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Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumours following high-dose methotrexate and neuraxis radiation therapy

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Abstract

High-dose methotrexate (HDMTX) is used increasingly to treat children with central nervous system (CNS) tumours. Although the neuro-imaging features of leukoencephalopathy associated with systemic or intrathecal methotrexate administered after cranial radiation have been well described, the extent to which the sequencing of HDMTX prior to cranial radiation in infants and children predisposes to late neuroradiological features of leukoencephalopathy is unknown. This report describes the National Cancer Institute (NCI) toxicity grade of leukoencephalopathy based on magnetic resonance imaging (MRI) findings in all patients who survived 4 or more years after treatment on an earlier phase II study. These patients, with newly diagnosed CNS embryonal tumours, were in the age range 3.5–14.2 years (median 6.9 years) at diagnosis, and received four courses of pre-irradiation combination chemotherapy, including HDMTX 8 g/m^2. Following completion of the 'up-front' phase II study, all patients received conventionally fractionated whole brain doses of 36–50.4 Gy. The radiation dose and treatment volumes were determined individually according to the primary tumour location and results of extent of disease evaluations. The most recent MRI brain scans, obtained 4.0–10.5 years (median 6.5 years) after radiation therapy and comprising a minimum of T1, T1 following gadolinium and T2 sequences, were reviewed centrally to assess the neuroradiological grade of leukoencephalopathy, based on the NCI Common Terminology Criteria for Adverse Events, v3.0. Grade I changes (mild increase in subarachnoid space, and/or mild ventriculomegaly, and/or small/focal T2 hyperintensities) were evident in 8 of the 12 patients and grade II changes (moderate increase in subarachnoid space and/or moderate ventriculomegaly, and/or focal T2 hyperintensities extending to the centrum ovale) were found in the remaining 4. In conclusion, treatment with multiple courses of HDMTX prior to 36–50.4 Gy cranial radiation did not result in moderate to severe MRI features of leukoencephalopathy. Future studies in paediatric neuro-oncology patients, involving HDMTX combined with prospective neuropsychological evaluations appear justified.

Keywords: Medulloblastoma; Methotrexate; Leukoencephalopathy; Radiation therapy

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1. Introduction

Methotrexate [1–5] and cranial radiation [6–12], either separately or together [5,13–22], have been associated with clinical or neuroradiological evidence of leukoencephalopathy in survivors of childhood leukaemia and central nervous system (CNS) or head/neck tumours. The incidence and severity of magnetic resonance imaging (MRI) appearances of leukoencephalopathy seems to increase with radiation dose and younger age [8,12,23]. Reduced normal-appearing white matter volumes (NAWM) among children surviving treatment for brain tumours have been associated with decreased attentional abilities, leading to declining intelligence quotient (IQ) and academic achievement [23].

Evidence of leukoencephalopathy has also been documented in patients receiving chemotherapy without cranial radiation [3,14,18,24]. Allen observed in a case report that high-dose methotrexate (HDMTX) with citrovorum factor rescue in the absence of cranial radiation could lead to clinical and computed tomography (CT) evidence of leukoencephalopathy. A decade later, Allen and colleagues reported two instances of leukoencephalopathy (transient in one) among 10 patients with CNS tumours receiving four courses of HDMTX 8 g/m^2 prior to cranial radiation therapy [14].

The relationship between CT or MRI features of leukoencephalopathy and significant neurological or neuropsychological decline have been inconsistent [26] or negative [21,25,27,28]. Other studies of white matter loss and neurocognitive deficits in children with medulloblastoma [12,13,23,25] and the relationship between neuroradiological findings and neuropsychological outcomes in children with leukaemia [20] have demonstrated at least a partial correlation between some aspects of neuropsychological function and neuroimaging findings, especially abnormalities demonstrated on MRI scanning.

The current study extends the phase II observations of our earlier study [29] and explores the incidence and severity of late neuroradiological features of leukoencephalopathy in children with high-risk CNS embryonal tumours receiving HDMTX immediately prior to craniospinal radiation therapy [29]. Our study failed to demonstrate more serious evidence of leukoencephalopathy than has been commonly associated with cranial radiation alone. Because of the original design of our upfront phase II study, which comprised mostly 'high-risk' patients with CNS embryonal tumours, a control population comprising children treated with radiation alone was not feasible.

2. Patients and methods

Patients with previously untreated newly diagnosed CNS embryonal tumours were originally enrolled on a neoadjuvant phase II study comprising four courses of carboplatin, etoposide and HDMTX conducted by the Australian and New Zealand Children's Haematology Oncology Group during the 1990s. The results of this study have been published [29]. Updated outcome data are provided for general interest only as the details of radiation treatment and the selection of post-radiation chemotherapy was at the discretion of the treating physician. Of the patients who received craniospinal radiation therapy and after a median follow-up of 8.1 years, the 5-year progression free (PFS) and overall survival (OS) for patients with medulloblastoma was 0.67 (SEM 0.14) and 0.83 (SEM 0.11), respectively, and for primitive neuroectodermal tumour (PNET)/pineoblastoma; 0.29 (SEM 0.17) and 0.43 (SEM 0.19), respectively.

The MRI-leukoencephalopathy status of all patients who received craniospinal radiation and survived 4 years or more are included in this report. Patients were monitored by periodic MRI scanning, comprising a minimum of T1, T2 and T1 with gadolinium sequences and the most recent MRI brain study from each patient was centrally reviewed by three of us (CKFW, SJK, JC) and graded according to the neuroimaging leukoencephalopathy toxicity grading criteria defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, (NCI CTCAE), Version 3.0 (Table 1). All participants or their guardians provided signed informed consent at the time of diagnosis after reviewing written information about the study, including details of follow-up investigations, in accordance with Institutional Ethics Committee requirements at each participating centre.

The treatment outline of the neoadjuvant phase II component of the original study is outlined in Table 2. The HDMTX infusion was administered over 4 h in 350 ml/m^2 of 5% dextrose with 1 mmol/kg $NaHCO_3$. At the completion of the HDMTX infusion, intravenous (i.v.) fluids at a rate of 2000 ml/m^2 were continued for at least 20 h and up to 48 h to maintain urine output. Leucovorin rescue (folinic acid) 10 mg orally every 6 h for 16 doses was commenced 24 h from the start of the HDMTX infusion. Additional leucovorin was used if the systemic MTX concentration exceeded 1×10^{-5} M at 24 h or $>3 \times 10^{-6}$ M at 48 h or until MTX concentrations fell below 5×10^{-7} M.

The characteristics of the patients are listed in Table 3. Scans from all 12 long-term survivors, aged 3.2–14.2 years at diagnosis, (median 6.6 years), who received craniospinal radiation therapy after completing the neoadjuvant phase II study were available for retrospective review. The follow-up interval from the time of radiation treatment to the most recent brain MRI study ranged from 4.0 to 10.5 years, (median 6.9 years). One patient (number 11) received additional frontal radiation therapy for a subfrontal recurrence of medulloblastoma 7.5 years prior to his most recent MRI brain scan.

Table 1
National Cancer Institute (NCI) common terminology criteria for adverse events, Version 3.0

	Grade			
	I	II	III	IV
Leukoencephalopathy radiographic findings	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (± multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation	–

Table 2
Neoadjuvant treatment outline

Day	Treatment	
1	Etoposide	100 mg/m^2 i.v. infusion over 1–2 h
	Carboplatin	350 mg/m^2 i.v. infusion over 1–2 h
2	Etoposide	100 mg/m^2 i.v. infusion over 1–2 h
	Carboplatin	350 mg/m^2 i.v. infusion over 1–2 h
3	HDMTX	8 g/m^2 i.v. over 4 h with i.v. fluids and folinic acid rescue

Four courses at 21–28 day intervals. i.v., intravenous; HDMTX, high-dose methotrexate.

The central acquisition and analysis of neuropsychological data for these patients was outside the scope of the original phase II study. Testing practices varied from centre to centre. In this setting, patients received HDMTX at a range of ages followed by craniospinal radiation. The whole brain and boost treatment volumes and prescriptions varied from patient to patient according to diagnosis, location of primary tumour, M-stage and best-established radiation therapy principles at the time of treatment.

3. Results

Our results are summarised in Table 4. Based on the NCI CTCAE, Version 3.0, 8 of 12 patients had grade I features of leukoencephalopathy and 4 of 12 had grade II changes. Neither the age at diagnosis nor follow-up duration differed significantly between patients with grade I or II changes.

Each of the 4 patients with grade II MRI changes of leukoencephalopathy received higher than typical craniospinal or whole brain radiation doses. Patient 8 received a standard craniospinal radiation dose and a supratentorial radiation boost to the primary site of 18 Gy, patient No. 9 received a whole brain radiation dose of 50.4 Gy because of neuraxis dissemination at diagnosis, patient 11 received a whole brain dose of 45 Gy followed 3 years later by a frontal boost of 25.2 Gy and patient 12 had a pineoblastoma treated with a craniospinal dose of 36 Gy and a conventional local boost to the primary site to a total of 54 Gy. The whole brain radiation therapy dose received by the patients with grade I MRI features of leukoencephalopathy ranged from 35 to 48.6 Gy, with a median of 36 Gy (see Figs. 1–4).

A review of the sequence of MRI brain scans from the 4 subjects with grade II changes revealed early onset of white matter changes within 1 year of radiation therapy together with progressive loss of white matter, reflected by increasing subarachnoid space and the relatively late appearance of lacunes, detected 5 and 6 years from the time of radiation treatment.

Table 3
Patient characteristics

Patient	Sex	Age (years)		Diagnosis	Radiotherapy					HDMTX (courses)
		Course # 1	Radiation start		Spine (Gy)	Whole brain (Gy)	Boost (Gy)	Fraction	Days	
1	M	10.8	11	Pineoblastoma	36	36	18	180	39	3
2	F	8.5	9.8	Medulloblastoma	36	36	18	180	41	4
3	F	3.2	3.4	Medulloblastoma	33	36	18	180	39	4
4	M	6.9	7.3	Medulloblastoma	36	36	18	180	41	4
5	M	5.8	6.3	Medulloblastoma	25	35	15	140	38	4
6	M	9.5	9.8	Medulloblastoma	30	35	15	60 boost 140	44	4
7	M	8.8	9.1	Medulloblastoma	45	48.6	–	60 boost 180	44	4
8	M	14.2	14.4	Pineoblastoma	36	36	18	180	46	4
9	M	6.8	7.1	Medulloblastoma	48.6	50.4	–	180	44	4
10	F	6.7	7.2	Medulloblastoma	35	35	19	140	45	4
11[a]	M	6.2	6.6	Medulloblastoma	45	45	6	150	67	4
12	F	3.5	3.8	Pineoblastoma	36	36	18	180	46	4

[a] Patient 11 received additional radiation treatment of 25.2 Gy to the frontal region (only) at recurrence 3.0 years after initial radiation therapy.

Table 4
Magnetic resonance imaging (MRI) findings

Patient	Latest MRI findings				Interval from radiation (years)	Review	
	T2	Flair	T1	T1 + G		Grade	Comments
1	Yes	Yes	Yes	Yes	10.5	1	Mild increase in subarachnoid spaces. Mild changes occipital white matter
2	Yes	Yes	Yes	Yes	7.8	1	Mild-moderate increase post. Ventricle horns. Minor changes periventricular white matter
3	Yes	Yes	Yes	Yes	4.9	1	Mild increase subarachnoid spaces. Occipital white matter changes
4	Yes	Yes	Yes	Yes	5.3	1	T1 +/– G, T1 flair +/– G. Extensive spread. Mild increase subarachnoid spaces. Mild post. White matter changes
5	Yes	Yes	Yes	Yes	8.1	1	T2, T1 + diffusion weighted flair. Mild increase subarachnoid spaces. Minimal white matter changes
6	Yes	No	Yes	Yes	9.4	1	Mild increase subarachnoid spaces. Mild changes white matter
7	Yes	No	Yes	Yes	4.3	1	Mild increase subarachnoid spaces. Cerebral atrophy. Slight occipital flare
8	Yes	No	Yes	Yes	5.9	2	Moderate increase subarachnoid spaces. Mild–moderate. Cerebral atrophy. Periventricular deep white matter changes, uniform L = R. Lacunae × 3, 5 mm
9	Yes	No	Yes	Yes	6	2	Mild–moderate increases subarachnoid spaces. Frontal/occipital/centrum semi-ovale periventricular white matter changes. Cerebral atrophy
10	Yes	No	Yes	Yes	7.1	1	Mild increases subarachnoid spaces. Mild white matter changes occipital. Mild cerebral atrophy
11	Yes	No	Yes	Yes	10.1	2	Temporal/frontal/occipital/centrum semi-ovale white matter changes. Lacunae × 5, small
12	Yes	No	Yes	Yes	4	2	Moderate atrophy. Occipital/centrum semi-ovale periventricular deep white matter changes

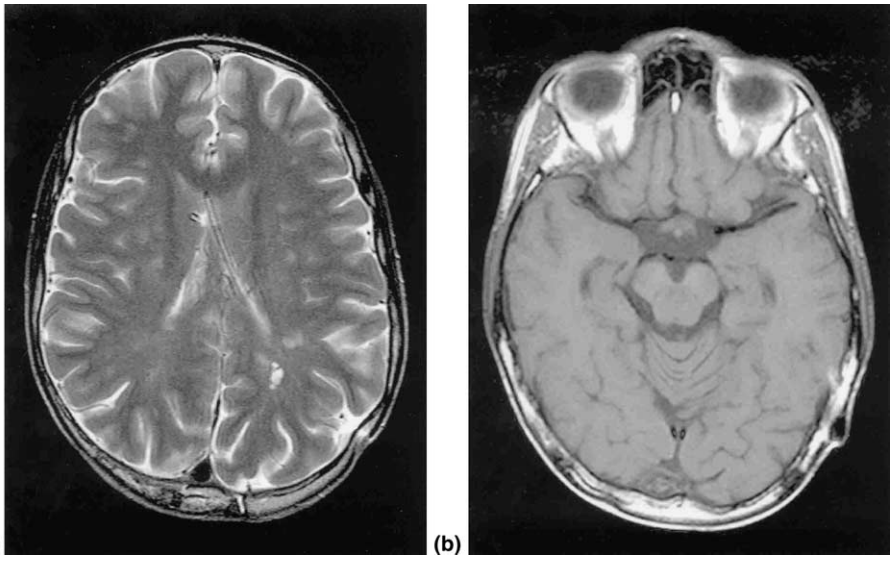

Fig. 1. Patient number 8. A 14-year-old boy with pinealoblastoma treated with a craniospinal axis dose of 35 Gy and a boost to the pineal region of 18 Gy. Follow-up time of 5.9 years. (a) Axial T2 image demonstrating grade II leukoencephalopathy with moderate increase in subarachnoid spaces, mild–moderate cerebral atrophy and periventricular white matter changes. (b) Axial T1 image demonstrating increased subarachnoid space.

4. Discussion

Our original study [29] enrolled children with newly diagnosed high-risk (defined by the presence of bulky residual disease or Chang staging of M2 or higher) embryonal CNS tumours. All surviving patients aged over 36 months at diagnosis received a whole brain dose of radiation of 36 Gy or higher after receiving repeated courses of high-dose i.v. methotrexate. Eight patients (of 12) had grade I MRI leukoencephalopathy changes only after a median follow-up of 7.5 years. Four children demonstrated grade II MRI features of leukoencephalopathy; 2 children presenting with pineoblastoma (numbers 8 and 12) received whole brain doses of 36 Gy and boost doses of radiation to the pineal region using parallel opposed fields to a total of 54 Gy. Two other patients with medulloblastoma complicated by neuraxis spread received whole brain radiation doses of 45 and 50.4 Gy. One of these patients (number 11) developed a localised frontal recurrence 3 years after

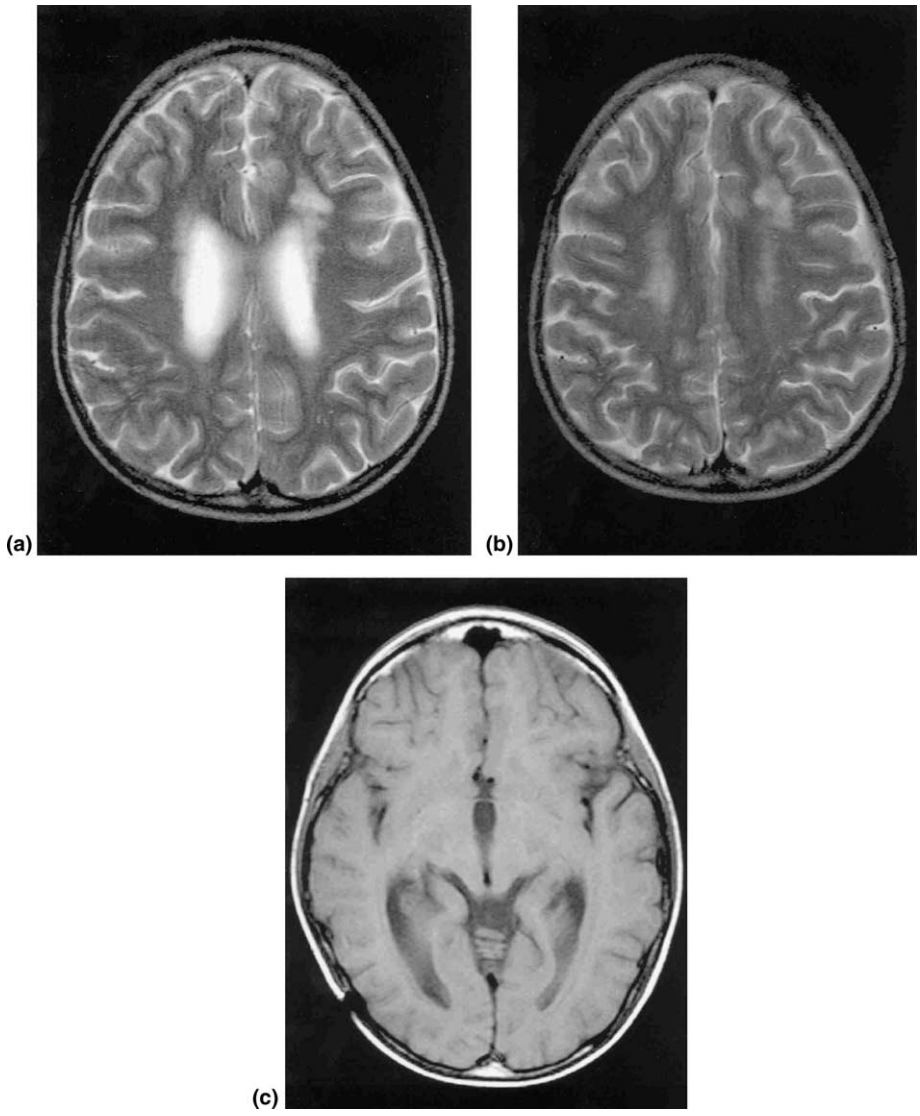

Fig. 2. Patient number 9. A 7-year-old boy with medulloblastoma who received a whole brain radiation dose of 50.5 Gy. Follow-up time of 6 years. Grade II leukoencephalopathy. (a) Axial T2 image. (b) Axial T2 image. (c) Axial T1 image. Images demonstrate mild-moderate increase in subarachnoid spaces and periventricular white matter changes.

diagnosis and received an additional boost to the frontal region increasing the dose to this area to 70.2 Gy.

Despite pre-radiation treatment with four courses of HDMTX, relatively young ages at diagnosis, generally high cranial radiation doses and long follow-up, we were unable to demonstrate any instances of moderate-to-severe MRI-neuroimaging evidence of leukoencephalopathy in this study. We could not demonstrate a relationship between age at the time of treatment or length of follow-up with leukoencephalopathy, however our observations suggest a relationship between higher supratentorial radiation doses and the risk of developing grade II changes.

The pathological findings of leukoencephalopathy at biopsy or autopsy are heterogeneous, but may range from scattered focal white matter lesions to diffuse lesions involving the periventricular or hemispheric white matter, diffuse cerebral atrophy related to loss of white matter, radiation associated vasculopathy and areas of radiation necrosis. Demyelination, axonal swelling and fragmentation, coagulative necrosis of the periventricular white matter and focal mineralisation associated with radiation therapy have been reported [17,30]. The pathogenesis of white matter changes appears to relate primarily to capillary endothelial cell damage, demyelination related to glial cell effects, particularly the oligodendrocytes, and possibly immune-mediated responses to antigens released from damaged glial cells [31–34].

Fouladi and colleagues reported the development of predominantly transient subacute white matter lesions at a median of 7.8 months after starting therapy for medulloblastoma or PNET. Sixteen patients (73%) demonstrated resolution at a median of 6.2 months after

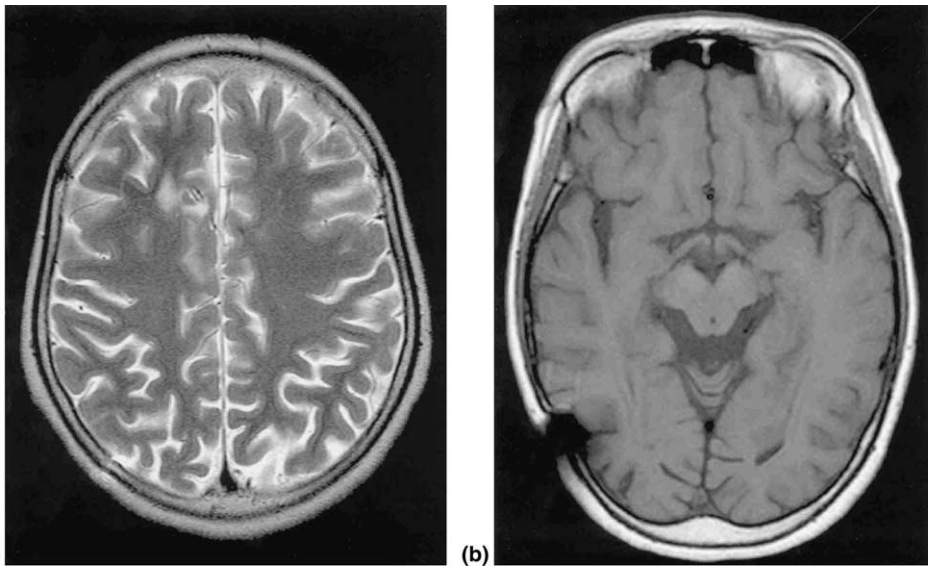

Fig. 3. Patient number 10. A 7-year-old girl with medulloblastoma treated with craniospinal axis radiation dose of 35 Gy with a boost of 19 Gy to the posterior fossa. Follow-up interval of 7.1 years. Grade I leukoencephalopathy. (a) T2 axial image. (b) T1 axial image.

onset and only 2 patients showed long-term white matter changes characterised by atrophy and necrosis. Fouladi and colleagues [25] documented lacunes, focal areas of white matter loss measuring up to 15 mm in diameter, in 25 patients among 421 CNS tumour patients treated with chemotherapy, radiation therapy or both and concluded they were incidental findings without corresponding clinical deficits. Two patients in our study were found to have white matter lacunes. Each of these patients had high supratentorial radiation doses – patient number 8 received a whole brain dose of 36 Gy with a conventional boost to the primary region to a total dose of 54 Gy. Patient number 11 received a whole brain dose of 45 Gy, followed 3 years later by a conventional boost to the frontal region of 25.2 Gy. Neither patient developed neurological deficits.

Previously, the NCI Common Toxicity Criteria Version 2.0 included lacunes as a criteria for grade III leukoencephalopathy. Version 3.0 of the CTCAE specifically excludes lacunes as a criteria for grading leukoencephalopathy. Leukoencephalopathy is currently defined as a diffuse white matter process, specifically not associated with focal necrosis.

White matter changes may be detected by conventional MRI scanning in up to 50% of patients receiving cranial radiation [23,34–36], however the correlation between quality of life and neuropsychological outcomes with the extent of white matter changes have been inconsistent [9,21,37–39]. More recently, detailed correlations between volumetric assessments using MRI scanning and neurocognitive evaluations by Mulhern and colleagues in children with medulloblastoma suggested that, at least for some cognitive functions, impaired development or loss of white matter after cranial radiation appeared to be associated with young age at the time of cranial radiation [12]. These observations have been expanded by Reddick and colleagues, who have developed a developmental model linking decreased normal appearing white matter with decreased attentional abilities associated with declining IQ and academic achievement [13]. Fouladi and colleagues [25] demonstrated declines in IQ, spelling scores and reading scores in patients with white matter lesions compared with those without.

Corn and colleagues [9] studied the incidence, course and clinical significance of white matter changes among 198 adults surviving longer than 18 months with malignant gliomas treated with hyperfractionated cranial radiation and carmustine (BCNU). They demonstrated that white matter sequelae were almost entirely confined to the radiation therapy portals and were related to older age and higher total radiation dose, however, they were unable to demonstrate a correlation between neuroimaging changes and changes in performance status.

CT evidence of leukoencephalopathy in children with leukaemia treated with cranial radiation and methotrexate as part of CNS-directed therapy was first reported by Peylan-Ramu in 1978 [27]. During the next decade, the clinical and radiological features of leukoencephalopathy complicating cancer therapy were well described including the increased risks of scheduling intrathecal or intravenous doses of methotrexate after cranial radiation [16,19,25,38,40,41].

Early observations by Ochs [42] and Peylan-Ramu [27] suggested that CT leukoencephalopathy was uncommon in patients with leukaemia receiving methotrexate without cranial radiation. Hertzberg and colleagues [20] also demonstrated that children with

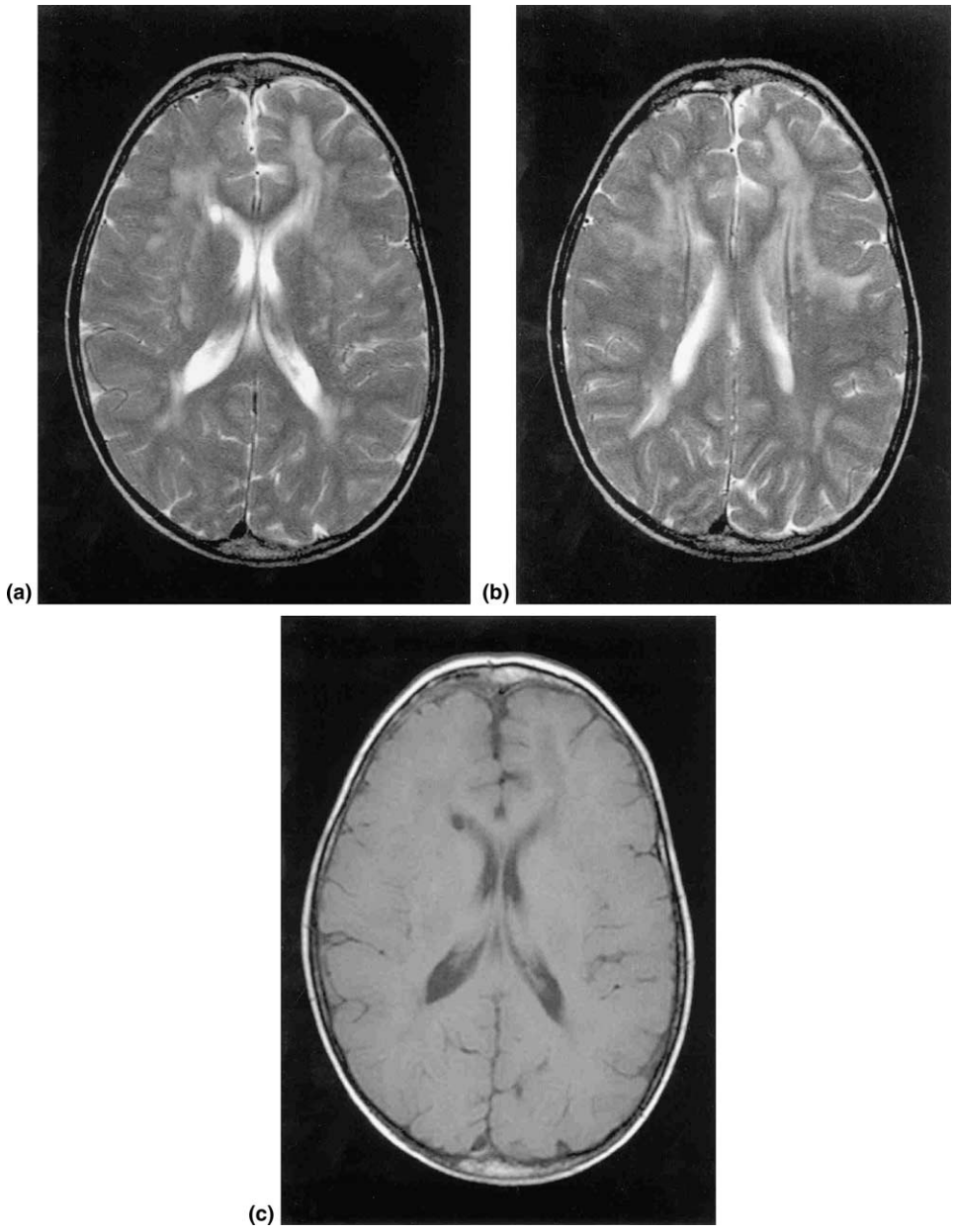

Fig. 4. Patient number 11. A 6-year-old boy with medulloblastoma and gross leptomeningeal disease who received a craniospinal dose of 45 Gy and a boost to the posterior fossa of 6 Gy. Follow-up interval of 10.1 years. He received additional chemotherapy and radiation therapy (25.2 Gy to the frontal region only) 3 years after diagnosis. Grade II leukoencephalopathy changes evident. (a and b) axial T2 images. (c) axial T1 image.

leukaemia receiving medium-high-dose methotrexate and/or intrathecal methotrexate alone were at less risk of leukoencephalopathy than those in whom methotrexate was combined with cranial radiation. Blay and colleagues [15] treating adults with primary CNS lymphoma, were able to demonstrate that the use of HDMTX prior to cranial radiation improved outcome, but was not associated with a higher risk of late neurotoxicity based on clinical features and CT or MRI examinations in 208 patients.

The findings of our study are similar to those of Packer and colleagues who performed MRI brain examinations in 11 patients from 12 months to 11 years (median 30 months) after cranial radiation therapy for varying conditions [35]. None of the patients received HDMTX. Based on an evaluation including ventriculomegaly, enlargement of cortical sulci, and presence, location and degree of white matter changes they demonstrated a similar profile of MRI changes to the 12 patients in our study.

Much of the data relating to the interactions between methotrexate, cranial radiation and the white matter relate to the 1980s during a phase of rapid improvement in the outcomes of children with acute lymphoblastic

leukaemia. Interest in the development of chemotherapy approaches to paediatric CNS tumours was relatively new at that time. During the past few years, the activity of HDMTX-containing chemotherapy combinations in high-risk patients with CNS embryonal tumours has been demonstrated and reported in preliminary form [43]. More recently, the Children's Oncology Group (United States of America (USA)) has developed a phase II/III proposal for newly diagnosed infants and young children with very high risk CNS embryonal tumours. This proposed study involves the randomised addition of HDMTX to a multidrug program and will enable a more accurate assessment of the activity of HDMTX in this setting. This proposed study will also enable prospective and consistent neuropsychological assessments to be conducted and significant differences between patients receiving or not receiving HDMTX may become apparent. The study will also enable prospective evaluation of serial MRI changes, particularly as some of the enrolled patients are expected to receive cranial radiation therapy (C. Mazewski, data not shown).

Our study was formulated as a phase II study of a HDMTX-containing regimen in previously untreated children with CNS embryonal tumours and was not designed to address long-term survival or neuropsychological outcomes nor provide clinical or radiological comparisons with a 'control' group who did not receive HDMTX. These limitations will be addressed in the forthcoming Children's Oncology Group Study. However, the present study provides a valuable insight into the absence of significant leukoencephalopathy in a group of paediatric patients who received intensive HDMTX followed by conventional-to-high doses of neuraxis radiation therapy compared with the changes commonly observed with radiation alone in this patient population. Prospective correlation of changes in normal-appearing white matter and neurocognitive performance are currently incorporated in virtually all phase III studies in infants and children with CNS tumours and will provide the opportunity of correlating the MRI and neurocognitive findings in patients receiving HDMTX prior to radiation therapy.

Conflict of interest statement

None declared.

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