To share your e-Eso experience use:
#e_ESO

Neurological emergencies

Expert: **Prof Christina Halsey**, Wolfson Wohl Cancer Research Centre, University of Glasgow, Glasgow, United Kingdom

Discussant: **Prof Arja Harila-Saari**, Uppsala University, Uppsala, Sweden

Neurological emergencies

Prof Christina Halsey
Wolfson Wohl Cancer Research Centre
Institute of Cancer Sciences
University of Glasgow
UK

Intended Learning Outcomes

- Know the different ways that chemotherapy-associated neurotoxicity in paediatric malignancies may present and how to formulate a differential diagnosis
- Understand the varied presentations of methotrexate related neurotoxicity
- Be aware of the appropriate investigations and supportive care for PRES/SLS/Seizures

Remember you can ask questions and send comments at any time

Spectrum of neurological conditions

- Primary neurological vs systemic
- Peripheral neuropathy vs central
- Focal signs vs diffuse alteration in higher mental function

Potential Causes

Infectious

Metabolic

Vascular – bleed or clot

Drugs

Radiotherapy

Immune-mediated

Tumour

Pre-existing neurological condition

AND THE INTERPLAY BETWEEN THESE !

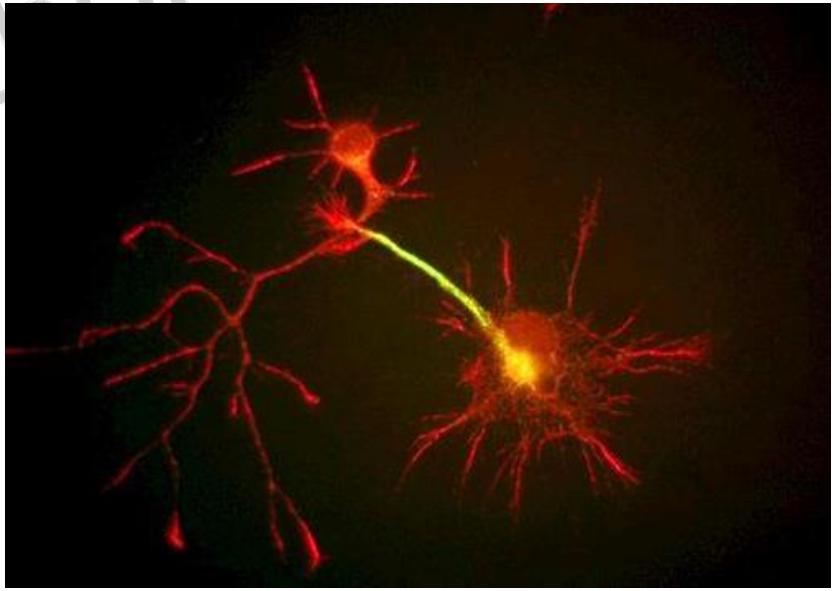


Figure from: http://www.stanford.edu/group/skmlab

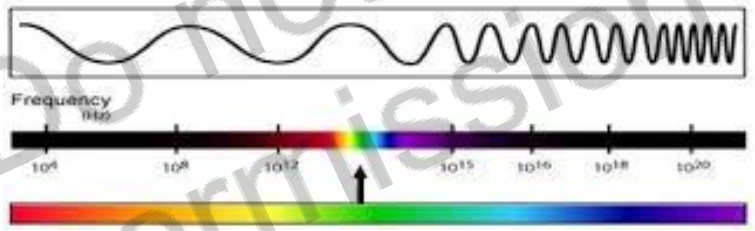
What we will not cover here

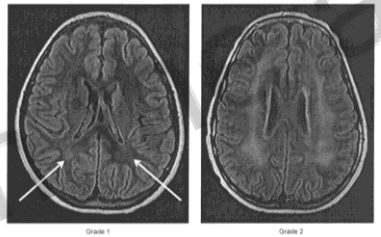
- Neurotoxicity secondary to underlying cancer or neurosurgical management of brain tumours
- Side-effects of cranial or craniospinal irradiation
- Neurotoxicity secondary to CNS or systemic infections
- Neurotoxicity secondary to systemic metabolic insults (e.g. liver failure, hyperammonaemia, hyponatraemia)
- Intracerebral haemorrhage
- Neurotoxicity related to Blinatumomab and CAR-T cells

ALTHOUGH THESE ARE ALL IMPORTANT AND NEED TO BE PART OF THE DIFFERENTIAL DIAGNOSIS!!

Burden of chemotherapy associated neurotoxicity

- Acute
- Seizures
- Stroke-like syndrome, PRES
- Neurocognitive
- CVST
- Mood disorders/ Psychosis
- Coma
- Encephalopathy (e.g.ifosfamide)





- Chronic
- Neurocognitive,
- Behavioural, Quality of Life
- ? Early onset dementia

	Standard therapy group (n=266)	Augmented therapy group (n=267)	p value for augmented vs standard therapy
Serious adverse events			
Any serious adverse event	91 (34%)	119 (45%)	0·02
Infection	44 (17%)	43 (16%)	0·91
Encephalopathy	20 (8%)	33 (12%)	0·06
Asparaginase hypersensitivity	2 (<1%)	18 (7%)	0·0003
Pancreatitis	1 (<1%)	8 (3%)	0·04
Avascular necrosis	16 (6%)	13 (5%)	0·57
Thrombosis	8 (3%)	10 (4%)	0·81
Neuropathy	6 (2%)	6 (2%)	1·00
Mucositis	3 (1%)	11 (4%)	0·05

Vora et al Lancet Oncology 2014 15(8) p809-818

Chemotherapy agents produce different patterns of neurotoxicity

- CVST – Asparaginase
- SLS/LE and Neurocognitive deficits – Methotrexate
- PRES – Vincristine and steroids
- Cerebellar symptoms – Nelarabine and Cytarabine
- Seizures – all of the above
- Psychosis – Steroids
- Encephalopathy - Ifosfamide
- Unknown? – New agents

BUT Multiagent therapy and delayed presentation can make identification of causative agent difficult

Differences in incidence across trial groups reflects chemotherapy differences and classification (especially SLS vs PRES)

Acute neurotoxicity may impact on treatment outcomes

Posterior Reversible Encephalopathy Syndrome: Risk Factors and Impact on the Outcome in Children With Acute Lymphoblastic Leukemia Treated With Nordic Protocols

Joanna S. Banerjee, MD, Mats Heyman, MD, PhD,† Maarit Palomäki, MD,‡ Päivi Lähteenmäki, MD, PhD,§ Mikko Arola, MD, PhD,‖ Pekka V. Riikonen, MD, PhD,¶ Merja I. Möttönen, MD, PhD,# Tuula Lönnqvist, MD, PhD,** Mervi H. Taskinen, MD, PhD,* and Arja H. Harila-Saari, MD, PhD†*

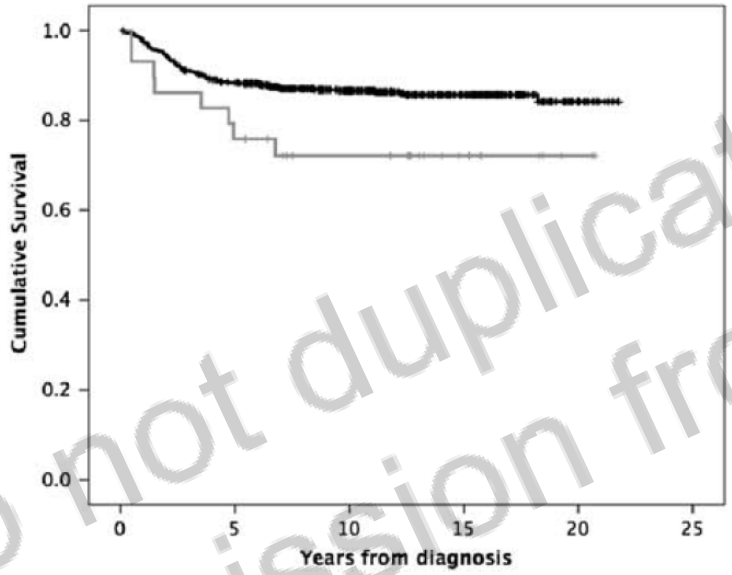


FIGURE 3. Overall survival is worse in patients with PRES (grey line, $P = 0.040$).

J Pediatr Hematol Oncol • Volume 40, Number 1, January 2018

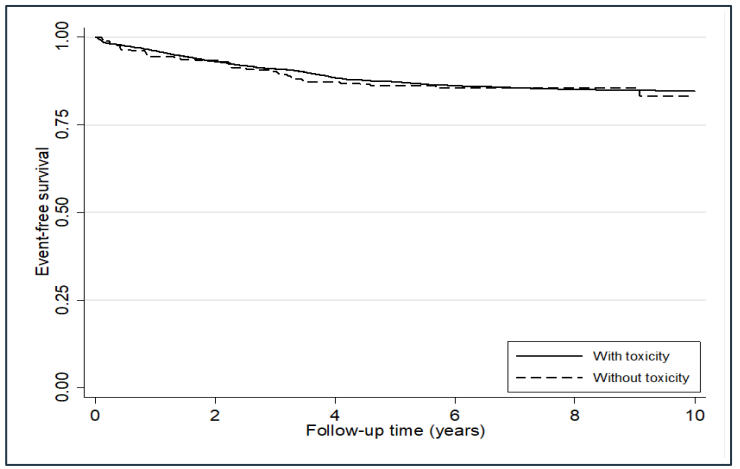
Table 3. Treatment comparison by neurotoxicity status among patients treated on ALL protocols, 2012–2017

	Mean (95% CI) treatment comparison by neurotoxicity		
	Neurotoxicity ($n = 28$)	No neurotoxicity ($n = 181$)	*P*
IV MTX dose, g/m^2	10.23 (8.33–12.13)	12.04 (11.37–12.71)	0.084
Number IT MTX doses	8.84 (8.36–9.33)	11.09 (10.92–11.26)	<0.01
Time to maintenance, days	296.9 (284.8–311.9)	290.0 (284.8–295.3)	0.408

NOTE: Model adjusted for treatment risk arm, age at diagnosis, BMI Z-score at diagnosis, and sex.
Abbreviations: IT, intrathecal; IV, intravenous; MTX, methotrexate.

Taylor et al, Clin Cancer Res, 2018, 24 p5012-17

6/39 (15%) relapsed vs. 13/241 (2%)



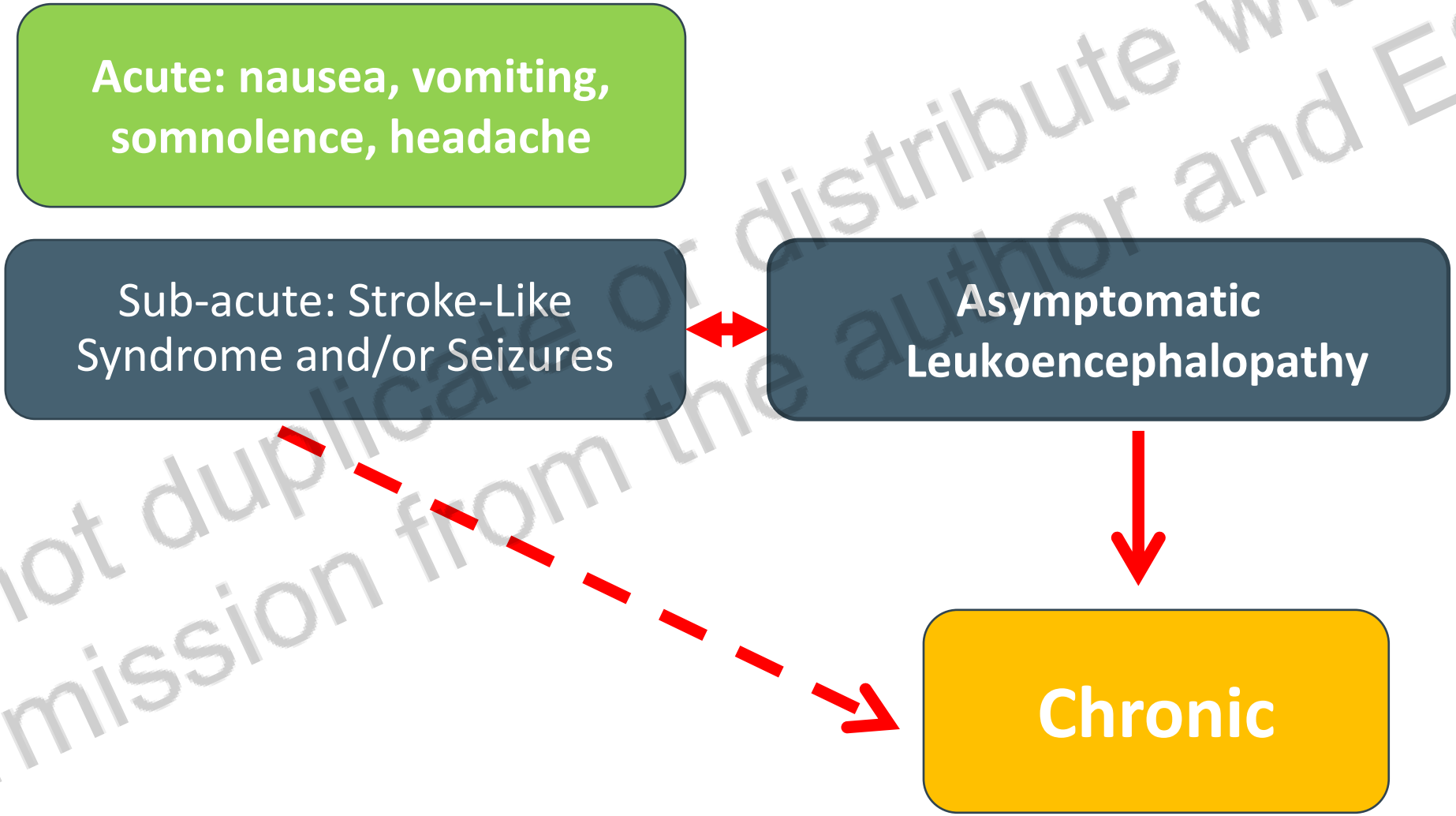
UKALL 2003 EFS

Ifosfamide encephalopathy

- 10-30% of patients can have encephalopathic reaction during or shortly after infusion
- Often confusion (80%) and reduced conscious level but can see agitation, hallucinations, psychosis. Also muscle twitching. Can occasionally result in coma and death
- EEG shows generalised slowing and triphasic waves
- Ifosfamide is metabolised to chloroacetaldehyde by cytochrome p450 - this is the likely causative agent which leads to:
  - direct neurotoxicity
  - cerebral glutathione depletion
  - inhibition of mitochondrial electron transport
- Reported association with previous cisplatin, impaired hepatic and renal function, aprepitant and also CYP2B6 polymorphism
- Management – stop infusion, correct fluid and electrolyte imbalance, supportive care plus consider intravenous methylene blue (although not much evidence) which can also be used prophylactically with subsequent courses

Methotrexate Neurotoxicity

Spectrum of methotrexate neurotoxicity



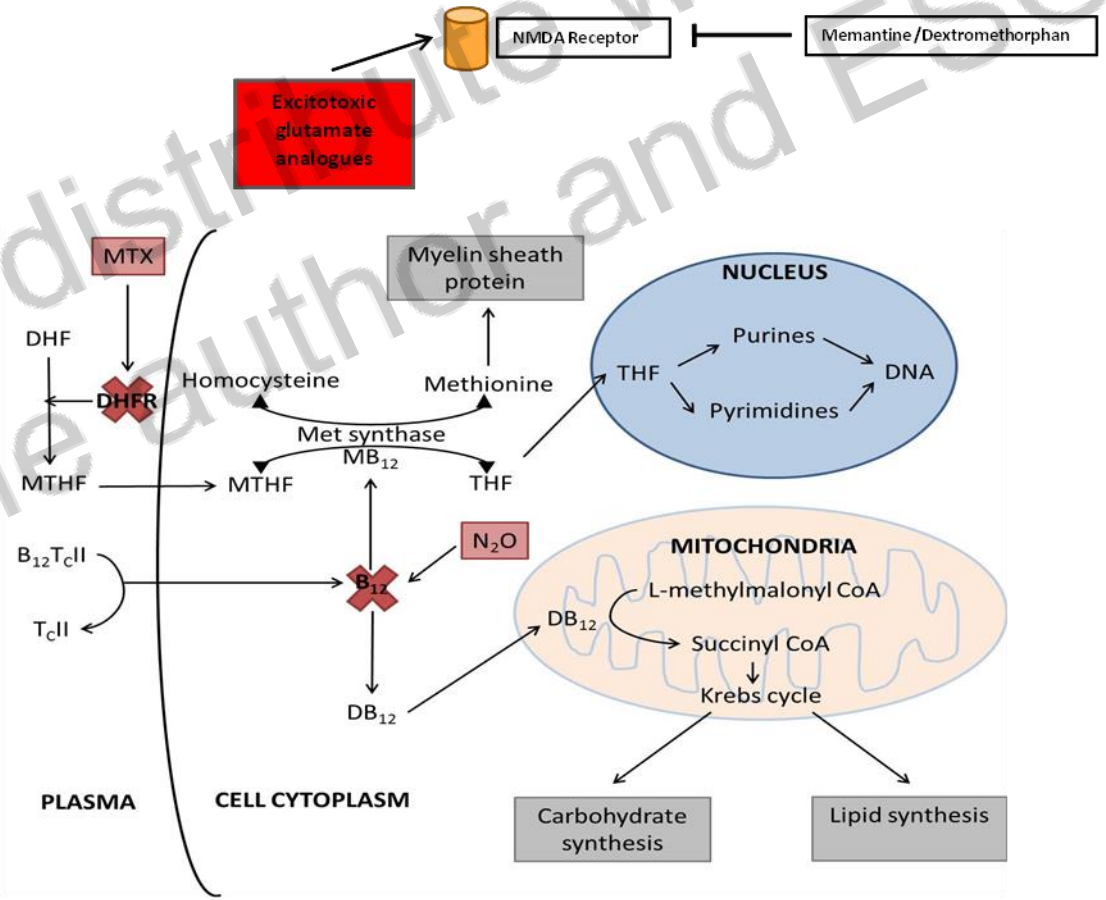
Mechanisms of methotrexate neurotoxicity

- Inadequate folinic acid rescue or high IT doses
- Acute adenosine release
- Elevated Homocysteine producing Neuroexcitatory metabolites (NMDA receptor)
- Low B12/nitrous oxide use
- Reduced Methionine
- Defective myelination due to triglial dysfunction

(Gibson et al, Cell 2019, 176 p43-55)

- GWAS implicates genes in neurodevelopmental pathways

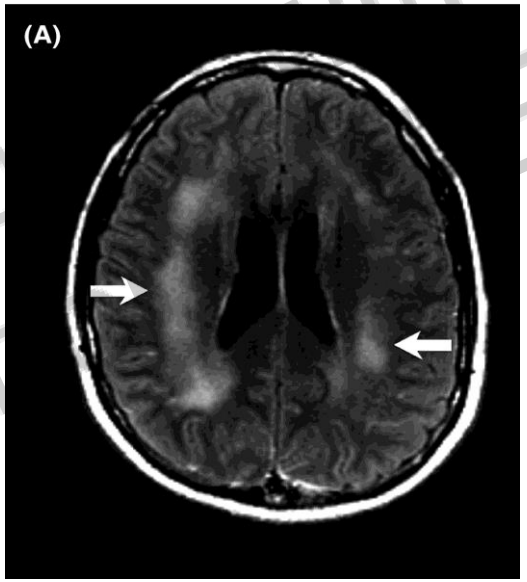
(Bhojwani JCO 2014, Mateos Haematologica 2021)



Forster et al **Cancer Chemotherapy and Pharmacology**, 2016, 78(5), pp. 1093-1096

Methotrexate Stroke-like Syndrome

- Focal neurological deficits or hemiparesis within 21-days of methotrexate
- Disturbances in speech and/or affect
- Wax and wane over the course of hours to days.
- CT scans are often normal.
- Leukoencephalopathy on MRI best seen on diffusion-weighted and T2-weighted images
- Usually complete resolution within 7days
- Commoner in older children
- ? Commoner with concurrent Ara-C and/or cyclophosphamide



Axial T2-weighted FLAIR MR image (A) demonstrates diffuse hyperintensity within the right periventricular white matter (arrow) and to a lesser extent on the left

M.T. Cruz-Carreras et al Clinical Case Reports 2017; 5(10): 1644– 1648

- **Often occurs after multiple exposures**
- **No clear relationship with MTX level**
- **Usually safe to re-expose!**

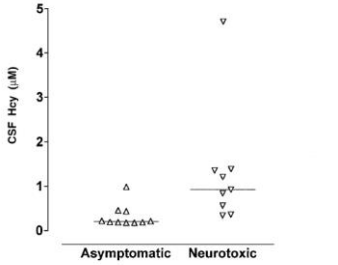
Management

- Whenever possible the diagnosis should be established using MRI scanning with diffusion weighted imaging (note CT scans are often normal).
- Exclude alternative causes for symptoms such as CNS infection, cerebral venous sinus thrombosis, haemorrhage, PRES or exposure to toxins.
- Many patients will have spontaneous resolution of symptoms without active treatment.
- Dextromethorphan and aminophylline have both been used to treat SLS but their efficacy is difficult to assess since the syndrome resolves spontaneously.

Dextromethorphan and Aminophylline

Dextromethorphan

- 1mg/kg orally up to three times daily or 2.5mg/kg once daily.
- Do not give to patients taking monoamine oxidase inhibitors or SSRIs due to the risk of severe drug interactions.
- Use with caution in children with atopy due to histamine release
- case reports of prophylaxis for subsequent MTX doses (1.5 mg/kg/dose BID) started prior to MTX and continued for 7 days) - efficacy of this is unknown.



	Asymptomatic	Neurotoxic
n =	10	9
Median	0.2005	0.9250 *
Range	0.17 – 0.98	0.34 – 4.71

FIGURE 1 CSF homocysteine (Hcy) measured by coulometric electrochemical detection in patients being treated with methotrexate (MTX). CSF Hcy was higher among patients with signs and symptoms of subacute MTX neurotoxicity. * $p < .01$; 2-tailed Mann-Whitney U test.

TABLE 1 Clinical Characteristics of 5 Patients with Severe Subacute MTX Neurotoxicity

Patient no.	Diagnosis	Age (yrs)	Sex	MTX therapy	Time since last MTX (days)	Physical findings	Normal diagnostic studies	CSF Hcy (μM)	DM dose	Time to initial response (min)	Time to resolution of symptoms	Sequellae
1	OS	16	M	12 g/m^2 IV	7	Dysarthria, CN VII palsy	CT, MRI	ND	1 mg/kg × 1	30	30 min	None
2	OS	13	M	12 g/m^2 IV	7	Right CN VII palsy, left hemiparesis, dysarthria, impaired gag	CT, MRI, MRA, EEG CSF cell count	0.93	1 mg/kg TID	45	3 days	None
3	ALL	19	M	7.5 mg IO weekly; 1 g/m^2 IV	12	Right CN VII palsy, right hemiparesis, dysarthria	CT, MRI, MRA, CSF cell count	1.39	1 mg/kg TID	180	10 days	None
4	ALL	15	M	12 mg IT; 100 mg/m^2 IV	7	Left hemiparesis	CT	0.45[a]	2 mg/kg × 1	30	6 h	None
5	NHL	32	M	12 mg IT	2	Headache, dysarthria, nausea, weakness, asthenia	CT, CSF cell count	4.71	1 mg/kg	180	24 h	None

[a]Measured 2 weeks after the resolution of neurologic symptoms, at the time of a scheduled lumbar puncture for the administration of prophylactic chemotherapy.
Note. All 5 patients experienced resolution of their symptoms after treatment with oral dextromethorphan. ND, not measured.

R.A. Drachtman et al (2002) Pediatric Hematology and Oncology, 19:5, 319-327

Aminophylline

- Aminophylline (2.5 mg/kg) as an intravenous infusion over 45-60 min

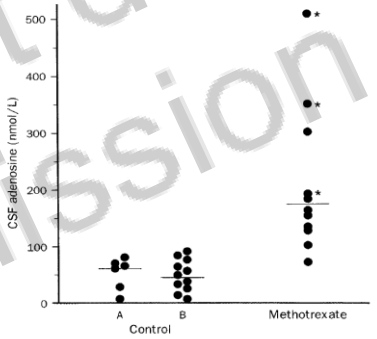


Figure: **Effects of methotrexate on the adenosine content of CSF**

THE LANCET

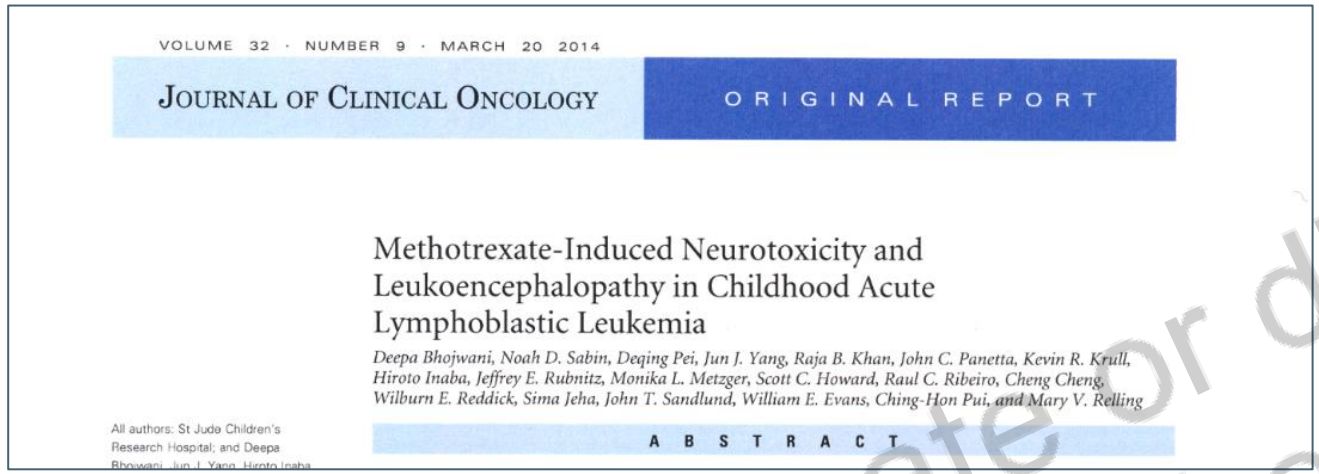
Patient	Diagnosis (sex/age)	Previous treatments	MTX route	Symptoms	Response
1	ALL (male/6 y)	Paracetamol & codeine, promethazine	PO IT	Nausea, emesis, headache, lethargy	CR
2	ALL (male/4 y)	Paracetamol & codeine, promethazine	CI IT	Nausea, emesis, headache, lethargy	CR
3	ALL (female/12 y)	Ondansteron, paracetamol & codeine, promethazine, epidural blood patch, steroids	PO IT	Nausea, emesis, headache, lethargy	PR
4 (1st dose)	NHL (male/14 y)	Ondansteron	IT	Nausea, emesis, headache	PR
(2nd dose)		Paracetamol, promethazine, ondansteron	CI IT	Nausea, emesis, headache, lethargy	PR
(3rd dose)		Aminophylline	CI IT	Nausea, emesis	PR
5	ALL (male/3y)	Paracetamol, promethazine	CI IT	Nausea, emesis, headache	CR
6	ALL (male/16 y)	Paracetamol, promethazine, ondansteron	CI (4·6 g over 4 h)	Nausea, lethargy, headache	CR

CI=methotrexate continuous infusion 1 g/m² over 24 h; IT=intrathecal methotrexate; PO=oral methotrexate 25 mg/m² over 6 h×4; CR=complete response; PR=partial response; ALL=acute lymphoblastic leukaemia; NHL=non-Hodgkin lymphoma.

Table 1: **Patient characteristics**

Bernini et al The Lancet 1995 345 p544-7

Asymptomatic Leukoencephalopathy



VOLUME 32 · NUMBER 9 · MARCH 20 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Methotrexate-Induced Neurotoxicity and Leukoencephalopathy in Childhood Acute Lymphoblastic Leukemia

Deepa Bhojwani, Noah D. Sabin, Deqing Pei, Jun J. Yang, Raja B. Khan, John C. Panetta, Kevin R. Krull, Hiroto Inaba, Jeffrey E. Rubnitz, Monika L. Metzger, Scott C. Howard, Raul C. Ribeiro, Cheng Cheng, Wilburn E. Reddick, Sima Jeha, John T. Sandlund, William E. Evans, Ching-Hon Pui, and Mary V. Relling

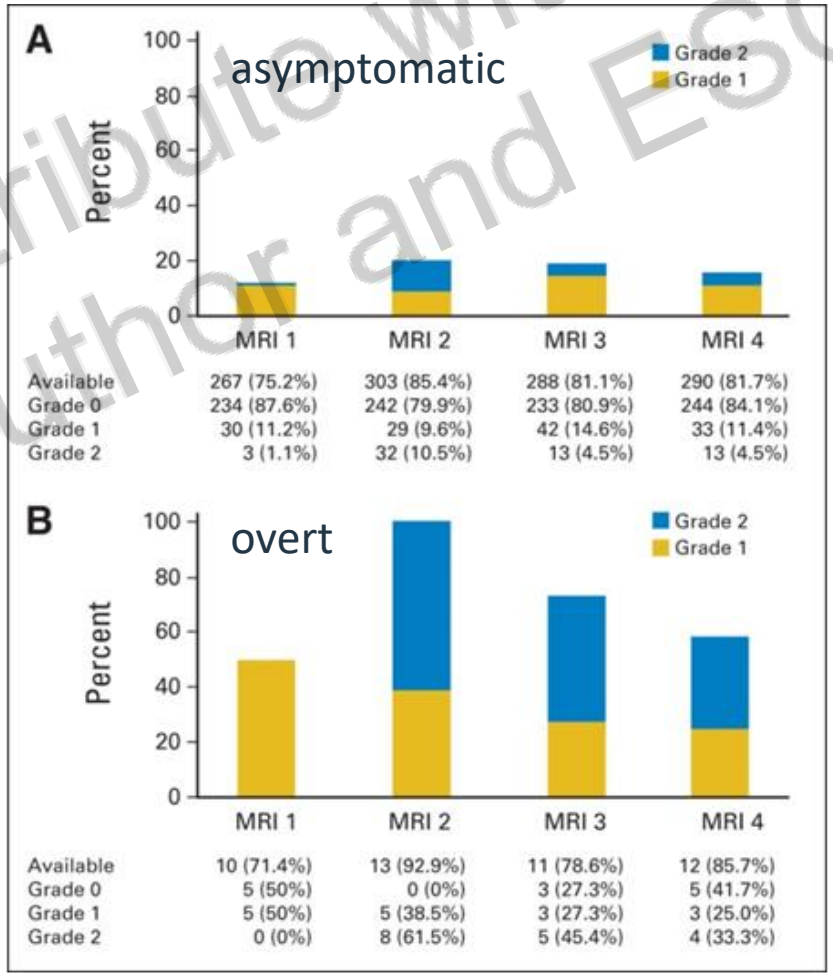
All authors: St Jude Children's Research Hospital; and Deepa Bhojwani, Jun J. Yang, Hiroto Inaba

ABSTRACT

3.8% children had overt neurotoxicity

21% (73/355) had LE on MRI

Of these 74% had persistently abnormal MRIs at end of therapy.



Deepa Bhojwani et al. JCO 2014;32:949-959

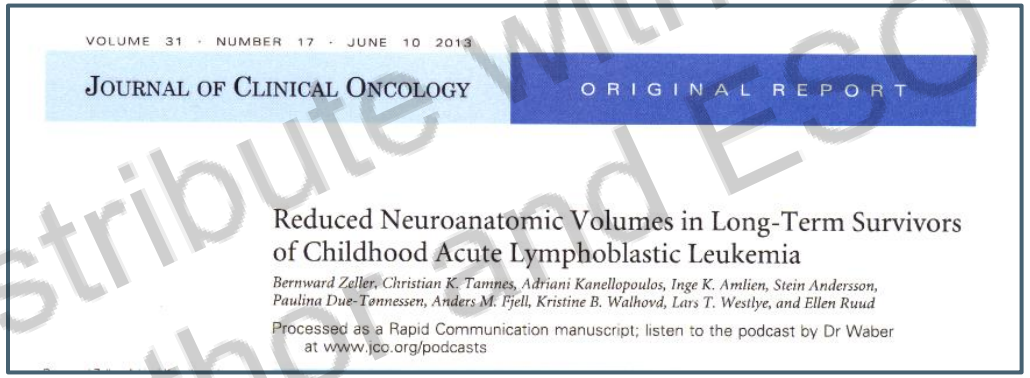
Chronic Neurotoxicity from Methotrexate

- Up to 40-60% of survivors have subtle neurocognitive defects, even in chemotherapy-only cohorts

- SJCRH cohort confirmed adverse neurobehavioural outcomes in asymptomatic LE patients Cheung et al, The Lancet Haematology 3, 2016, e456–e466

- Association with SNPs in genes involved in folate pathways and oxidative stress

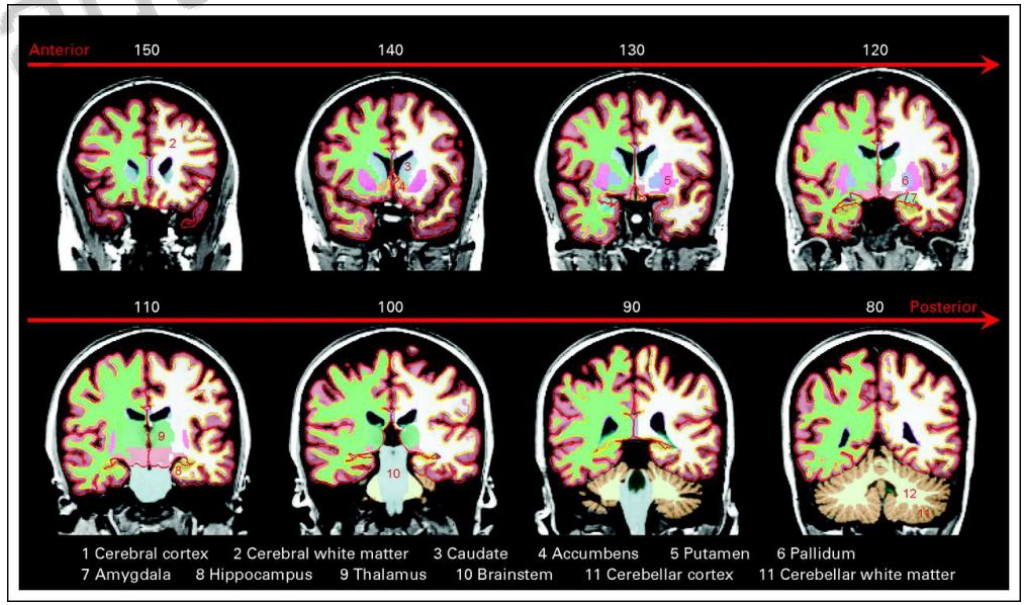
- Evidence of accelerated ageing in the CNS. Is there an increased risk of early-onset dementia?


VOLUME 31 · NUMBER 17 · JUNE 10 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Reduced Neuroanatomic Volumes in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

Bernward Zeller, Christian K. Tamnes, Adriani Kanellopoulos, Inge K. Amlien, Stein Andersson, Paulina Due-Tønnessen, Anders M. Fjell, Kristine B. Walhovd, Lars T. Westlye, and Ellen Ruud

Processed as a Rapid Communication manuscript; listen to the podcast by Dr Waber at www.jco.org/podcasts



Seizures

- Seizures seen in 3%-10% of ALL patients
- 25% occur in the first 6 weeks after diagnosis with 75% occurring within18 months
- Diverse aetiology:
  - 60% related to chemotherapy toxicity (PRES/MTX)
  - 10% intracranial haemorrhage
  - 8% cerebral venous sinus thrombosis (CVST)
  - 6% CNS infections
  - 16% idiopathic
- Other reported causes include hyperviscosity and electrolyte imbalance (especially severe hyponatraemia).
- Those with idiopathic seizures more likely to have LE and subsequent neurocognitive deficits

Received: 11 July 2016 | Revised: 7 December 2016 | Accepted: 7 December 2016
DOI: 10.1002/pbc.26436

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Neurocognitive outcomes among children who experienced seizures during treatment for acute lymphoblastic leukemia

Stephanie L. Nassar[1] | Heather M. Conklin[2] | Yinmei Zhou[3] | Jason M. Ashford[2] | Wilburn E. Reddick[4] | John O. Glass[4] | Fred H. Laningham[5] | Sima Jeha[6] | Cheng Cheng[3] | Ching-Hon Pui[6]

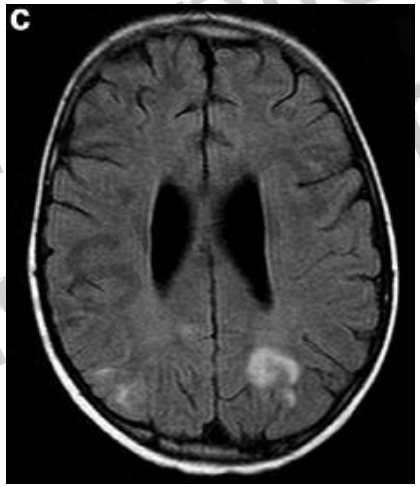
Management of seizures

- Prevent prolonged seizure activity
- Identify and (where possible) treat the underlying cause
- Many seizures are brief and self-terminating, but for prolonged seizures local protocols for use of benzodiazepines and other anti-seizure medications should be followed
- It should be noted that where possible the long-term use of anti-epileptics that induce Cytochrome P450 3A4 should be avoided (e.g.phenytoin), as these may interfere with subsequent anti-leukaemic therapy. **Levetiracetam (Keppra) is often the treatment of choice**
- Re-exposure once seizure activity is under control is generally considered safe
- Risk of seizures can be minimized by careful attention to fluid balance and glucose and electrolyte levels. Hydration fluids should be isotonic where possible and regular monitoring of sodium levels should be performed

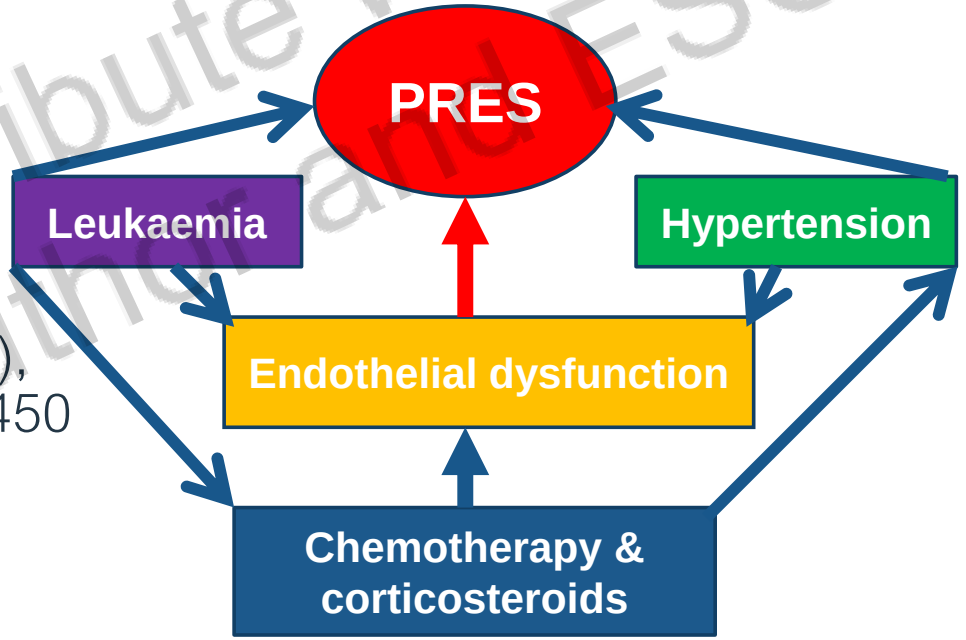
Posterior Reversible Leukoencephalopathy Syndrome (PRES)

remember you can ask questions and send comments at any time

- Clinico-radiological entity characterized by seizures, headache, altered mental status and visual impairment
- MRI shows bilateral sub-cortical or cortical oedema typically in parieto-occipital regions
- Usually associated with hypertension
- Risk factors ? high-dose vincristine (constipation, hyponatraemia), steroids, aggressive hydration and use of azoles (Cytochrome P450 3A4 inhibitors)



EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 14 (2010) 539–545



- **Key event – endothelial dysfunction**
- **Leaky vessels lead to vasogenic oedema**
- **Wide variation between trial groups**

NOPHO Experience of PRES

Received: 12 October 2018 | Revised: 4 December 2018 | Accepted: 7 December 2018
DOI: 10.1002/pbc.27594

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: Clinical characteristics, risk factors, course, and outcome of disease

Stavroula Anastasopoulou[1] | Mats A. Eriksson[1] | Mats Heyman[1] | Chen Wang[1] | Riitta Niinimäki[2] | Sirje Mikkel[3] | Goda E. Vaitkevičienė[4] | Inga Maria Johannsdottir[5] | Ida Hed Myrberg[6] | Olafur Gisli Jonsson[7] | Bodil Als-Nielsen[8] | Kjeld Schmiegelow[8] | Joanna Banerjee[9] | Arja Harila-Saari[10] | Susanna Ranta[1]

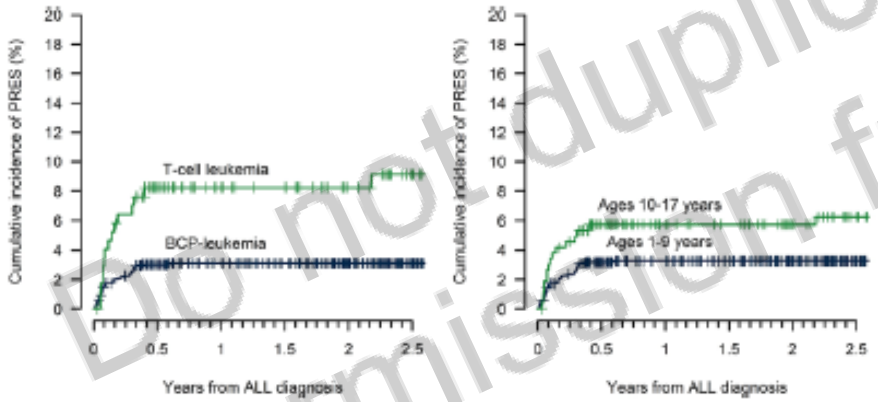
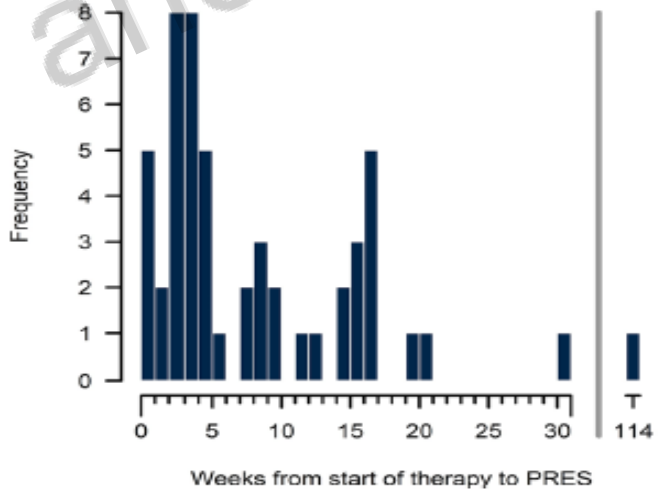


TABLE 2 Symptoms, signs, laboratory findings, and treatment strategies in patients with PRES

Neurological symptoms	Number of patients
Seizures	43/52 (82.7%)
Encephalopathy	33/51 (64.7%)
Visual field defects	17/51 (33.3%)
Pyramidal weakness	14/52 (26.9%)
Headache	15/51 (29.4%)
Dysphasia	10/51 (19.6%)
Nausea	10/50 (20.0%)
Sensory disturbances/paresthesia	7/51 (13.7%)
Dyspraxia	3/50 (6.0%)
Psychosis	1/52 (1.9%)
Signs	
Hypertension	41/52 (78.8%)
Fever	11/50 (22.0%)
Other symptoms	
Constipation	27/52 (51.9%)
Abdominal pain	28/52 (53.8%)
Pancreatitis	4/36 (11.1%)
Ileus	1/36 (2.8%)
Infection	22/49 (44.9%)

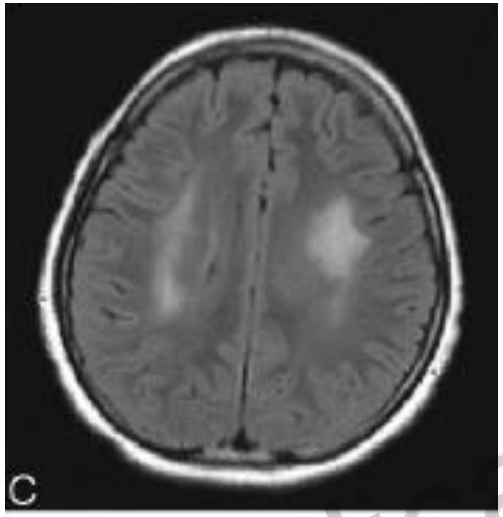


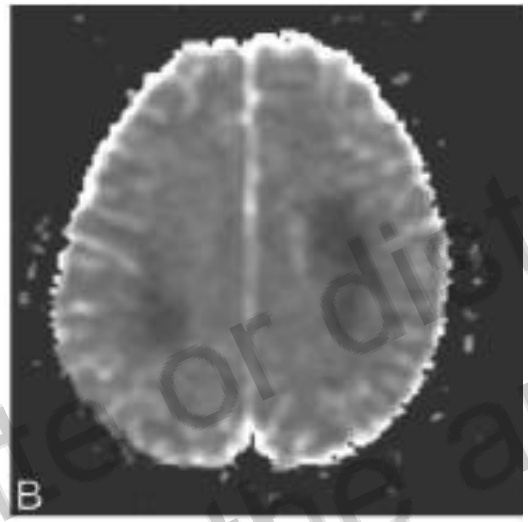
PRES and SLS – Differences & Similarities

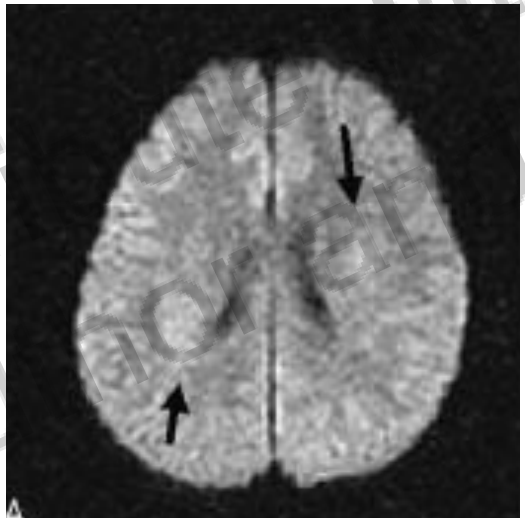
PRES	SLS
Headache, **confusion**, **visual disturbances**	**Confusion**, **mental status altered affect**, **paresis/paralysis**, **aphasia/dysarthria**
Seizures,	**Seizures,**
Spontaneous resolution	**Spontaneous resolution**
Hypertension prominent	**Waxing and waning pattern**
Early-onset – first 3-4 months	Usually consolidation/intensification
Association with Vincristine	**Within 21 days of Methotrexate**
CT can be normal	**CT often normal**
MRI T2- hyperintense cortical / subcortical lesions	**MRI T2- hyperintense subcortical lesions**
DWI –normal or **hyperintense**	DWI – **hyperintense**
ADC **(classically) increased**	ADC **decreased (low signal)**

Imaging of SLS and PRES

SLS

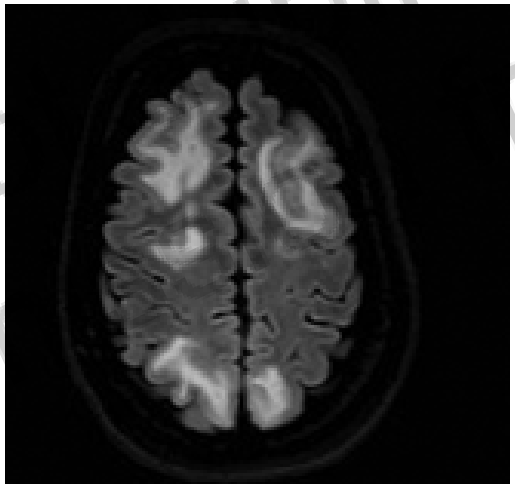


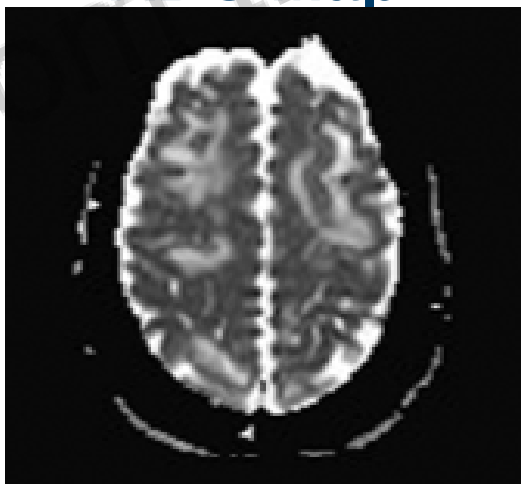




T2 Axial FLAIR | **ADC Map** | **DWI**

PRES





PRES – leaky vessels – **increased H_20 diffusion**

SLS - restricted H_20 diffusion

DWI shows distribution of H_20 so restriction appears bright

BUT calculated Apparent Diffusion Coefficient (ADC) is reduced so restricted diffusion is darker on these software generated images

Terminology is complex and leads to confusion in reports!

Management

- Treat hypertension (aim for 10-20% acutely then to normal range)
- Withhold causative agent
- Maximise supportive care including platelet transfusion
- Intrathecal treatment should be postponed until normalization of clinical findings and MRI.
- Missed doses should be caught up where possible

Cerebral Venous Sinus Thrombosis

- Strongly associated with Asparaginase treatment in combination with corticosteroids +/- other procoagulant risk factors (immobility, infection, dehydration)
- Seen in 1-2% (? Higher)
- Usually occurs in consolidation phase of ALL treatment
- Presents with headache, N&V, seizures, fatigue, depressed consciousness or CN palsies (but can be asymptomatic)
- Diagnosed on CT scan – may see concurrent haemorrhage and infarction
- Often low AT levels but not always, D-Dimers may be normal
- Treat with LMWH therapeutic dose at least 3-6 months (until 3/52 after last Asp dose), then prophylaxis for high-risk periods
- If extensive haemorrhage at initial diagnosis, withhold anticoagulation and rescan
- Withhold asparaginase for at least 4 weeks, rescan to ensure stabilisation or improvement if planning to re-expose

- *Management guideline: Sibson et al British Journal of Haematology, 2018, 180, 511–525*

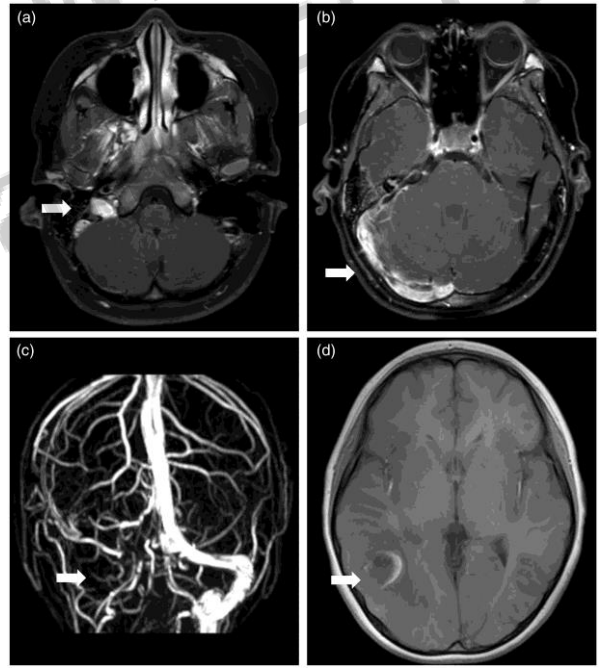
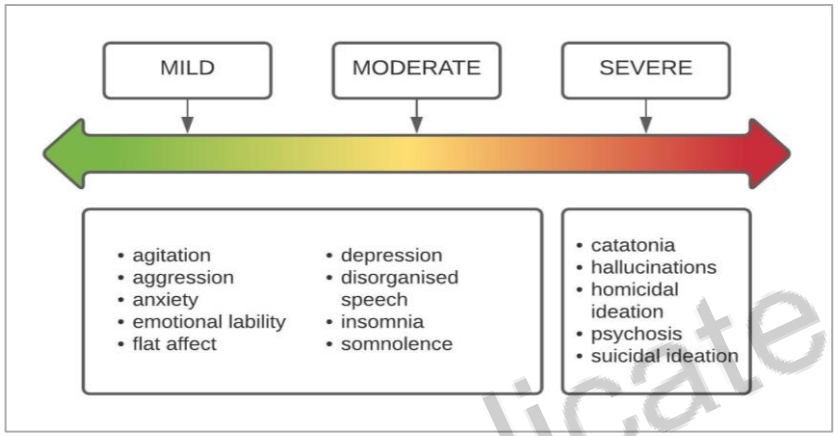
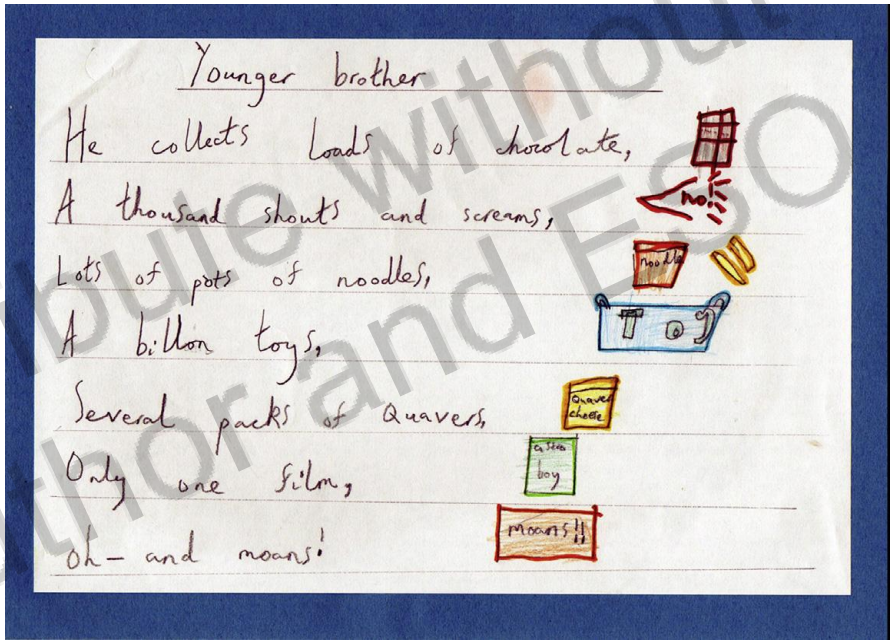


Figure 1. Magnetic resonance imaging (MRI) of vascular plaque in our patient's head and neck revealed right internal jugular vein, transverse sinus, and sigmoid sinus thrombosis (a, b, c). Head MRI showed right temporal-parietal lobe hemorrhage
Liu J, Yang C, Zhang Z, Li Y. Journal of International Medical Research. January 2021. doi:10.1177/0300060520986291

Steroid Psychosis

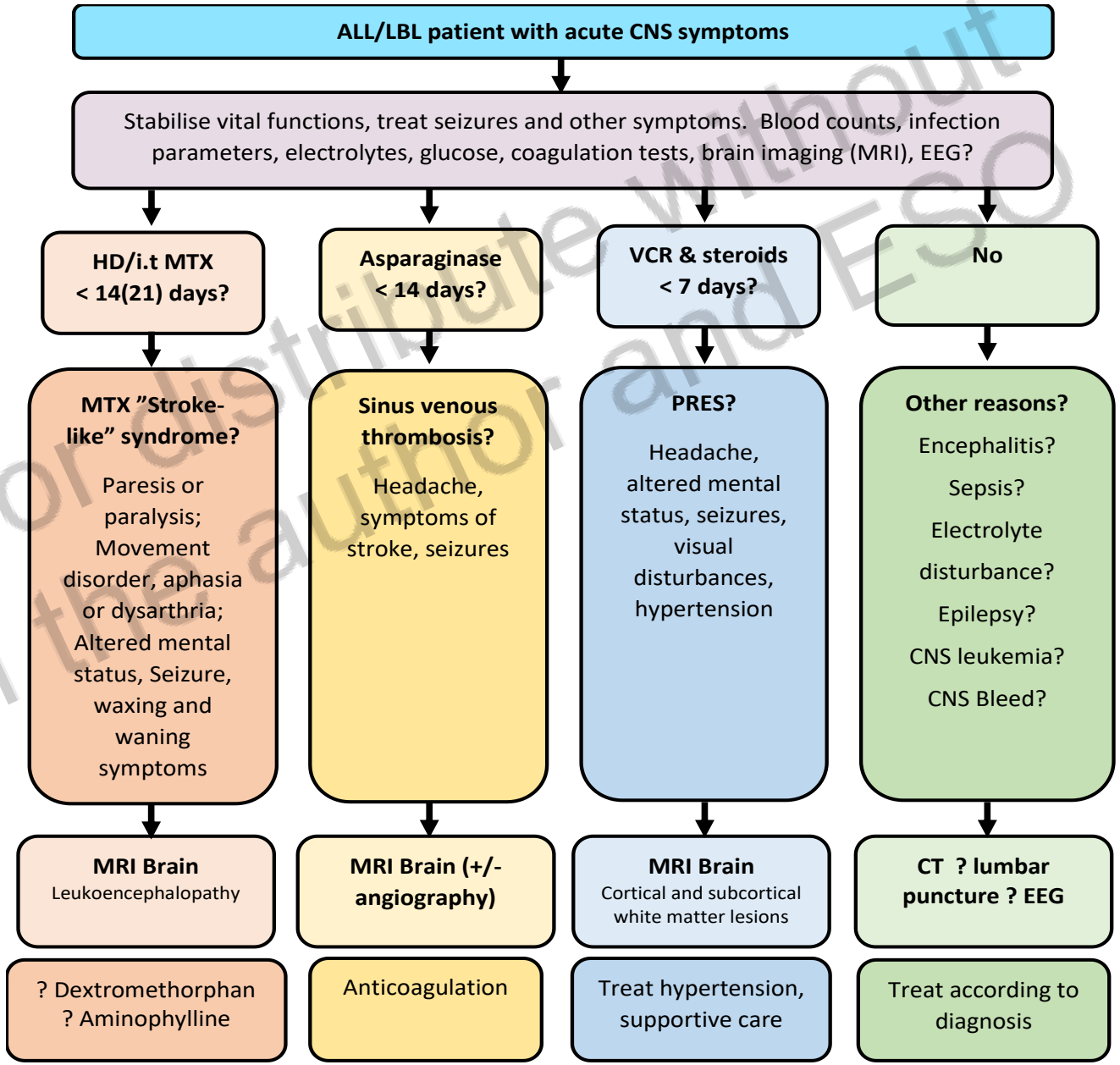
- Spectrum of adverse psychological symptoms





- Dexamethasone>Prednisone (relative risk,4.55; 95% CI, 2.45-8.46; P<.001)
- Frank psychosis commoner in TYA population
- Usually early during treatment but can occur after cessation
- Management: steroid cessation or dose reduction
- Benzodiazepines (Lorazepam), supportive care
- Risperidone has been reported to be useful
- Reviewed in: Drozdowicz & Bostwick Mayo Clin Proc. June 2014;89(6):817-834

A practical approach



ALLTogether Protocol Neurotoxicity Guidelines

Take home messages

- Neurotoxicity during treatment is common and may be a direct or indirect side effect of chemotherapy agents or the underlying cancer
- There is a complex interplay between genetic, drug and environmental factors
- Careful attention to avoiding drug interactions and fluid and electrolyte disturbance may minimise incidence of neurotoxicity
- A thorough history, review of medication chart & phase of treatment and neuroimaging will usually establish the most likely cause
- Management is largely supportive – evidence based treatments are lacking

Remember you can ask questions and send comments at any time

Peter Cole, Albert Einstein College, New York
Arja Harila-Saari & Tania Christoforaki, Uppsala, Sweden
Victoria Forster and Frederik van Delft, Newcastle, UK
UKALL 2011 Toxicity Interest Group
All the participating investigators and centres
The ALLTogether BRAIN consortium

The PdL/iBFM Neurotoxicity Working Group

Christina Halsey & Ainy Wahid (UKALL),
Kjeld Schmiegelow & Arja Harila-Saari (NOPHO),
Deepa Bhojwani & Naomi Winick (COG),
Shlomit Barzilai (Israel),
Peter Cole (DFCI),
Mary Relling & Hiroto Inaba & Jun Yang (SJCRH),
Der-Cherng Liang (TPOG),
Michihiro Yano (JPLSG),
Gabriele Escherich (COALL),
Daniel Erdelyi & Judit Sagi (Hungary/BFM),
Caterina Putti & Maria-Grazia Valsecchi (AIEOP),
Glenn Marshall, Toby Trahair, & Marion Mateos (ANZCHOG),
Andishe Attarbaschi (Austria-iBFM),
Inge van der Sluis (DCOG),
Anja Moricke (BFM).
Iveta Janotova & Ester Zapotocka (CPH)
Alexandra Kolenova (Slovakia)