Pediatric Neurology 101 (2019) 2–10

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

A Review of Chronic Leukoencephalopathy among Survivors of Childhood Cancer

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ARTICLE INFO

Article history:
Received 12 December 2018
Accepted 8 March 2019
Available online 21 March 2019

Keywords:
Chronic leukoencephalopathy
Radiation therapy
Chemotherapy
Stem cell transplant
Childhood cancer
Survivorship

ABSTRACT

Currently, there are an estimated 400,000 long-term survivors of childhood cancer in the United States. Chronic leukoencephalopathy is a potential devastating late effect that can manifest as a range of neurological and neurocognitive sequelae. Survivors of the acute lymphocytic leukemia, central nervous system tumors, and stem cell transplant have frequently been exposed to cranial radiation, systemic and intrathecal chemotherapy, which places them at risk of developing chronic leukoencephalopathy. Defining leukoencephalopathy and its neuroimaging characteristics, the population of survivors at risk, its long-term consequences, and identifying prevention and intervention strategies can potentially mitigate the morbidity of these survivors. Better understanding of those at risk of leukoencephalopathy and its symptoms can lead to an improved quality of life for these cancer survivors.

Introduction

As the number of childhood cancer survivors has incrementally increased because of improved multimodal therapy, chronic treatment-related neurological complications have been increasingly recognized among cancer survivors, including leukoencephalopathy (LE). The prevalence and pathogenesis of LE to the central nervous system (CNS) are poorly understood.

LE results from defects in formation and maintenance of the myelin sheath, the lipid membrane enveloping nerve cells within the cerebral white matter (WM). LE has multiple causes and has been associated with certain cancer diagnoses and therapies. Imaging abnormalities may be seen in asymptomatic survivors or those with seizures, headaches, cognitive changes, motor, and sensory symptoms.[1] LE may manifest as signal changes on magnetic resonance imaging (MRI) and mineralization on computed tomography (CT).

This review presents an overview of chronic LE among childhood cancer survivors. Acute and transient LE that may occur during treatment is not addressed in this article. The goals of this review include review of pathophysiology and imaging characteristics of LE, identifying populations at risk, summarizing clinical sequelae, assessment, and possible interventions. Areas of deficiency in the current understanding of LE and need for future research are highlighted.

Conflict of interest and source of funding statement: The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

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https://doi.org/10.1016/j.pediatrneurol.2019.03.006
0887-8994/

Methods

Chronic LE was defined as long-term irreversible changes in WM among survivors of childhood cancer that can be attributed to the cancer and its treatment. For the purposes of this review, the following databases were searched to identify relevant English-language articles published between January 1960 and October 2018: Medline using the PubMed interface, PubMed in process citations, Scopus, Science Citation Index Expanded through the Web of Science search interface, Cochrane Database of Systematic Reviews, and American College of Physicians Journal Club. Using best practices search methodology, we retrieved a comprehensive set of relevant articles using subject and combinations of keyword search terms (Table 1).

We reviewed the bibliographies of full articles and relevant studies were included. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants in regard to time from exposure, and methods of assessments (Fig 1).

Part 1. Leukoencephalothy: pathophysiology and imaging features

Chemotherapy

Methotrexate-associated LE

Methotrexate (MTX), a folic acid analogue that is essential for treatment of acute lymphoblastic leukemia (ALL), lymphoblastic lymphoma, and osteosarcoma, has been implicated as a major cause of LE. MTX inhibits tetrahydrofolate reductase, depleting intracellular folate, and causing biochemical changes that affect the CNS.[2] Although there are no validated biomarkers to identify those at risk of developing LE, treatment-related changes in cerebrospinal fluid (CSF) folate and homocysteine concentrations have correlated with increased neurocognitive dysfunction and MRI changes consistent with LE, demonstrating the importance of folate metabolism.[3] A study of transmethylation status of CSF among children with ALL who develop LE proposed that MTX can result in subclinical CNS hypomethylation, as evidenced by lower concentrations of *S*-adenosylmethionine and higher concentrations of *S*-adenosylhomocysteine in CSF compared with children with ALL but without LE, and normal control subjects. These findings suggest that progressive hypomethylation may contribute to demyelination in MTX-induced LE.[4]

Higher MTX doses[5] and concurrent MTX with cranial radiation therapy (CRT)[6] increase the risk of neurotoxicity and development of LE. Route of MTX administration and the addition of leucovorin rescue also influence the risk; intrathecal (IT) delivery is associated with higher risk of LE compared with intermediate or high-dose intravenous (IV) administration.[7] Duffner et al. reported MRI findings and neurocognitive performance of ALL survivors more than 2.6 years after completion of therapy with either intensive MTX [five doses of IT MTX without leucovorin rescue during consolidation followed by postconsolidation MTX (25 mg/m^2/dose orally every six hours × four doses every two weeks followed by leucovorin for six months; Pediatric Oncology Group 9605; n = 31)] or less intensive MTX [IT MTX followed by leucovorin rescue during consolidation and standard-dose intramuscular MTX (20 mg/m^2/dose weekly; Pediatric Oncology Group 9201; n = 23)].[8] Forty percent of all enrolled subjects had verbal intelligence quotient (IQ) and performance IQ scores less than 85. Twenty-one (68%) of 31 patients treated with intensive MTX were found to have LE compared with five (22%) of 23 patients treated with less intensive MTX ($P = 0.001$). Although the presence of LE was not associated with below average verbal or performance IQ scores ($P = 0.36$), the presence of LE was associated with lower performance on measures of attention, processing speed, and visual-motor integration. Although only 43 of 54 potentially eligible patients completed both MRI and neuropsychological testing, the findings may be limited by selection bias.

CNS leukemia at diagnosis increases the risk of LE, in part because of the additional IT MTX, CRT, or IT MTX and CRT required. Furthermore, because MTX is eliminated by reabsorption of CSF, reduced CSF flow, which often occurs among patients with meningeal leukemia, leads to increased CSF concentrations of MTX, potentially increasing the risk of adverse neurological effects.[9]

After the recognition of late effects associated with CRT in ALL survivors, CRT has largely been eliminated from ALL treatment regimens, and in nearly all cases, prophylactic CRT has been replaced by systemic and IT chemotherapy. As a result, in many respects, the prevalence of radiographic findings of chronic LE among leukemia survivors is largely reflective of an older era of therapy and does not represent patients receiving contemporary treatments. From various convenience cohorts of ALL survivors with median follow-up of 18 months to 11.7 years, the prevalence of LE ranges from 18% to 52%.[6,10,11] Risk factors for chronic LE include younger age at diagnosis, exposure to MTX, and doses of CRT of greater than 24 Gy, which are used primarily for CNS relapse but not during primary ALL therapy (Table 2).[6,10,11,14]

A study by Kadan-Lottick et al.[15] examined neurocognitive outcomes among 171 five-year survivors of childhood ALL previously randomized to receive either IT MTX (n = 82) or "triple" IT chemotherapy with a combination of MTX, cytarabine, and hydrocortisone (n = 89). Neurocognitive performance was largely similar, although survivors exposed to IT MTX alone were more likely to have impaired processing speed ($P = 0.02$). It is not clear why patients treated with triple IT chemotherapy had superior processing speed, other than to note that the rationale for the addition of hydrocortisone to IT therapy was prevention of chemical arachnoiditis because of anti-inflammatory properties rather than because of its antileukemia activity[16]; perhaps, hydrocortisone may spare some cognitive deficits as well.

TABLE 1.
Search Strategy Database: Medline Through the PubMed Interface

Search Set	Query	Results (N)
1	"Methotrexate" [Mesh] OR "methotrexate" [All Fields]	50,769
2	"Leukoencephalopathies" [Mesh] OR "leukoencephalopathy" [All Fields] OR "leukoencephalopathies" [All Fields]	32,654
3	"white matter disease" [All Fields] OR "white matter diseases" [All Fields]	1035
4	"Demyelinating diseases" [Mesh] OR "Demyelinating disease" [All Fields] OR "demyelinating diseases" [All Fields]	92,361
5	"Antineoplastic agents" [Mesh] OR "chemoradiotherapy" [Mesh] OR "radiotherapy" [Mesh]	528,825
6	"Infant, newborn" [Mesh] OR "Infant" [Mesh] OR "Child, Preschool" [Mesh] OR "Child" [Mesh] OR "Adolescent" [Mesh]	3,281,752
7	#2 OR #3 OR #4	102,968
8	#1 OR #5	570,358
9	#7 AND #8 AND #6	315

Dates (inclusive) from January 1960 to October 2018.

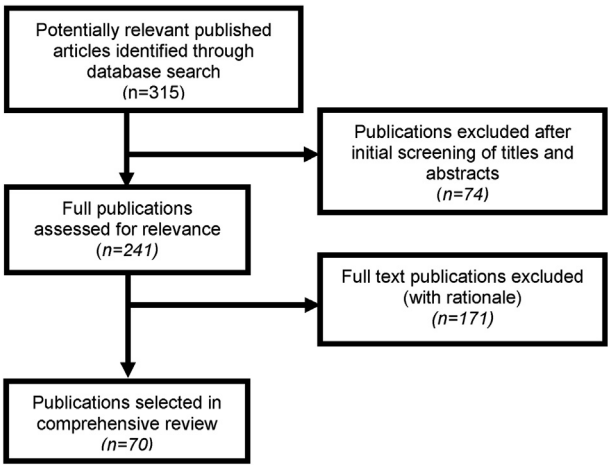

FIGURE 1. Publication selection for comprehensive review.

Childhood cancer survivors exposed to combinations of MTX and CRT are at greater risk of developing radiographic LE than those treated with chemotherapy alone. Hertzberg et al.[11] compared rates of LE among 118 survivors of childhood ALL (median follow-up of 7.2 years after completion of therapy) treated with one of three types of CNS prophylaxis: group A was treated with IV and IT MTX without CRT (n = 39), group B was treated with IV and IT MTX in addition to CRT (mean exposure = 16.8 Gy; n = 41), and group C was treated with IT MTX and CRT (mean exposure = 17.1 Gy; n = 38). Sixty-one patients (52%) had abnormalities on CT, MRI or both. All three groups had imaging abnormalities, but more were observed among those exposed to radiation (group B = 56% and group C = 61%) than in those with chemotherapy only (group A = 39%; $P = 0.043$). Neuroimaging abnormalities, including cerebral atrophy, LE, mineralization, or gray matter changes, correlated with deficiencies on neuropsychological testing. The study was limited by the sample size and limited statistical power to detect differences because of age at diagnosis and interval of follow-up. Moreover, many of the study subjects would not receive prophylactic CRT included contemporary ALL treatment regimens. In Matsumoto's report of childhood leukemia survivors exposed to CRT (18 to 24 Gy) and IT MTX without leucovorin rescue but not high-dose IV MTX, 7 (18%) of 38 patients developed LE.[6] A higher risk of LE was associated with age less than six years at leukemia diagnosis and treatment with 24 Gy CRT.

Schuitema et al.[12] quantified WM microstructure by fractional anisotropy (WMFA) from diffusion tensor imaging (DTI) MRI among 93 twenty-five–year survivors of childhood ALL or lymphoma. In their study, survivors exposed to CRT had significantly decreased WMFA in frontal, parietal, and temporal WM tracts compared with control subjects. Also, survivors exposed to CRT demonstrated decline in WMFA with greater age at assessment. Younger age at exposure to CRT and higher dosage were associated with worse WMFA. In contrast, trends for lower WMFA were found among survivors who were only treated with chemotherapy compared with control subjects. Importantly, decreases in WMFA correlated with worse neuropsychological function.

Studies of childhood ALL survivors treated with contemporary therapies, which include IV and IT MTX but not CRT, remain at risk for reduced WM integrity and long-term neurobehavioral problems. For example, Cheung et al. examined LE and neurocognitive outcomes among survivors of childhood ALL who were not exposed to CRT.[13] Of 190 five-year ALL survivors examined, 51 patients (27%) had a history of acute LE during treatment. Thirty-six of these patients had evidence of chronic LE by MRI more than five years after ALL diagnosis. Survivors with a history of prior acute LE were found to have impaired WMFA in the frontostriatal tracts, frontal lobes, and parietal lobes. Abnormalities in WMFA were associated with impaired neurobehavioral outcomes, which were most frequently associated with WM integrity deficits in the frontostriatal tract.

Radiation therapy

The pathophysiology of radiation-induced neurotoxicity is likely multifactorial. It has been hypothesized that CRT-associated LE results from demyelination, which is supported by findings of elevated myelin basic protein in the CSF of subjects with symptomatic LE compared with subjects without LE.[17] In preclinical models, cognitive impairment arises in the setting of brain capillary loss in irradiated rats who demonstrate no other gross pathologic changes, suggesting that capillary loss may play an important role in radiation-induced neurocognitive decline.[18] However, rats do not have an equivalent degree of WM compared with humans and the relevance to human disease is uncertain. An autopsy study of four children with cancer (three medulloblastoma and one ALL) exposed to CRT demonstrated persistent inflammation of microglia in post-irradiated hippocampi was accompanied with cessation of neurogenesis.[19] In a related rat model, radiation exposure results in decreased neurogenesis, accompanied by disruption of microvascular angiogenesis and increased activation of microglia within the neurogenic zone.[20] It remains uncertain if capillary loss results in LE; however, in patients treated with high dosage, small volume stereotactic radiosurgery, there is evidence of progressive vascular changes, which sometimes extends outside the prescribed treatment volumes.[21] It is yet to be determined if these progressive vascular changes outside the treatment volumes play a role in the development of LE and radiation-induced cognitive decline and this warrants further study.

Risk of LE is correlated with dose and volume of brain exposed to radiation. Radiation exposure to the whole brain at doses greater than 24 Gy increases the risk of LE,[6,22] but LE has also been identified when doses of 18 Gy are combined with high-dose IV or IT MTX.[10,11,23-25] Focal radiation exposure is also associated with LE, especially when involving the supratentorium.[26] Children who receive CRT at younger ages may be especially vulnerable to radiation-induced LE. The literature is conflicting with regards to long-term outcomes of radiation-induced LE; some studies support an increased prevalence of LE over time,[26] but others suggest a decrease with longer intervals of follow-up.[24] In a study of medulloblastoma survivors treated with whole brain CRT, WM integrity was decreased in the frontal lobes compared with the parietal lobes, suggesting the frontal lobes may be inherently more susceptible to developing LE.[27]

At present, the use of CRT is rare in childhood ALL therapy and overall radiation doses are being reduced for many CNS tumors; thus fortunately the prevalence of LE among childhood cancer survivors may decline in the future. Furthermore, it is not known whether the recent widespread adoption of intensity-modulated radiation therapy and proton beam irradiation will reduce the prevalence of radiation-induced LE.

Risk factors for LE among CNS tumor survivors include younger age at diagnosis, hydrocephalus requiring CSF diversion, exposure to, treatment volumes and dosage of CRT, and longer duration of follow-up (Table 3).[22,25,26,28] CNS tumor treatment regimens that include MTX may have increased rates of LE.[23,24] Kellie et al.[25] examined 12 long-term (median = 6.9 years) survivors of CNS embryonal tumors who were treated with carboplatin, etoposide, and high-dose (8 gm/m^2/dose) IV MTX followed by CRT (35 to 50.4 Gy). Of these 12 CNS tumor survivors, eight had findings of grade 1 LE and four had grade 2 LE. Kellie et al. concluded that the

TABLE 2.
Chronic Leukoencephalopathy Among Survivors of Childhood Acute Lymphoblastic Leukemia

Author (Date)	n	Mean Age/Sex	Treatment	Findings
Matsumoto et al. (1995)[6]	38	• Range = 1.1-14.9 years • 19 Females and 19 males	• Prophylactic CRT (18-24 Gy) • IT MTX • Oral MTX (25 mg/m2/week) during maintennce	• 7 of 38 (18%) subjects had evidence of LE by MRI • Risk increased for younger age at diagnosis and higher RT dose (especially for children aged <6 years at diagnosis and receiving ≥24 Gy CRT)
Duffner et al. (2014)[8]	66	• Age at diagnosis: 4 years • Age at study: 12 years • 37 Females and 32 males	Two groups: • P9201 (n = 28) • IT MTX with leucovorin rescue • No postconsolidation intensive therapy • P9605 (n = 38) • IT MTX without leucovorin rescue • +postconsolidation intensive therapy	Frequency of LE by imaging • P9201: 5/23 (22%) • P9605: 21/31 (68%) Frequency of neurocognitive impairment • P9201: • 4/17 (24%) below average on cognitive measures • Full scale IQ = 100.4 • P9605: • 14/17 (82%) below average on cognitive measures • Processing speed IQ = 90.1 • Abnormalities in attention were more likely to be observed among subjects with LE, but no other measures
Iuvonne et al. (2002)[10]	21	• Age at diagnosis: 44.7 months • Age at study: 142.4 months • 8 Females and 13 males	• Prophylactic CRT (18-24 Gy) • IT MTX	• 10 of 21 (48%) subjects had evidence of LE by MRI • Visual-motor integration impairment correlated with LE • Age at diagnosis and sex did not correlate with LE • 5 of 21 (24%) subjects had calcifications by CT • Calcifications correlated with lower cognitive scores • Cognitive impairment more frequent among females
Hertzberg et al. (1997)[11]	118	• Age at diagnosis: 5.8 years • Age at study: 14.7 years • 60 Females and 58 males	Three groups: • Group A (n = 39): IT MTX and HD MTX • Group B (n = 41): CRT (16.8 Gy), IT MTX, and HD MTX • Group C (38): CRT (17.1 Gy) and IT MTX	Frequency of LE by imaging • Group A: 15/39 (39%) • Group B: 23/41 (56%) • Group C: 23/38 (61%) Imaging abnormalities correlated with cognitive impairment and with age but not sex
Schuitema et al. (2013)[12]	93	• Age at diagnosis: 5.3 years • Age at study: 20-40 years; mean 26.7 years • 42.9% males control subjects; 52.3% males CRT; and 57.1% males chemotherapy alone	Three groups: • CRT (n = 44); 20-25 Gy • Chemotherapy alone (n = 49): cumulative IT MTX 116.4 mg/m2 and HD MTX 18,224.5 mg/m2 • Healthy control subjects (n = 49)	• Significant decreases in FA in frontal, parietal, and temporal WM associated with CRT • Trend for decreases in FA in frontal, parietal, and temporal WM associated with chemotherapy alone • Steep decline in FA for survivors receiving CRT compared with chemotherapy alone and control subjects • Decreases in FA correlated with neuropsychological dysfunction • Effects more pronounced in survivors who received CRT
Cheung et al. (2016)[13]	190	• Age at diagnosis: 4 years • Age at study: 12 years • 37 Females and 32 males	• Childhood ALL patients who received HD and IT MTX (no CRT) • Compared with population norms	• ALL survivors had more neurobehavioral problems with working memory, organization, initiation, and planning compared with population norms • ALL survivors scored worse than the general population on direct measures of memory span, processing speed, and executive function • Survivors with a history of acute LE had more neurobehavioral problems than survivors with no history of LE • Survivors with acute LE had reduced WM integrity in the frontostriatal tract with lower FA, higher axial diffusivity, and radial diffusivity • Reduction in WM integrity at follow-up was found to correlate with neurocognitive deficits

Abbreviations:
ALL = Acute lymphoblastic leukemia
CT = Computed tomography
CRT = Cranial radiation therapy
FA = Fractional anisotropy
HD= High dose
IQ = Intelligence quotient
IT = Intrathecal
LE = Leukoencephalopathy
MRI = Magnetic resonance imaging
MTX = Methotrexate
RT = Radiation therapy
WM = White matter

order of administration of MTX and CRT (e.g., MTX before CRT) may reduce the severity of LE in young children undergoing therapy for a CNS tumor. These studies are limited by their retrospective design, small sample sizes, selection bias, relatively brief duration of follow-up, and radiographic evaluation from time of exposure. Furthermore, long-term follow-up data on these patients are inherently limited by referral patterns. Patients may travel to specialized centers for treatment and return to their home

TABLE 3.
Leukoencephalopathy Among Survivors of Childhood Brain Tumors

Author (Date)	Diagnosis	n	Mean Age	Treatment	Findings
Russo et al. (1999)[22]	Medulloblastoma/ PNET	21	• 17.5 years at the time of study • 3.3 years after diagnosis	• Surgery • Hyperfractionated radiation therapy • Vincristine, cisplatin, CCNU	MRI changes in all patients: • 7/21 with WM changes • 5/21 with cerebral atrophy • 2/21 with combined WM changes/cerebral atrophy No correlation identified between clinical symptoms and extent of radiographic changes

Riva et al. (2002)[23]	Medulloblastoma	21	• Not stated; all were aged <18 years at diagnosis	• Surgery
				• Vincristine
				• HD MTX (8 gm/m^2)
				  • Group 1: IT MTX: 10 mg/m^2 × 4
				  • Group 2: no IT MTX
				• CRT:
				  • 3-10 years: 20 Gy
				  • >10 years: 35 Gy
				• Vincristine and CCNU
					Results — Leukomalacia by MRI
					Grade 0 / Grade 1 / Grade 2 / Grade 3
					Group 1: 0 / 3 / 4 / 4
					Group 2: 4 / 0 / 5 / 1

Rutkowski et al. (2005)[24]	Medulloblastoma	23	• Not stated; all patients were aged <3 years at diagnosis	• Surgery • Intraventricular MTX • HD MTX (5 gm/m^2) • Vincristine, cyclophosphamide, carboplatin, and etoposide • No CRT	Asymptomatic LE by MRI seen in 83% (19 patients) • 4/19 mild (spotted, circumscribed) • 9/19 moderate (patchy) • 6/19 severe (confluent) LE most severe at 1 year after therapy, with decreasing severity among 10/18 patients with long-term follow-up
Kellie et al. (2005)[25]	Medulloblastoma/ PNET	12	• 7.6 years at diagnosis	• Surgery • Etoposide and carboplatin • HD MTX (8 gm/m2) • CRT: 36-50.4 Gy	MRI changes: • 8/12 mild increase in SAS, VM, with periventricular WM changes • 4/12 moderate increase in SAS, moderate VM, and WM changes into centrum semiovale • HD MTX before exposure to cranial radiation may result in less severe WM changes than is reported when radiation occurs before exposure to MTX
Dietrich et al. (2001)[26]	Malignant brain tumors	44	• 8.4 years at diagnosis	• Surgery • RT (n = 39, 89%), chemotherapy (n = 34, 77%)	WM disease in 64%, including circumscribed WM lesions and diffuse atrophy Risk factors for WM disease included: • Age at diagnosis <5 years • Supratentorial tumor location • Follow-up of >5 years • Presence of ventricular shunt No comment on impact of WM disease on neuropsychological functioning

Abbreviations:
CCNU = Lomustine
CRT = Cranial radiation therapy
HD = High dose
IT = Intrathecal
LE = Leukoencephalopathy
MRI = Magnetic resonance imaging
MTX = Methotrexate
PNET = Primitive neuroectodermal tumor
RT = Radiation therapy
SAS = Subarachnoid space
VM = Ventriculomegaly
WM = White matter

institution for follow-up, where resources for neuroimaging and formal neurocognitive testing may be limited.[25]

Imaging features of LE

Advances in MRI have improved detection of radiation injury with greater sensitivity than CT.[29,30] WM may show diffuse or focal, symmetric, or asymmetric T2-weighted high intensity signal abnormalities and may be associated with volume loss, with more severe findings correlating with larger volumes of irradiated tissue and higher radiation dose (60 to 70 Gy).[29,31] Concurrent MTX and radiation has been shown to hasten the development of these imaging findings and is associated with higher incidence of clinical LE.[32]

Imaging features of chronic treatment-related neurotoxicity are variable and reflect the underlying spectrum of pathologic changes that include vascular damage, demyelination, cytotoxic injury, and necrosis.[33-36] Imaging findings may also be affected by age at exposure or diagnosis, treatment modality and intensity, and survival duration.[31] Visible changes can evolve over time, ranging from resolution to progressive or chronic or residual damage.[37-40] CT is a relatively insensitive modality to visualize LE, but hypodensity of the periventricular WM and mineralization at the gray-white junction may be observed. With MRI, chronic LE manifests as signal intensity abnormalities within the centrum semiovale and corona radiata with T2-hyperintensity or atrophy in chronic or severe involvement (Fig 2).[40,41] In a chronic state, imaging features of cerebral microvascular disease of older adults may be indistinguishable from radiation-induced demyelination and gliosis.[42]

In addition to the typical imaging changes of LE demonstrated on MRI, advanced functional imaging demonstrates reduced

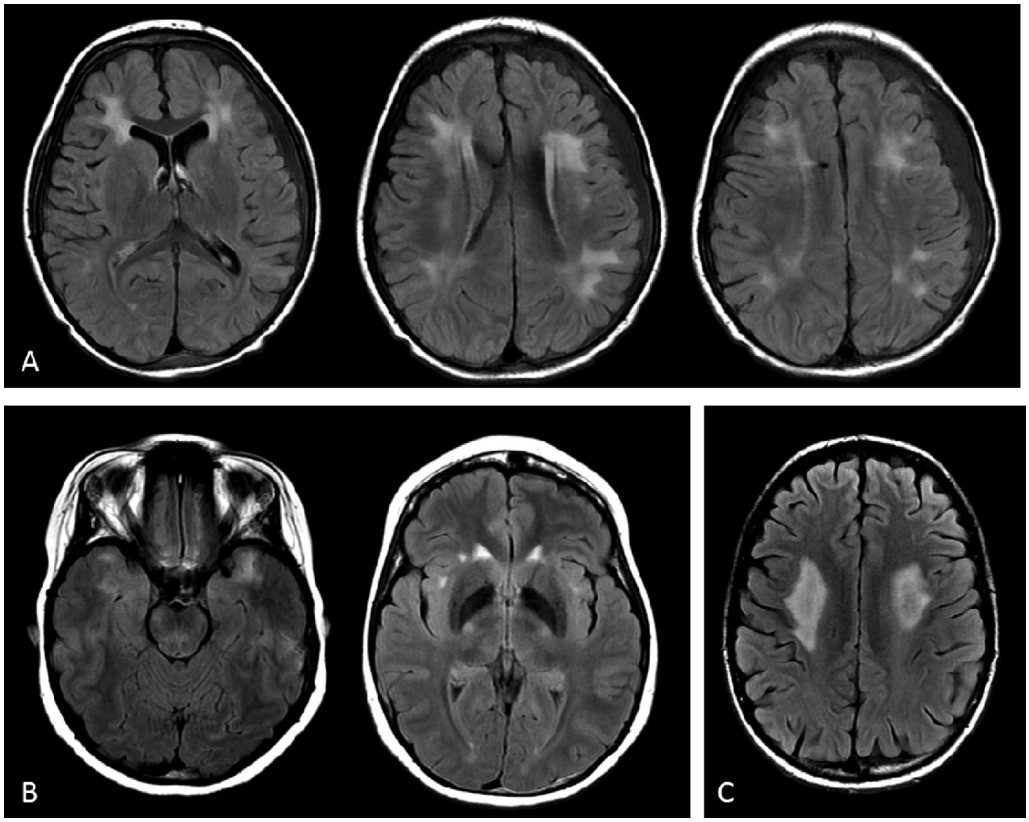

FIGURE 2. Axial MRI of chronic leukoencephalopathy on fluid-attenuated inversion recovery sequences. (A) Patchy bilateral nonspecific WM intensity abnormality and mild volume loss is seen in a six-year-old boy four years after treatment of post-treatment lymphoproliferative disorder. (B) Bilateral mineralization of the basal ganglia with diffuse WM disease in a 25-year-old woman treated with chemotherapy (without MTX) at age one year and craniospinal radiation at age three years for multifocal pilocytic astrocytoma. (C) Chronic subcortical WM changes in an 18-year-old man treated with MTX for high-risk acute lymphoblastic leukemia with cerebral disease seen six months after acute episode of MTX-induced encephalopathy. MRI, magnetic resonance imaging; MTX, methotrexate; WM, white matter.

diffusion within the periventricular WM that is associated with LE. For example, diffusion-weighted imaging (DWI) is a functional MRI technique that is highly sensitive in the early identification of ischemic tissue injury, frequently before conventional MR sequences identify pathologic changes. DWI provides qualitative information by differentiating between vasogenic and cytotoxic edema. A special kind of DWI, DTI, is also used to map WM tractography to identify normal and abnormal brain microstructure by quantifying direction and magnitude of diffusion. These morphologic changes in the WM have been studied in childhood cancer survivors and correlated with LE and decline in neurocognitive function.[13]

Pathologic correlates of LE

Autopsy data from patients with delayed or late radiation injury revealed a variety of morphologic brain changes. Pathologic findings from 25 adult autopsies (ages 29 to 75 years) with late radiation toxicity after exposure to 50 to 60 Gy for treatment of brain tumors included vascular abnormalities (hyalinization and thickening of arteriolar walls), gliosis, demyelination, and WM necrosis. In addition, regions of diffuse cerebral edema were noted within the radiation field. Other pathologic findings associated with LE included diffuse reactive astrocytosis, axonal degeneration, spongiosis, circumscribed demyelination and coagulative necrosis, and mural thickening with luminal narrowing of microvessels.[43] These have been correlated with neurocognitive and radiographic changes associated with LE in leukemia patients.[44] These changes appear to be related to combined effects of exposure to CRT and chemotherapy; however, the exact contribution of various components of treatment exposures is not well understood.

Part 2. Identification of At-Risk populations

Reported risk factors for development of chronic LE include cancer diagnosis of CNS tumor or leukemia, exposure to CRT, treatment with IV or IT MTX, and older eras of treatment. Although the reported prevalence of LE in children during cancer therapy ranges from 11% to 68%,[45-47] much of this LE is acute and transient.

LE among hematologic stem cell transplant survivors

Few reports address chronic LE after hematologic stem cell transplant (HSCT). Two reports describe resolution of acute LE after discontinuing immunosuppressive therapy, suggesting a causal association between immunosuppressive agents and acute LE.[48,49] Reports of neurocognitive function among HSCT survivors are contradictory; some claim “minimal risk of late cognitive and academic sequelae”[50] whereas others report “progressive declines in neurocognitive function.”[51] Reports of risk factors include primary cancer diagnosis, age at transplant, socioeconomic status, graft-versus-host disease, pretransplant CRT and chemotherapy, and immunosuppressive agents (tacrolimus, cyclosporine A, and fludarabine). Further studies are required to elucidate the prevalence of LE and the association with neurocognitive performance after HSCT.

Part 3. Clinical sequelae of LE

Cognitive deficits related to LE

Extensive literature exists regarding the deleterious effects of CRT on the developing brain and the potential risk factors and contributors to severity of deficits. Females, younger patients, and individuals exposed to higher doses and volumes of radiation are more vulnerable to neurocognitive late effects after exposure to CRT.[52,53] Furthermore, neurocognitive impairment may begin soon after completion of treatment, but may be delayed up to seven years after therapy.[54,55] The literature regarding the neurocognitive dysfunction related to LE is less robust and consists of data from relatively small numbers of patients, which may manifest selection bias and may not be representative of all survivors. Studies often are limited by relatively brief intervals of follow-up, mixed patient populations (leukemia and brain tumor survivors), and may be impeded by the availability and expense of formal neurocognitive testing.

Among children treated for ALL, a prospective study using MRI and correlative neurocognitive assessments demonstrated a correlation between WM abnormalities and poor performance on visual-motor integration in approximately 50% of patients treated with CRT and IT MTX.[10] Anatomic changes correlated with neurocognitive performance on tasks of attention[56] as well as concentration, IQ, and arithmetic.[11] Riva et al. compared two groups of children with cerebellar medulloblastoma with their cousins and siblings, assessing intelligence, executive function, attention, visual perception, and short-term memory. Both groups were treated with surgery followed by the same combined chemotherapy and radiation regimen, but differed in that only one group received IT MTX (10 mg/m^2/dose $\times$ four doses).[23] In this small study, the extent of WM loss or leukomalacia demonstrated on MRI correlated with poor performance among children exposed to IT MTX across a range of measures, including IQ, visuospatial planning, short-term memory, and arithmetical reasoning.[23]

In a study of 30 survivors of medulloblastoma or ALL and 55 healthy age-matched control subjects,[57] Khong et al. examined the relationship between WMFA and IQ. They found that differences in WMFA significantly correlated with IQ even after controlling for age, time interval since exposure, and CRT dosage, suggesting that WMFA may provide a clinically useful indicator of treatment-related neurotoxicity. This study supported previously published data indicating that approximately 70% of the association between age at CRT exposure and IQ was explained by diminished WM volumes.[58] Aukema et al.[5] used DTI to measure WMFA among 17 ALL and medulloblastoma survivors three years after completion of treatment, and 17 age-matched control subjects. There was a correlation between processing speed and decreased WMFA in the WM tracts of the right inferior fronto-occipital fasciculus as well as the body and splenium of the corpus callosum. Law et al.[59] reported impaired working memory scores among patients who were exposed to CRT compared with age-matched control subjects or patients treated with surgery only. They also discovered that working memory is related to WMFA of cerebellothalamocerebral connections, and that reduced WMFA and higher radial diffusivity within this pathway predicted lower working memory scores.

A recent study of long-term adult survivors of childhood ALL, those treated with CRT (n = 39) had significantly reduced WMFA compared with those treated with chemotherapy alone (n = 36) and healthy control subjects (n = 23).[60] Survivors treated with CRT had lower IQ, visuomotor accuracy, and working memory along with other processing deficits. Decreases in WMFA were seen in chemotherapy-only treated patients, but were not as severe as the survivors exposed to CRT. WM changes in children treated for medulloblastoma have been shown to correlate with neurological dysfunction.[61]

Interventions for cognitive deficits related to LE

No interventions exist that can reverse LE, and thus interventions should focus on reducing the symptoms of LE. Although the sequelae from LE may have ongoing implications for academic and cognitive functioning, providers, parents, and teachers should be aware of potential educational issues that may arise, given the higher risk for learning and memory problems. For patients with LE, monitoring of neurocognitive functioning is recommended and, in some cases, a more comprehensive assessment battery. Specific domains to be targeted should include IQ, attention and working memory, processing speed, visual-motor integration, and academic achievement. Repeat testing may be indicated as some cognitive issues may not appear until years after treatment.

Given the prevalence of neurocognitive dysfunction in childhood cancer survivors, efforts to determine effective forms of cognitive remediation are imperative. Educational interventions may include in-class accommodations such as specialized seating, use of assistive devices (keyboard), reduced academic load, extended testing time, and tutoring in specific academic domains. Creating an individualized educational plan facilitates customized resources for the child. Prior studies have used directed, intensive training programs for improving problem solving, general cognitive skills, memory and attention, and demonstrated positive gains.[62,63] However, participation rates were low and the feasibility for families with limited resources or those living at a distance from a specialty care center was challenging, which further highlights the need to develop effective interventions that can be administered without prohibitive costs, travel, or time commitments for the patient and provider. One such intervention is home-based, computerized cognitive training programs. Pilot studies have shown improvements in attention and working memory in a small sample of childhood cancer survivors.[64] This may be useful in improving survivors' neurocognitive functioning, although it is not clear whether these interventions provide sustained improvements and more research in this area is clearly indicated.

Several studies have examined the use of pharmacologic agents to enhance cognitive performance among brain tumor survivors. For example, Conklin et al.[65-67] conducted several clinical trials of the stimulant methylphenidate for survivors of childhood leukemia or brain tumors with cognitive impairment. Collectively, these studies demonstrate that treatment with methylphenidate is well tolerated and associated with improvements in attention, cognitive flexibility, and processing speed. Male gender, older age at treatment, and higher intelligence were predictive of better response to methylphenidate.[65]

Neurological sequelae of LE

Many of the clinical symptoms that appear at the time of onset of LE are thought to be transient, although there has been no prospective study to evaluate any specific long-term neurological consequences. Gross and fine motor weakness has been reported at the time of presentation of LE. Studies that assess long-term patterns of motor disabilities in children after treatment for leukemia are limited. There are reports of weakness, fatigue, and neuropathy in ALL survivors, although it is difficult to determine if these are related to LE.[68,69] In one study, 25% of leukemia survivors (n = 18) were found to have chronic issues with fine motor and handwriting skills over two years after therapy.[70] These nonradiated children had all been exposed to treatment regimens that included combinations of systemic and IT MTX, in addition to agents known to

contribute to peripheral neuropathy, such as steroids and vinca alkaloids. Wright et al. examined musculoskeletal and gross motor functioning among 36 ALL survivors and age-matched and sex-matched control subjects. The subjects were able to perform most basic gross motor functions, such as walking, running, and jumping, at levels similar to age-matched and sex-matched control subjects. However, activities focused on strength, balance, running speed, and agility were significantly poorer than control subjects. Handgrip and dorsiflexion had the greatest differences, suggesting a peripheral component.[69] Unfortunately, this study and most others report on motor function deficits in children that do not directly correlate clinically with LE. Therefore it is difficult to distinguish late effects because of LE from those that result from other cancer treatments.

Conclusions

This review summarizes and highlights deficiencies in the literature for childhood cancer survivors with chronic LE. The pathophysiology, risk factors, and treatment of LE need further elucidation. Genetic variability in drug metabolism, blood-brain barrier integrity, and radiation repair mechanisms likely influence the risk of developing LE, but are currently poorly understood. The neurological and cognitive outcomes of childhood cancer survivors who have imaging findings are unknown and merit further study. Prospective longitudinal studies using advanced imaging modalities during and after treatment may help clarify the relationship between WM changes and functional and cognitive outcome. Defining high-risk populations may allow for the identification of subtle cognitive impairments and facilitate provisions for appropriate school-based support services. Currently, the strategies to modify or eliminate LE are limited to reducing the exposure to radiation and high-risk chemotherapies, thus future research is needed to treat and prevent LE in survivors.

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