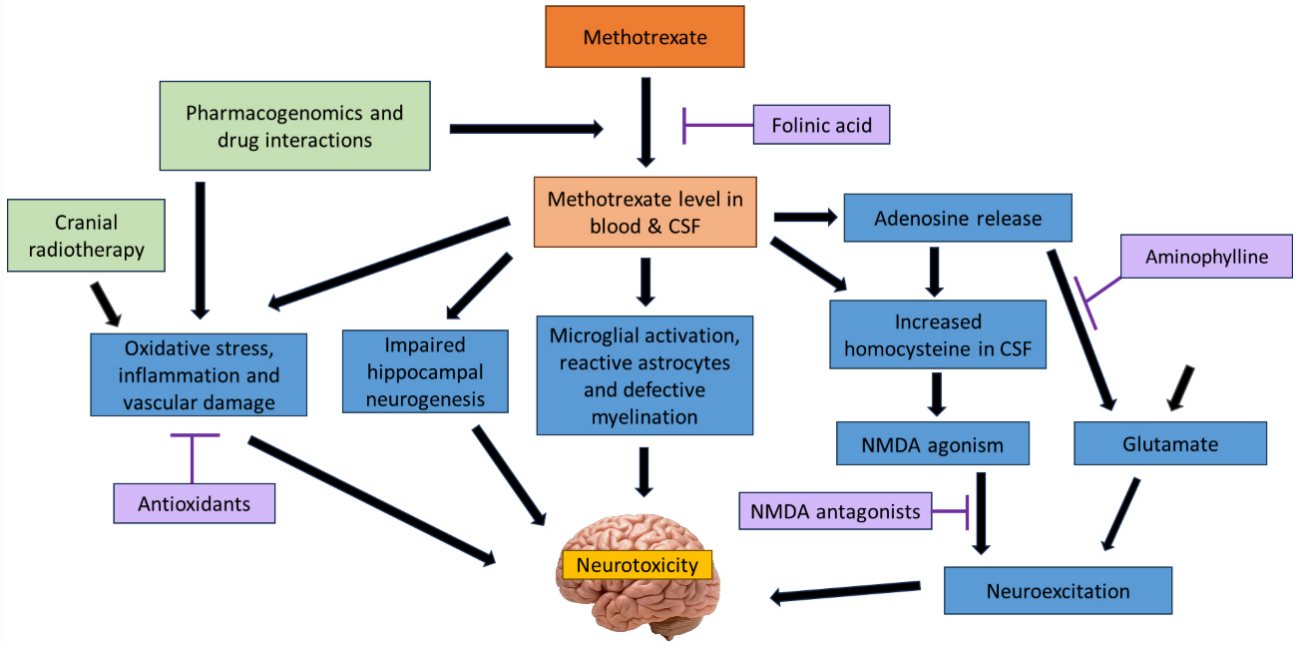

Fig. 2. Overview of potential mechanisms of methotrexate-related neurotoxicity. Potential mechanisms are shown in blue, and other contributing factors are in green. Proposed treatments (purple) are shown in relation to their potential sites of action. Abbreviations: CSF, cerebrospinal fluid; NMDA, N-methyl-D-aspartate. Original diagram created using Canva (https://www.canva.com/zh_cn/).

2.6 Myelopathy

Myelopathy/transverse myelitis is the rarest neurological side-effect of methotrexate. It has been described in case reports and series as a condition which mimics subacute degeneration of the spinal cord following IT-MTX administration, with patients experiencing lower limb weakness/paraesthesia and/or bladder/bowel dysfunction [75–77]. Pinnix and colleagues [78] present a case series of MTX-induced myelopathy in paediatric and adult patients with ALL in which 7 of 8 patients with data available had either below normal folate or increased homocysteine levels, which may suggest that folate antagonism provided by methotrexate is implicated in this process. Despite this potential cause, folate replacement did not result in clinical improvement [78]. Some cases of methotrexate-induced myelopathy appear to improve over the course of a few months; however, it is unclear what role (if any) folate replacement or proposed treatments such as dextromethorphan may play, given that only case reports are available [79,80]. Methotrexate-induced myelopathy appears to be primarily associated with intrathecal administration, although greater knowledge of the causes and course of the disease is needed.

3. Mechanisms of Methotrexate Neurotoxicity

3.1 Overview of Potential Pathophysiology

There are a number of proposed mechanisms for methotrexate-induced neurotoxicity, including inadequate folinic acid rescue, production of neuroexcitatory neurotransmitters and defective myelination, among others, illustrated in Fig. 2. Indeed, the primary mechanisms involved in acute, sub-acute and chronic methotrexate neurotoxicity may differ [7].

It has been hypothesised that reduced folic acid (in part due to the action of MTX as a folate antagonist), may contribute to the development of MTX-related neurotoxicity by preventing normal neuronal cell division and regeneration [78,81,82]. Folinic acid or ‘leucovorin’ rescue has been included in HD-MTX protocols to aim to reduce toxicities, with careful attention paid to dosing to ensure adequate folinic acid rescue, and dose timing to ensure that the chemotherapeutic benefit of MTX is maintained [7].

Furthermore, adenosine may play a role in the development of acute MTX-related neurotoxicity, given that methotrexate promotes adenosine release and that adenosine is raised in CSF following methotrexate administration [26,83]. This effect may be modulated by reduced dihydrofolate reductase activity, leading to increased adenosine and homocysteine, producing a neuroexcitatory effect [84].

Homocysteine is elevated in the CSF of children with neurotoxicity [85]. Homocysteine is metabolised to excitotoxic glutamate analogues which act on the N-methyl-D-aspartate (NMDA) receptor, leading to neuroexcitation and subsequent neurotoxicity such as seizure activity [86]. NMDA blockade is associated with improved cognitive tests in rats and provides the mechanistic rationale for dextromethorphan use in MTX-SLS [87,88].

There are a number of mechanisms which have been suggested for chronic methotrexate-related neurotoxicity,

including reduced myelination, oxidative stress and impaired hippocampal neurogenesis. In murine models, Gibson and colleagues [89] showed that methotrexate-induced cognitive impairment was associated with dysfunction of three subtypes of glial cells, leading to reduced myelination. Further mouse and rat models showed that methotrexate reduces Brain-derived neurotrophic factor, which is required for myelination, potentially by epigenetic modification by methotrexate [90,91]. These findings support reduced myelination as another potential mechanism of chronic methotrexate -related toxicity.

Methotrexate has been shown to produce reactive oxygen species, which can lead to cell/tissue death, contributing to cognitive impairment in mice/rat models [92,93]. Furthermore, these trials have proposed antioxidant mechanisms to reduce free radicals and subsequent neurotoxicity, which merit further clinical consideration [92,94]. The potential role of oxidative stress in methotrexate neurotoxicity is further supported by genome-wide association studies (GWAS) implicating genes involved in this process [19,95].

Rat and mouse models have also shown that cell proliferation may be reduced in the hippocampus following methotrexate administration [96,97]. Animals in these studies had issues with memory/cognition and, in one study, depressive behaviours [96,97]. In a small pilot study of 10 children who had undergone HD-MTX treatment, the cerebral blood flow to the hippocampus strongly negatively correlated with visual memory scores [98]. These studies offer a potential mechanism for methotrexate-related cognitive issues by impaired hippocampal neurogenesis; however, larger studies would be required to confirm this mechanism.

Although various mechanisms for methotrexate-related neurotoxicity have been proposed, greater work is needed to fully understand the pathophysiology of this condition and how we may use this knowledge to prevent and treat patients.

3.2 Potential Causes/Exacerbating Factors

There are various factors which may predispose individuals to neurotoxic side effects. From the literature, high-dose and intrathecal methotrexate appear to carry a much higher risk of neurotoxicity. Furthermore, higher levels of methotrexate exposure at 42 hours were associated with increased rates of leukoencephalopathy in children with ALL, suggesting that careful adjusted dosing should be considered [31].

Paediatric patients appear to be at greater risk, with a prevalence of 7.4% in children compared to 3.1% of adults receiving IV or IT MTX in one retrospective study [16]. However, conversely, a study of 203 adults with ALL showed a prevalence of MTX neurotoxicity of 7.3%, which is similar to rates reported in the paediatric population [99]. For children with ALL, neurotoxicity may be multifactorial, including the effects of other potentially neurotoxic agents used during treatment, CNS disease, coagulopathy and infection [22]. Age greater than 10 years was shown to be a risk factor for methotrexate SLS and for neurotoxicity in ALL more generally [18,44]. Bond and colleagues (2013) [44] hypothesised that age may predict SLS risk due to a correlation between age and higher National Cancer Institute (NCI) risk, and therefore more intense chemotherapy, although further analysis of all neurotoxicity events in the trial showed age $>$10 years as a risk factor even among patients on the same treatment regimen [18].

Potential exacerbating biological factors have been described, such as vitamin B12/folate deficiency and drug interactions, such as with nitrous oxide. Vitamin B12 deficiency has been reported as an exacerbating feature of MTX neurotoxicity in a small number of case reports [82,100]. There is a mechanistic basis for this theory, with vitamin B12 required as a co-factor for methionine synthase, which converts homocysteine to methionine, leading to excess homocysteine and a deficiency of methionine—both putative causes of neurotoxicity (see above). Therefore, optimising folinic acid replacement and vitamin B12 levels may be potential methods of reducing MTX neurotoxicity. Furthermore, there is some evidence that nitrous oxide may increase the risk of MTX-related neurotoxicity, potentially due to shared metabolic pathways converging on inactivation of B12 and consequent impairment of methionine synthase activity [100,101]. This is especially pertinent as children with ALL often undergo numerous procedures requiring sedation/anaesthesia during treatment.

As discussed, GWAS studies have been useful in identifying possible mechanisms for MTX-related neurotoxicity, and suggest that some genetic variants may increase the risk of developing neurotoxicity [19,95,102]. Understanding of this area is still in its infancy; however, GWAS may enable us to better predict patients at high risk of MTX neurotoxicity in the future.

4. Management of Methotrexate Neurological Toxicity

4.1 Prevention

There is currently no proven preventative strategies for methotrexate neurotoxicity apart from limiting exposure to methotrexate. Despite this review focusing on the potential toxic effects, it is important to acknowledge that HD/IT MTX is used because it is highly effective as an anti-cancer agent, especially in preventing CNS relapse in ALL. Where other chemotherapeutic agents are feasible, these should, of course, be considered; however, they often come with their own toxicities. Concurrent administration of IV cyclophosphamide and Cytarabine was found to increase the risk of SLS in the UKALL 2003 trial, illustrating the need to consider neurotoxicity within the broader clinical picture [44].

Given that higher cumulative doses of MTX have been associated with increased risk of neurotoxicity, there has been a focus on optimising chemotherapy regimens and risk

stratification strategies to balance the risk of relapse versus potential neurotoxicity [103,104]. This is essential for reducing the unnecessary harms of methotrexate while ensuring adequate cancer treatment.

A recent meta-analysis of reported studies concludes that protocols using HD-MTX with low levels of folinic acid rescue have higher rates of neurocognitive adverse outcomes and that this can be prevented by adequate folinic acid rescue [105]. However, the role of folinic acid replacement in preventing neurocognitive toxicities from intrathecal therapy is currently unknown.

Practical steps to minimise the risk of neurotoxicity should include careful attention to avoiding potential drug interactions and ensuring adequate vitamin B12 levels [100]. Avoiding concurrent nitrous oxide may also minimise neurotoxicity, although direct clinical evidence is limited [82,101].

4.2 Treatment and Management Strategies

At present, the majority of management for acute methotrexate-related neurotoxicity is supportive [31]. Medications such as dextromethorphan and aminophylline have been tried as potential treatments; however, robust evidence for these agents is currently limited.

Dextromethorphan is a low-affinity uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, with proponents suggesting that this may reverse or prevent some of the neurotoxic effects of MTX [85]. The clinical utility of dextromethorphan is unclear, given that only a few case series have been reported, and methotrexate neurotoxicity often shows rapid spontaneous improvement [85,88,106,107]. However, there is some suggestion that starting dextromethorphan within the first few hours may shorten the duration of symptoms, compared to patients where treatment is started after 24 hours [107]. No case series including a control group of untreated patients or randomised controlled trials have been performed, meaning that a strong evidence base for intervention with dextromethorphan is lacking. However, given its favourable side-effect profile and long experience of use as an anti-tussive in children, dextromethorphan is often used clinically in this setting. It is, however, important to be aware of its prolonged elimination in Cytochrome P450 2D6 (CYP2D6)-deficient individuals and the potential for serotonin syndrome in patients on selective serotonin reuptake inhibitors (SSRIs) [108,109]. Other serious adverse effects include rhabdomyolysis, acute kidney injury and the potential for psychological dependence [110,111].

Even more anecdotally, dextromethorphan has been used as “prophylaxis” around the time of any re-exposure to methotrexate after a first episode of neurotoxicity [107,112]. The low rate of recurrence and the lack of any randomised or case-control studies in this context make it impossible to accurately evaluate the efficacy of this approach.

Aminophylline has also been tried as a potential treatment and works as an adenosine antagonist. The initial report of aminophylline use was in patients experiencing nausea, emesis, headache and lethargy—suggestive of acute MTX neurotoxicity rather than sub-acute MTX-SLS [27]. More recently, Razi and colleagues [113] reported that 25 of 30 (83%) children with ALL experiencing acute MTX neurotoxicity (mainly seizures and acute loss of consciousness rather than classic MTX-SLS) improved with aminophylline; however, similar to dextromethorphan above, it is unclear what proportion of cases would have resolved with conservative management alone due to lack of an untreated control population.

Given the preclinical evidence of association between oxidative stress and neurotoxicity, the use of antioxidants may be another promising approach. This has been investigated in small preclinical studies, with some positive impacts, but further testing in clinical cohorts is awaited [114]. More recently, erythropoietin (EPO) has been reported to reduce hippocampal oxidative stress in rats experiencing methotrexate neurotoxicity; however, no in-human trials have been reported as yet [115]. It should be noted that reducing oxidative stress may improve leukaemic blast survival as well as neuronal survival, so unintended impacts on leukaemia outcomes should be carefully evaluated [116].

In survivors of childhood cancer, there has been interest in developing interventions to improve long-term neuropsychological outcomes, such as cognitive interventions and group therapy [56]. However, the evidence for long-term benefit is sparse, and these findings are yet to be incorporated into guidelines on screening for or managing long-term cognitive difficulties in these patients. Developing successful intervention strategies is particularly pertinent to our discussion on high-dose/intrathecal methotrexate, given that it is primarily used in cancers affecting children and young people, such as ALL, lymphoma and sarcoma.

4.3 Re-Exposure Following Methotrexate Neurotoxicity

Understandably, there can be a degree of hesitancy to re-challenge patients who previously experienced methotrexate-related neurotoxicity. However, only a small proportion of patients will experience recurrent neurotoxicity [31,44]. For instance, 28/31 (90%) of patients in the UKALL 2003 cohort with SLS were re-exposed to IT-MTX and 23/28 (82%) had no recurrence of neurological symptoms, suggesting that SLS should not necessarily preclude CNS-directed therapy from continuing [44]. Recent evidence has shown that re-exposure is not only safe but may also reduce relapse rates and improve long-term survival [19]. This retrospective study of 1251 children treated with HD/IT methotrexate for ALL demonstrated a recurrence rate of just 12.9% of patients; however, rates of CNS relapse and 5-year overall survival were significantly improved in patients who continued on methotrexate throughout treatment compared to those with a truncation of therapy [19].

These findings illustrate that while some patients will experience recurrence of methotrexate neurotoxicity, most patients will successfully be able to re-commence methotrexate therapy.

5. Research Gaps

HD and IT methotrexate are utilised heavily in a number of paediatric cancers, most notably in ALL, in which it forms a cornerstone of CNS-directed therapy. We have previously described the need to balance the risk of CNS relapse from under-treatment with the risk of neurotoxicity from over-treatment to achieve a 'goldilocks approach' for children with CNS leukaemia, aided by developing robust prognostic biomarkers for CNS relapse risk as well as predictive biomarkers for neurotoxicity risk [103]. This will require large-scale datasets and new approaches to developing risk stratification models, such as that developed by Harris and colleagues (2025) [117] using machine learning.

As discussed above, methotrexate neurotoxicity is a significant problem causing morbidity, increased healthcare burden and long-term impacts on health and wellbeing. Despite this, the research in this field is patchy. The vast majority of studies are observational, and randomised evidence-based interventions are lacking. Appropriate treatments and preventative agents lack robust evidence at present, with no randomised clinical trials, meaning that this is a key area for further research. Management will be aided by large-scale studies investigating pathogenesis and predisposing factors.

Some progress is being made with the use of sensitive computerised cognitive tests during therapy, currently being tested for their prognostic value in picking out patients at high risk of long-term adverse neurocognitive outcomes early during therapy [118,119]. Such early identification is essential if interventions are to have the best chance of preventing long-term damage. Alternatively, the discovery of CSF biomarkers might identify patients with subclinical neurological insult, thus acting as a predictive biomarker as well as providing possible mechanistic insight and new therapeutic targets.

Recent studies have begun to utilise GWAS to identify candidate predisposition genes, and potentially, in the future, genetic testing could be used to identify patients most at risk [19,95]. It is important to highlight that while GWAS studies may be helpful in improving our understanding, predictive value may be low as there are likely to be many gene-environment interactions. Therefore, it is imperative for future studies to further understand genetic, epigenetic, and environmental factors which may predispose to methotrexate neurotoxicity.

The majority of neurotoxicity is reported with high-dose and intrathecal methotrexate administration; however, neurotoxic effects are still possible in patients on LD-MTX. Given how widely LD-MTX is used, further work to delineate neurotoxic effects at lower doses is important for optimising quality-of-life outcomes for patients.

Evidence-based guidelines on screening and intervention for chronic effects of MTX are also needed to identify patients at risk and offer enhanced support to maximise academic and social functioning.

In summary, key clinical research gaps include: discovery science to better understand the aetiology of the whole spectrum of methotrexate neurotoxicity, development of predictive and prognostic biomarkers to identify high-risk populations, randomised controlled trials of proposed treatments/preventative measures such as NMDA antagonists and antioxidants in these high-risk patients and a better understanding of how to manage chronic neurotoxicity.

6. Conclusion

Methotrexate neurotoxicity is an important and potentially serious toxicity, more prevalent in those receiving high-dose or intrathecal methotrexate. It can have a very heterogeneous presentation with acute, sub-acute and chronic symptoms, which can lead to significant morbidity. The pathophysiology of methotrexate neurotoxicity remains poorly understood. Appropriate treatments, predictive biomarkers and preventative agents lack robust evidence at present, representing a key area for future research.

Key Points

• Neurological toxicity is an important and potentially life-threatening complication of high-dose or intrathecal methotrexate treatment.

• The delayed onset of stroke-like syndrome and seizures can lead to emergency presentation out of hours to acute care providers; widespread awareness is needed to avoid inappropriate management, such as thrombolysis.

• The mechanism of methotrexate neurotoxicity is yet to be fully elucidated; however, it is likely complex and multifactorial.

• Current treatments lack robust evidence, and the mainstay of care is supportive.

• Research gaps include: understanding fully the mechanisms of methotrexate neurotoxicity, identifying reliable biomarkers for predicting risk and developing evidence-based treatments.

Availability of Data and Materials

Not applicable.

Author Contributions

CH and AW designed the work. CH and AW wrote the manuscript. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have partici-

pated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was generously supported by a Cancer Research UK (CRUK) Programme Foundation Award to CH (DRCPFA-Nov21\100001), and a Children with Cancer UK award to CH (2014/170).

Conflicts of Interest

Figs. 1 and 2 were created using Canva (https://www.canva.com/zh_cn/). The authors have no financial or personal relationship with Canva, and the use of this tool does not imply any endorsement. The authors declare no conflicts of interest.

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