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Central nervous system imaging in childhood leukaemia

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Abstract

The aim of this study was to document the imaging abnormalities seen in the central nervous system (CNS) in cases of childhood leukaemia or as complications of its treatment. Magnetic Resonance (MR) images and Computed Tomographic (CT) scans were reviewed retrospectively in 22 children and adolescents with neurological manifestations/complications of leukaemia or its treatment. Among the 22 patients, nine had two or more different CNS abnormalities. The imaging abnormalities seen in 15 patients before or during treatment included sinus thrombosis, cortical vein thrombosis, cerebral haemorrhage, meningeal leukaemia, infections, skull leukaemic infiltration and treatment-related neurotoxicity. After therapy, seven patients had CNS abnormalities, including secondary brain tumours, skull tumour, mineralising microangiopathy, leucoencephalopathy, transient white matter abnormalities, spinal intradural haematoma, chronic subdural haematoma, radiation necrosis, meningeal leukaemia and leukaemic infiltration at the vertebral body. CNS complications are related to the inherent risk of leukaemia itself, to the treatment method and to the duration of survival.

Keywords: Children; Leukaemia; Nervous system; Images

1. Introduction

Leukaemia is the commonest form of childhood cancer and accounts for approximately one-third of new 'tumours'. One reason for improved survival and cure rates in children with leukaemia is the successful management of central nervous system (CNS) manifestations. However, successful control of CNS disease is inevitably accompanied by complications of treatment and, sometimes, treatment failure. Histologically, effects of the disease may involve the leptomeninges, brain parenchyma or intracranial vessels [1]. The commonest early manifestations of CNS leukaemia are symptoms of increasing intracranial pressure. Periodic examination of the cerebrospinal fluid (CSF) is used in the management of children once they are diagnosed with leukaemia. Accordingly, CNS involvement is often detected before clinical signs appear [1].

Radiologically, treatment-related CNS complications include white matter lesions, small-vessel calcifications, cerebrovascular disorders, treatment-induced tumours, infections and enlargement of ventricles and/or widening of sulci – a sign of cortical atrophy [1]. Both 'early' and 'late' CNS complications can be related to the neurotoxicity of the chemotherapy regimens, and radiation therapy, including bone marrow transplantation, or to immunosuppression caused by the disease itself or its treatment. Children and adolescents who survive leukaemia may develop endocrinopathies and/or neurocognitive deficits caused by the 'late effects' of their treatment.

The purpose of this retrospective study was to answer the following questions: (1) How often do children with leukaemia have imaging-detectable CNS abnormalities? (2) Of those abnormalities, how many are cerebral or spinal complications? (3) What are the commonest underlying disease processes? (4) Are there differences

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between patients with acute lymphoblastic leukaemia (ALL) and those with acute myeloid leukaemia (AML)? (5) Are there differences between patients with early complications and those with late complications? and (6) Do children more often have CNS abnormalities due to complications of leukaemia itself, or to its treatment?

2. Patients and methods

2.1. Subjects

From January 1996 to December 2000, 135 consecutive patients underwent treatment for leukaemia (98 with ALL, 25 with AML, 7 with ALL relapse, 2 with B-ALL and 3 with chronic myeloid leukaemia (CML) at our Institute.

At diagnosis, all patients underwent Magnetic Resonance Imaging (MRI) of the CNS, as is 'standard practice' in our Department to rule out CNS involvement in children with leukaemia. Additional MR images were obtained if the patient developed new neurological abnormalities. Of the 135 cases, only 22 patients (16%) showed CNS abnormalities that were detectable by imaging. These patients were selected for this retrospective study. Long-term monitoring with MRI is not routinely carried out unless the patient becomes symptomatic.

The patients (12 male and 10 female, aged 1–18 years (media age 8.5 years) had one of 2 types of childhood leukaemia, including 14 cases of ALL, 7 cases of AML and one patient who had ALL, developed AML and presented with acute paraplegia. CNS cytology was positive for leukemia. These patients were divided into two groups: Group 1 included 15 patients who had CNS abnormalities as detected by imaging carried out before and during therapy or within 3 months of completion of treatment; Group 2 consisted of 7 patients with CNS abnormalities detected by imaging that occurred as late effects of leukaemia and its treatment. Patients were also analysed according to the type of leukaemia. CNS abnormalities were divided into cerebral (intra- and extracerebral) and spinal complications.

The medical records were reviewed with attention to the type of treatment given, the time of onset of symptoms, and the outcome of the various CNS complications. Results of surgical biopsies of the brain lesions were also reviewed. Neurological development and psychosocial function were not assessed.

Informed consent has been obtained from their parents or from their respective guardians for each imaging study.

2.2. Imaging studies

MR images were obtained in most patients with a 1.5-T scanner (Siemens Vision). The cranial imaging sequences comprised spin-echo T1-weighted, 450–650/15–20/1–2 (repetition time/echo time/excitations) sections obtained before and after intravenous (i.v.) injection of gadopentetate dimeglumine (0.1 mmol/kg), and T2-weighted, 3200–3650/90–100/1–2 sections. Additional fluid-attenuated inversion recovery (FLAIR) (9000/105/1) and diffusion sequences (0.8/123/1) were obtained in 11 patients. Time-of-flight MR angiography was performed in patients with cerebrovascular disorders. The parameters used with this technique were as follows: 30/9/1; field of view, 22–25 cm; matrix, 219×250; flip angle, 50°; section thickness, 3 mm; section slab thickness, 3–7.5 cm.

The spinal imaging sequences comprised spin-echo T1-weighted, 640/12 (repetition time/echo time) images before and after i.v. injection of gadopentetate dimeglumine (0.1 mmol/kg). T2-weighted sequences, 5000/112 (repetition time/echo time) were also performed. In most patients, CT scans were carried out before treatment was started.

3. Results

Twenty two (16%) showed CNS abnormalities on MR images and/or CT scans, with or without neurological symptoms. Patients with cortical atrophy as an isolated finding were not included. Proportionately, CNS abnormalities were more often found in patients with AML (28%) than in patients with ALL (14%). Among the 22 patients with abnormalities, 9 had two or more different CNS abnormalities identified on CT scans or MR images. From these retrospectively determined CNS abnormalities, 18 were intracerebral, 9 extracerebral, and 5 were spinal complications (Tables 1 and 2).

Cerebrovascular complications ($n = 7$) were the most common CNS abnormality found, followed by meningeal leukaemia ($n = 4$) and leucoencephalopathy ($n = 3$). Seven patients with AML with imaging abnormalities included 6 in imaging carried out before ($n = 2$) and during ($n = 2$) therapy or within three months of completion of treatment ($n = 2$) and one patient with CNS abnormalities that were identified within 5 months of completion of treatment. One child (case 15) was diagnosed with ALL at 2 years of age and later developed AML.

The 14 patients with ALL who showed imaging abnormalities included nine patients with CNS abnormalities that occurred before treatment ($n = 2$) or within 3 months of completion of treatment ($n = 7$) and five patients with CNS abnormalities that occurred as 'late effects' of leukaemia and its treatment.

In this series, CNS abnormalities were more often seen as early complications of childhood leukaemia: 15 patients (four before therapy, two during therapy and

Table 1
Clinical information, symptoms and type of treatment for the 22 patients with leukaemia who had CNS abnormalities

No.	Age (years)/ gender	Leukaemia type	Treatment[a]	Age (years)/ interval[b]	Symptoms and signs
1	9/M	ALL	Chemo + RT	9/before treatment	R abducens nerve palsy + diplopia + thrombocytopenia
2	6/F	ALL	Chemo + RT	6/before treatment	Meningeal irritation
3	7/F	ALL	Chemo	7/2 months	Headache
4	9/M	ALL	Chemo	9/18 days	Seizures, R hand weakness
5	11/M	ALL	Chemo	11/19 days	Focal seizures, headache
6	14/M	ALL	Chemo + RT	4/10 years	Acute bilateral facial paralysis
7	9/F	ALL	Chemo	9/17 days	Headache + change of mental status + seizures
8	14/M	ALL	Chemo	14/8 days	Headache
9	9/M	ALL	Chemo + RT + BMT	6/2 years	Exophthalmos
10	16/F	ALL	Chemo + RT	2/8 years	Headache
11	8/M	ALL	Chemo + RT	2/6 years	R parieto-occipital skull mass
12	18/M	ALL	Chemo + RT	3/15 years	Headache + R arm ataxia
13	6/M	ALL	Chemo + BMT	3/40 days	Seizures
14	4/F	ALL	Chemo + RT	1/1 month	Seizures + change of mental status
15	4/F	1. ALL 2. AML	Chemo	2/2 years	Acute paraplegia + bladder incontinence
16	11/M	AML	Chemo + RT	11/before treatment	Headache + change of mental status + thrombocytopenia
17	5/M	AML	Chemo	5/'routine' before therapy	No neurological complaints
18	9/F	AML	Chemo	9/during treatment	Fever + change of mental status + seizures
19	7/F	AML	Chemo + RT	7/during therapy	Meningeal irritation + sepsis + fever
20	6/M	AML	Chemo + BMT	5/6 weeks	Headache
21	7/F	AML	Chemo + BMT	6/5 months	Paraplegia + bladder incontinence
22	1/F	AML	Chemo	1/1 month	Sepsis + change of mental status + seizures

i.v., intravenous; M, male; F, female; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; RT, radiation therapy; Chemo, Chemotherapy; BMT, bone marrow transplant; CNS, central nervous system; R, right.

[a] Most treatment methods are listed. CHEMO: ALL-BFM-90/95; German chemotherapy protocol and includes vincristine, daunorubicin, *E. coli* asparaginase, cyclophosphamide, and cytarabine i.v. + prednisone and 6-mercaptopurine oral + intrathecal methotrexate. CHEMO AML-BFM-93; German chemotherapy protocol and includes: vincristine, *E. coli* asparaginase, cytarabine, etoposide i.v + dexamethasone oral + intrathecal methotrexate.

[b] Age when the diagnosis of leukaemia was made and interval between the last antileukaemic treatment and the onset of neurological symptoms.

nine up to 3 months after completion of treatment). Most of the CNS complications that occurred during therapy or within three months of completion of treatment were cerebrovascular disorders, infections, meningeal leukaemia and treatment-related neurotoxicity.

Seven patients showed CNS abnormalities that occurred as late effects of leukaemia or its treatment (three months after completion of treatment). The most frequent change in this group was leucoencephalopathy. CNS abnormalities that occurred as 'late effects' of leukaemia and its treatment were in all but one case found in patients with ALL.

Among the 32 CNS abnormalities identified (22 patients), 14 were treatment-related, and 12 were complications of leukaemia. For 6 CNS abnormalities seen on CT or MR scans, the pathology was uncertain. For example, a variety of immune deficiencies may occur in the leukaemia patients, partly due to therapy and partly due to the malignancy.

The clinical profiles of the 22 patients are given in the tables. MR and CT findings (see Figs. 1–5) of the CNS abnormalities in the patients with leukaemia are similar to the neuroimaging characteristics seen in patients with the same CNS abnormalities (i.e., haemorrhages, infarcts, meningioma), but no evidence of leukaemia. Some of the MR findings were regarded as a manifestation of leukaemia, such as meningeal/epidural leukaemia in patient 2 or the diffuse leukaemic infiltration of the skull base in patient 17.

Table 2
Imaging and outcome of 22 patients with leukaemia who had CNS abnormalities

No.	CNS diagnosis defined by imaging	Biopsy or CSF study	Imaging	Outcome
1	Multiple cerebral haemorrhage	CSF cytology positive for leukaemia	CT/MR: several cerebral haematomas	Improved
2	1. R occipital meningeal leukaemia. 2. DL (later)	1. CSF cytology negative for leukaemia. 2. Negative CSF culture	MR: enhancing R occipital epidural mass with permeation of skull and extracerebral soft-tissue component	Improved
3	SVT	NP	MR/MRA: SSS thrombosis, R transverse and sigmoid sinus	Died
4	1. Presumed asparaginase-encephalopathy. 2. Meningeal leukaemia (later)	CSF cytology positive for eukaemia	MR: HS bilateral corticosubcortical in frontal and occipital lobes on T2; MRA: normal	Recovered
5	1. R cerebral haemorrhage. 2. Presumed transient WM abnormalities (later)	NP	CT: R frontal bleeding; MRA: normal	Recovered
6	1. Lymphoma. 2. DL	Biopsy: lymphoma	MR: bilateral well-demarcated round, parasellar enhancing masses. HS in periventricular WM on T2	Improved
7	Cortical vein thrombosis with transient parenchymal ischaemia	NP	MR/MRA: focal HS in R parieto-occipital cortex on T2. R cortical vein thrombosis.	Recovered
8	SVT	NP	MR/MRA: SSS thrombosis	Recovered
9	1. Chronic subdural haematoma. 2. Radiation necrosis	NP	CT: abnormally thin skull with lytic areas + hygroma	–
10	1. CNS lymphoma. 2. DL	Biopsy: lymphoma	CT: enhancing hyperdense mass in R temporal lobe	Died
11	1. Mineralising microangiopathy. 2. Osteoma	NP	CT: calcifications in the basal ganglia bilaterally + osteoma R parieto-occipital	–
12	Meningioma	Surgery: meningioma	CT/MR: extra-axial mass in L frontal lobe with intense enhancement after contrast	Recovered
13	Presumed cyclosporine-induced neurotoxicity	Negative CSF culture and cytology	CT/MR: multiple HS on T2 L frontal, R temporal and parietal bilaterally corticosubcortical	Died
14	Cytomegalovirus-infection	Positive CMV-IgG	CT: enhancing nodule after cont. in R frontal lobe. Small calcifications in L frontal lobe and cerebellum	Recovered
15	1. Spinal haematoma. 2. Meningeal leukaemia. 3. Tumour infiltration at T6/T7 vertebral bodies	CSF cytology positive for leukaemia	MR: intradural inhomogeneous mass at L3/4 level on T1 without Gd and T2. Signal abnormalities in T6/T7 vertebral bodies.	Died
16	SAH + intraventricular haemorrhage	NP	CT: SAH + intraventricular haemorrhage; MRA: normal	Recovered
17	Presumed diffuse leukaemic infiltration of the skull base	NP	MRCT: multiple small spheroid osteolytic lesions in the skull base	Deteriorated
18	Presumed encephalitis	Negative CSF culture and cytology	MR: HS in the occipital lobe bilaterally	Recovered
19	Presumed *Aspergillus* infection	Responded to amphotericin B therapy	CT: enhancing nodules after cont. in R temporal lobe and L parietal lobe	Improved
20	Multiple cerebral haemorrhage	NP	MR: multiple intracranial bleeding (different ages/phase)	Died
21	1. Meningeal leukaemia 2. Tumour infiltration in L3	CSF cytology positive for leukaemia	MR: leptomeningeal enhancement on T1 with Gd. Diffuse leukaemic infiltration of bone marrow with pathological fracture in L3	Died

Table 2 (*continued*)

No.	CNS diagnosis defined by imaging	Biopsy or CSF study	Imaging	Outcome
22	Presumed *Aspergillus* infection	Brain and lung biopsy negative	MR: disseminated tiny nodules in brain on T2; on T1 enhancement with Gd	Died

ALL: acute lymphoblastic leukaemia, AML: acute myeloid leukaemia, T1: T1-weighted images, T2: T2-weighted images, HS: high signals, WM: white matter, DL: diffuse necrotising leucoencephalopathy, CNS: central nervous system, CSF: cerebrospinal fluid, SVT: sinus venous thrombosis, R: right, L: left, NP: not performed, SSS: superior sagittal sinus, CMV: cytomegalovirus, IgG: immunoglobulin G, Gd: gadopentetate dimeglumine, RT: radiation therapy, BMT: bone marrow transplantation, MR: magnetic resonance, MRA: magnetic resonance angiography, CT: computed tomography, CHEMO: chemotherapy, SAH: subarachnoidal haemorrhage, cont: contrast.

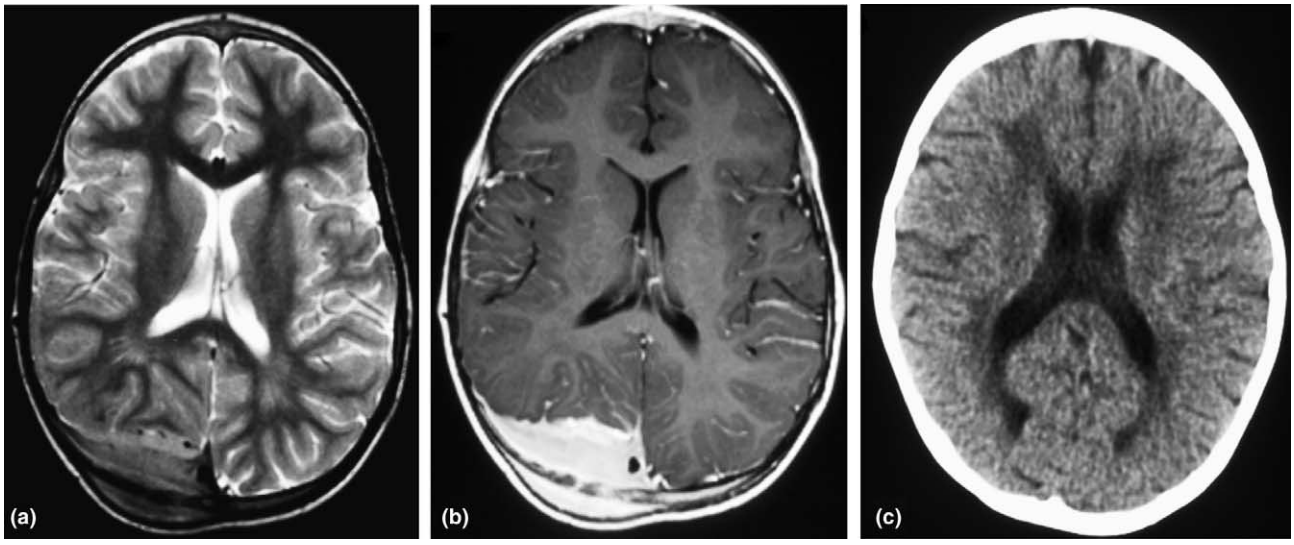

Fig. 1. Case 2: 6-year-old girl with right occipital meningeal leukaemia. (a)/(b): T2- and T1-weighted MR images after contrast show an enhancing right occipital epidural mass with permeation of skull and extracerebral soft-tissue component. (c): CT scan after radiation and chemotherapy therapy shows no enhancement and the development of diffuse necrotising leucoencephalopathy.

4. Discussion

Contemporary risk-directed therapy now cures at least 70–75% of children with ALL. However, the use of increasingly more intensive therapy has led to the emergence of new adverse sequelae, especially in high-risk cases. Currently, many of the CNS complications seen in connection with ALL are related to the neurotoxicities of various chemotherapeutic regimens, such as the acute and delayed effects of CNS radiation [2,3], coagulopathy caused by the disease or by asparaginase [4], and breakdown of the immune mechanism resulting from the leukaemia itself or from bone marrow suppression following intensive chemotherapy.

CNS imaging abnormalities in childhood leukaemia were more often seen as early complications. Most of the CNS complications that occurred during therapy or within three months of completion of treatment were cerebrovascular disorders, infections, meningeal leukaemia and treatment-related neurotoxicity. Thrombosis is a serious complication of remission induction with prednisone–vincristine–asparaginase. The underlying basis of this complication was unknown until recently. According to Nowak-Gottl and colleagues [5] most patients with thrombotic complications have one or more hereditary prothrombotic defects. Of 6 patients with cerebrovascular accidents, three were presumably related to asparaginase. Treatment with asparaginase leads to the depletion of plasma proteins involved in both coagulation and fibrinolysis and has been linked to cerebrovascular complications, including cortical infarcts, dural sinus thrombosis and intracerebral haemorrhage and haemorrhagic infarcts [4,6]. Cerebrovascular thrombosis or haemorrhage can also occur during antileukaemic treatment as a result of leucocytosis, thrombocytopenia, sepsis and coagulopathy. Of the cerebrovascular accidents in 6 patients, 3 were apparently not related to asparaginase [7].

Transient abnormalities in the cerebral white matter are seen in children who have undergone treatment for ALL. Classically, leucoencephalopathy has been associated with a rapidly deteriorating clinical course and demyelination of the periventricular white matter that can be seen as early as 9 months after treatment with cranial irradiation and intrathecal methotrexate [8]. The incidence of transient abnormalities in children who

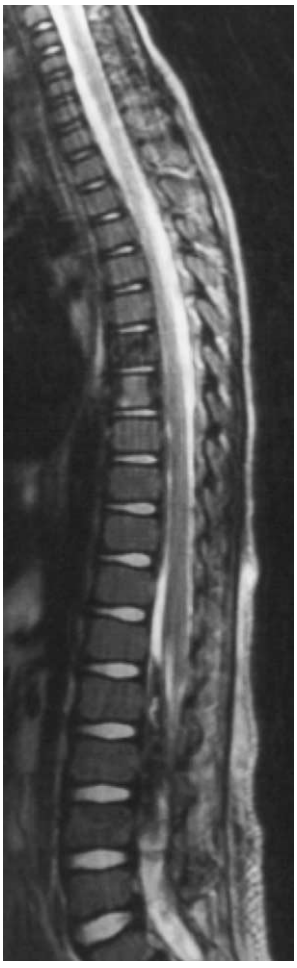

Fig. 2. Case 15: 4-year-old girl with intradural spinal haematoma and leukaemic relapse, CSF cytology positive for leukemia. Note on T2-weighted images the inhomogeneous intradural mass at L3/L4 level. Signal abnormalities in T6/T7 vertebral bodies are due to tumour infiltration.

undergo sequential MR scans during the treatment of ALL varies between 11% and 68% [9]. The hyperintensity seen on T2-weighted MR images is believed to be caused by increased interstitial fluid on the myelin sheath [9]. It is not yet clear, whether transient abnormalities in the cerebral white matter may be an additional risk factor for the subsequent development of leucoencephalopathy [10].

Children with leukaemia may acquire the 'common' infections of childhood. In addition, the immunocompromised status of many of these children leaves them susceptible to opportunistic neurotropic organisms, especially fungal infections. When cultures are negative in patients with clinically suspected CNS fungal infection, MRI may be helpful in demonstrating anatomical evidence and in monitoring the response to treatment.

Headache and neck stiffness are fairly common and benign symptoms and correspond with transient abnormalities of the CSF or meninges during CNS-directed therapy for ALL. It has been reported that CSF abnormalities, with or without CNS symptoms ('chemical meningitis'), may develop in 10–60% of patients who have received intrathecal injections [11]. Leptomeningeal enhancement of the brain in patients with leukaemia may result from CNS leukaemia/relapse or infection or, rarely, both [6]. Enhancement of the cauda equina in patients with leukaemia warrants a vigilant search for the precipitating factor. CNS arachnoiditis may occur with intrathecal administration of chemotherapeutic agents, such as methotrexate or cytarabine. Other causes of nerve root enhancement on contrast-enhanced MR images of patients with leukaemia include post-surgical arachnoiditis, mechanical root compression with associated inflammation, cytomegalovirus polyradiculopathy in patients with acquired immunodeficiency syndrome, and inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) [6].

Spontaneous spinal haematomas in children with leukaemia are rare, but one should be aware of this possibility in the presence of predisposing factors such as haemostatic disorders or leukaemic CNS infiltration [12].

Before the advent of CNS-directed therapy for childhood leukaemia using CNS irradiation and intrathecal methotrexate, the incidence of CNS leukaemic relapse was high. Unfortunately, the late effects of these so-called 'prophylactic' measures can result in mineralising microangiopathy or arteriopathy, which involves injury to the small and medium-sized cerebral arteries, often found in the basal ganglia and subcortical white matter [13], with calcium deposition.

Radiation-induced tumours, especially brain tumours, are the commonest 'second malignant neoplasms' in survivors of childhood ALL [2]. Approximately 1% of patients who receive cranial irradiation will develop brain tumours; the mean latency period ranges from 9 years for high-grade gliomas to 19 years for meningiomas [1]. Although cranial irradiation has clearly been implicated in the development of secondary brain tumours [2], cases of a 'second malignant tumour' in the CNS in survivors of childhood leukaemia who had no history of prophylactic irradiation have been reported [14]. Mechanisms such as loss of immune surveillance and genetic factors have been proposed [14]. Glioma has been reported as the most common secondary brain tumour, followed by ependymoma, lymphoma and meningioma [15,16].

In our series, 'second brain tumours' developed in the brain in three patients after initial treatment. Osteosarcoma is the most frequent 'second tumour' of the skull in children after cranial irradiation [17]. In one patient, a secondary osteoma developed in the setting of mineralising microangiopathy 6 years after the initial ALL treatment including cranial irradiation. To date, there have been no previous reports of the development of an

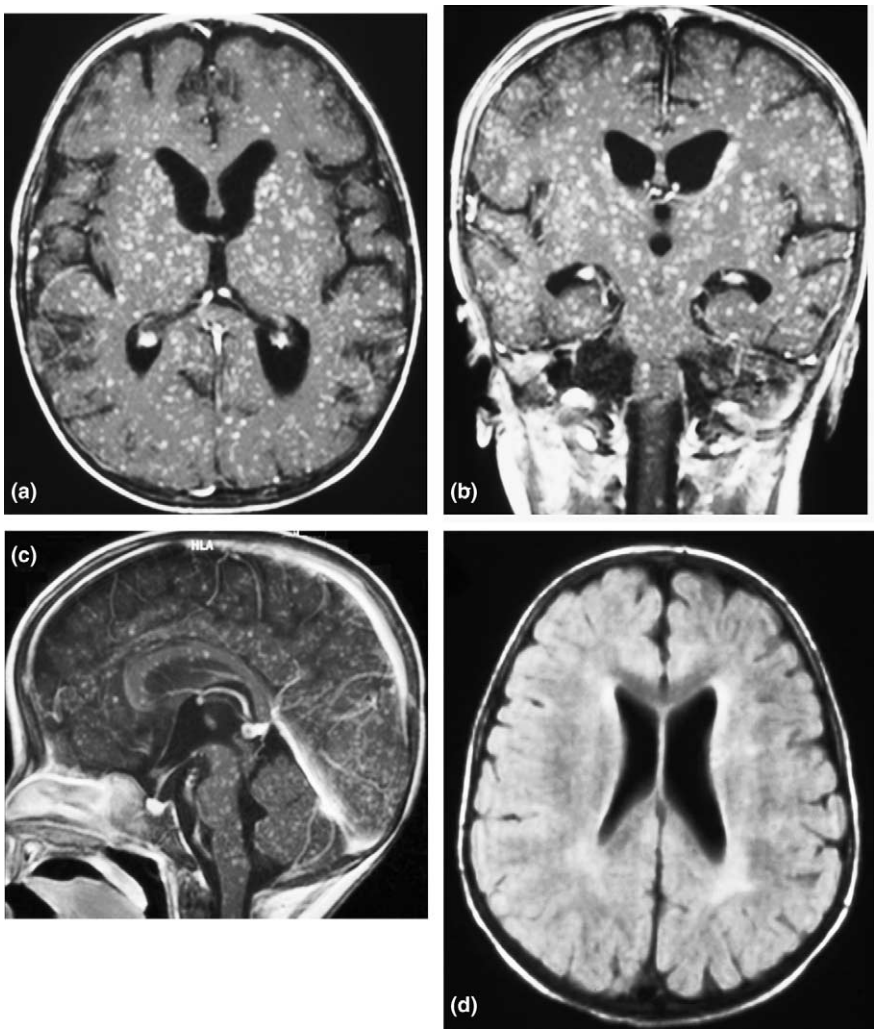

Fig. 3. Case 22: 1-year-old girl with presumed *Aspergillus* infection. (a)–(c): T1-weighted MR images after contrast show disseminated enhancing nodules in the brain and cerebellum. (d): Follow-up MRI after 5 months showed complete resolution of the cerebral lesions.

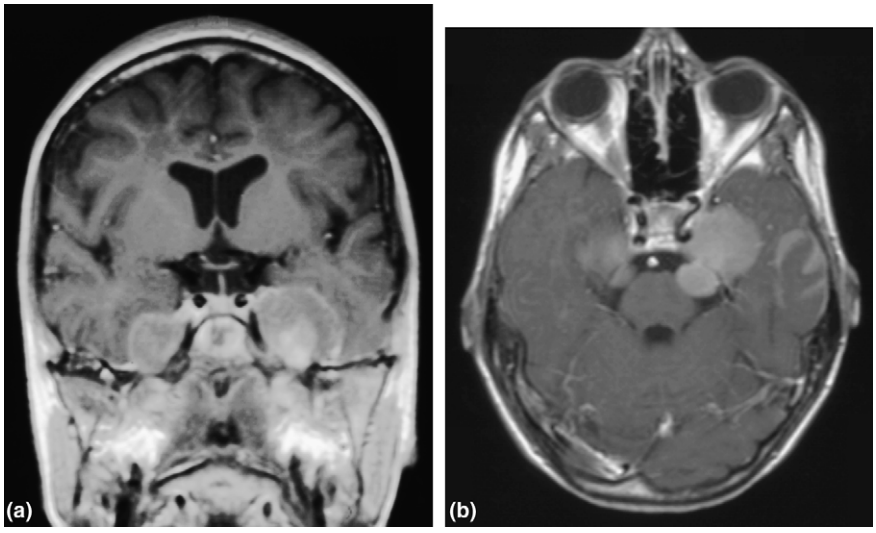

Fig. 4. Case 6: 14-year-old boy 10 years after treatment for leukaemia who developed NHL (Non-Hodgkin's Lymphoma). (a): T1-weighted coronal view after contrast shows bilateral well-demarcated round, parasellar enhancing masses. (b): T1-weighted axial view, after contrast.

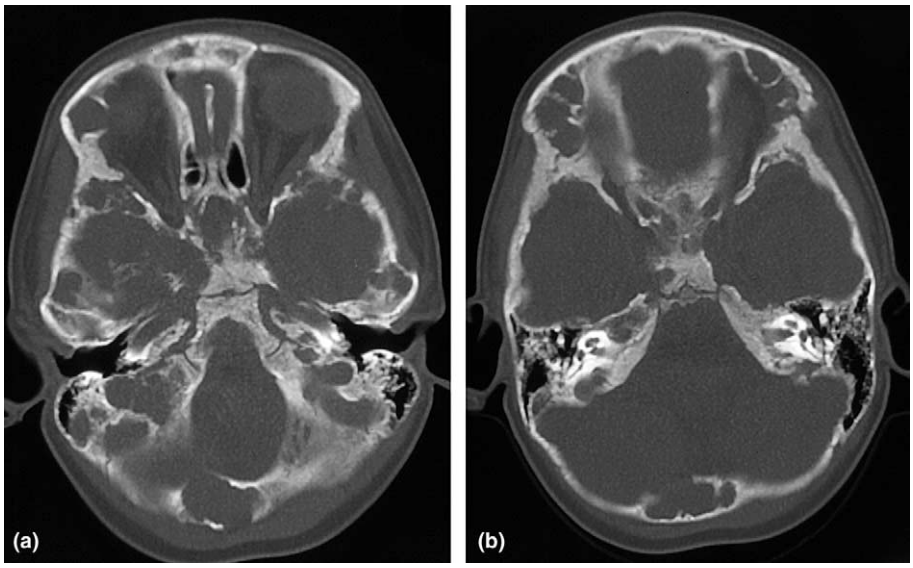

Fig. 5. Case 17: 5-year-old boy with diffuse leukaemic infiltration of the skull base. (a)/(b): CT scans, bone window, show multiple, small, spheroidal, osteolytic lesions in the skull base.

osteoma as a second benign neoplasm following irradiation.

Granulocytic sarcoma (chloroma) is an uncommon manifestation of myelogenous leukaemia (3–8%) in which focal masses of immature myeloid cells of granulocytic lineage infiltrate bone and soft tissue [18]. Chloromas have been described in almost every location, but most commonly arise in the skull, orbits and sinuses [19]. They are commoner in children with AML than in adults and may present at onset of the leukaemia or as a feature of relapse [20].

'Atrophy' of the brain is a known late finding after irradiation, and was believed to be related to a diffuse white matter injury [3], but other studies have suggested that the atrophic changes may be related to chemotherapy, with cranial irradiation playing a lesser role [21]. Whether the brain atrophy in the irradiated patients results from a more serious disease, the more-intensive chemotherapy treatment and/or the cranial irradiation, remains an open question [22,23]. In the present review, patients with cortical atrophy as an isolated finding were not included.

The wide spectrum of CNS abnormalities that occur during and after treatment for leukaemia is related to the inherent risk of the leukaemia itself and to the treatment. Because many neurological complications of leukaemia are treatable, early diagnosis is essential. Because the overall long-term event-free survival rate in children with ALL approaches 80%, emphasis is now placed on risk-directed therapy so that patients are neither over-treated nor under-treated. Studies to identify genetic polymorphisms with pharmacokinetic and pharmacodynamic significance may permit further refinement of treatment strategies and will allow the maximisation of anticancer effects with acceptable toxicity. Improved neuroimaging techniques especially high resolution MRI, have helped characterise CNS abnormalities caused by direct leukaemic involvement of CNS structures, as well as cerebrovascular disorders, infections, treatment-related neurotoxicity (e.g., apparent diffusion coefficient (ADC)-maps and second malignant tumours). Knowledge of risk factors may help in the early recognition of disease or treatment-related neurological disorders, allowing for timely intervention.

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