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Dural Sinus Thrombosis in Children With Cancer

Roel E. Reddingius,[1] Catherine Patte,[1]* Dominique Couanet,[2] Chantal Kalifa,[1] and Jean Lemerle[1]

Dural sinus thrombosis (DST) has been reported in association with cancer in both adults and children. We describe the seven patients seen with this complication in our centre between 1981 and 1995. Diagnosis was confirmed by either cerebral CT scanning, MRI or angiography. Median age was 13 years (range 8–15). Six patients were boys. Six children were being treated for non-Hodgkin lymphoma and one for neuroblastoma. Presenting symptoms were seizures and transient neurologic deficit, often preceded by headaches. The probable cause of DST was found in two cases. Tumour localisation in the central nervous system (CNS) probably caused DST in one patient who was treated for Ki 1 lymphoma. Dehydration in combination with a poor general condition seemed to be the cause of DST in the patient with neuroblastoma. In five children with stage III or IV non-Hodgkin lymphoma (three lymphoblastic lymphoma; two Burkitt's lymphoma), etiology remained unknown. In these children, DST occurred early in the course of therapy. The median interval between start of chemotherapy and onset of symptoms was 19 days (range 8–40). No child had received L-asparaginase. Prognosis was favourable, with symptoms completely disappearing without therapy within 1 to 5 days. The incidence of DST in patients with advanced stage non-Hodgkin lymphoma during induction and consolidation was calculated to be below 3%. We conclude that DST is rarely diagnosed in children with cancer. Occurrence during the initial phase of therapy for non-Hodgkin lymphoma is associated with a benign prognosis. Med. Pediatr. Oncol. 29:296–302, 1997.

Key words: dural sinus thrombosis; non-Hodgkin lymphoma

INTRODUCTION

The occurrence of dural sinus thrombosis (DST) has been reported in patients with cancer [1,2]. In children the occurrence of DST has been predominantly described in patients with leukaemia [3–6]. The presumed etiology is the hypercoagulability due to the asparaginase-induced antithrombin III deficiency [7]. Dural sinus thrombosis was also established in children treated for non-Hodgkin lymphoma, even in those not treated with L-asparaginase [8]. The objective of this retrospective study was to study this complication in a population of children treated for solid tumours.

MATERIALS AND METHODS

The medical files were studied of all children in whom treatment of a malignancy was complicated by DST between 1980 and 1995. All radiographs were reviewed. Patients were only admissible if the diagnosis was confirmed by one or more radiological studies. This could be either a cerebral CT scan showing spontaneous hyperdensity of the sinuses or the empty delta sign after contrast administration, an MRI showing abnormal signal intensities of the sinuses with loss of high signal intensity on fast spin-echo images or an angiography showing occlusion [9,10].

RESULTS

The study population consisted of seven children. Six of them were boys. The median age of these children was 13 years (range 8–15). Six out of seven children (patient nos. 1–6) had a non-Hodgkin lymphoma and one child suffered from neuroblastoma. Clinical data of all patients are given in Table I.

The main presenting symptom in all patients was the occurrence of seizures. Although all children eventually had convulsions, this was the first symptom in three children. While they were confined to one day in the majority of the patients, recurrence during a five-day period was seen in one of them. Seizures were focal in five out of seven children. In three children, a severe headache was the primary complaint. Transient neurologic deficit occurred in four children. The median total duration of symptoms was 2 days (range 1–50).

The diagnosis of DST was confirmed only by cerebral CT scan in three cases, by CT in combination with angiography in two cases, by MRI in combination with

[1]Department of Paediatrics, Institut Gustave-Roussy, Villejuif, France.

[2]Department of Radiology, Institut Gustave-Roussy, Villejuif, France.

*Correspondence to: Catherine Patte, Institut Gustave-Roussy, 94805 Villejuif Cedex, France.

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TABLE I. Clinical Data of the Studied Patients: Patient Number, Sex, Age, Year of Diagnosis, Diagnosis, Drugs Received During the Last Chemotherapy Course Before Onset of Symptoms, Day of Onset of Symptoms, Symptoms, Duration of Symptoms and Neuroimaging, Including the Day the Investigation was Performed

Patient no.	Sex	Age in years	Year	Diagnosis	Protocol and drugs received during chemotherapy course before onset of symptoms	Day	Symptoms (day 1 = start of chemotherapy)	Duration of symptoms	Day		Neuro imaging (day 1 = beginning of symptoms)
1	M	9	1985	lymphoblastic lymphoma stage IV	LMT81 [12]: CPM[a]; VCR[a]; PRED[a]; IT-MTX[a] (induction)	10	hemiconvulsions of the left side of the body	24 hours	1	CT +[a]	postcontrast enhancement in right frontoparietal area
									14	CT +	frontal lesion persists; empty delta sign, consistent with sagittal sinus thrombosis
2	M	14	1989	lymphoblastic lymphoma stage IV	LMT81 [12]: HD-MTX[a]; IT-MTX; 6-TG[a]; CYT-ARA[a] (consolidation)	37	headaches; focal seizures of the left side of the face and the left arm	48 hours	3	CT +	empty delta sign, consistent with sagittal sinus thrombosis
									4	angio	sagittal sinus thrombosis + partial thrombosis of lateral sinuses
3	M	12	1987	lymphoblastic lymphoma stage IV (with CNS involvement)	LMT81 [12]: CPM; VCR; PRED; IT-triple[a] (induction)	8	hemiconvulsions and hemiplegia of the left side of the body	5 days	−6	CT +	normal
									2	CT +	spontaneous hyperdensity in right parietal area
									6	angio	normal
					idem + HD-MTX	19	reappearance of symptoms 11 days later: bizarre sensations of the right side of the body and right hemiparesis	48 hours	2	CT +	hypodensity in right parietal area; spontaneous hyperdensity of the sagittal sinus + positive delta sign after contrast, consistent with sagittal sinus thrombosis
									4	angio	complete sagittal sinus thrombosis and partial right lateral sinus thrombosis
									9	MRI	sagittal sinus thrombosis; hemorrhage in the right parietal area
4	M	15	1983	Burkitt's lymphoma stage III	LMB81 [14]: CPM; VCR; PRED; HD-MTX; IT-MTX; ADRIA[a] (COPADM1)	19	headaches; generalized convulsion	5 days	2	CT +	nonconclusive
									14	CT +	delta sign positive, consistent with sagittal sinus thrombosis
									19	angio	partial thrombosis of the superior sagittal sinus
5	M	13	1993	Burkitt's lymphoma stage III	LMB89 [13]: CPM; VCR; PRED; HD-MTX; IT-MTX; ADRIA (COPADM2)	40	hemiconvulsions and hemiparesis of the right side of the body; complete amaurosis	48 hours	1	CT +	spontaneous hyperdensity of the sagittal sinus + positive delta sign after contrast, consistent with sagittal sinus thrombosis
6	F	15	1985	Ki 1 lymphoma stage III	COPAD [11]: CPM; VCR; PRED; ADRIA	13	headaches; diplopia with dysfunction of the right abducens nerve; gradually worsening condition with hemiconvulsions of the left side of the body just prior to death	until death 50 days later	12	CT +	hypodense lesion in the left cerebellum
									20	angio	partial thrombosis of the left lateral sinus
									32	CT +	multiple hyperdense lesions in cerebrum and cerebellum
									37	CT +	an increase in number and extent of these lesions
									39	MRI	sagittal sinus thrombosis
									46	angio	thrombosis of right and left lateral sinus and partial thrombosis of the sagittal sinus
7	M	8	1990	neuroblastoma	5FU; folic acid	[b]	change of conscience with desorientation in time and space; generalized convulsion	1 month	1	CT	multiple hypodense areas in the two parietal lobes; spontaneous hyperdensity of the sagittal sinus, consistent with sagittal sinus thrombosis

[a]6-TG, 6-thioguanine; ADRIA, adriamycine; CPM, cyclophosphamide; CT +, CT scan, including contrast administration; CYT-ARA, cytosine-arabinoside; IT-triple, intrathecal injections with MTX, hydrocortisone and cytosine-arabinoside; MTX, methotrexate (IT, intrathecal; HD, high dose); PRED, prednisone; VCR, vincristine.
[b]In patient no. 7, symptoms appeared during a period of intensive chemotherapy, 3 years after initial diagnosis and 11 months after recurrence of the disease.

angiography in one case and by all three investigations in one case. In two children, in whom diagnosis was eventually confirmed by CT scan, initial CT scans did not establish the presence of DST. In the four children in whom angiography was performed, CT scanning had failed to confirm the diagnosis in one case. In this case, an MRI was realized, affirming diagnosis. There were no cases with either a positive CT or MRI in combination with a negative angiography.

A lumbar puncture was performed in five children. In patient no. 6, abnormalities were found consistent with meningitis. This patient is discussed later. In the other four, results were normal or practically normal, yielding only a slightly elevated protein content (range 0.29–0.66 g/L).

Simple haemostatic studies, including assessment of activated thromboplastin time, prothrombin time and fibrinogen levels, were performed in six children, disclosing no major abnormalities. In three children, more extensive studies established the absence of a deficiency of protein C, protein S or antithrombin III.

The probable cause of DST could be established in two children, patient nos. 6 and 7. In patient no. 6, neurologic symptoms appeared 13 days after start of chemotherapy. Cerebrospinal fluid was consistent with meningitis, with high cell counts and low levels of glucose. Cytological studies showed a predominance of polymorphonuclear neutrophils, but no evidence of malignancy. However, bacteriological studies remained negative. Neuro-imaging revealed multiple hyperdense lesions in cerebrum as well as cerebellum. These lesions were suspected to be localisations of the disease in the brain. The chemotherapeutic regimen was continued [11]. Dural sinus thrombosis was established later in the course of the disease. It was decided to treat the patient with heparin. Subsequently, the clinical condition of the patient deteriorated and a CT scan demonstrated a cerebral haematoma. The patient died. At autopsy, central nervous system (CNS) localisation of Ki 1 lymphoma was established with extensive perivascular infiltration. In this patient, it seems likely that DST was caused by the presence of tumour cells in or in the vicinity of the sinus. Patient no. 7 developed DST during a period of intensive chemotherapy for recurrent neuroblastoma, 3 years after initial diagnosis. Dehydration in combination with a poor general condition as a result of treatment may explain the occurrence of DST in this patient. There was a complete clinical and radiological recovery from DST in this patient.

The cause of DST was not clear in five children with lymphoma (patient nos. 1–5). One of these patients, patient no. 3, had initial CNS disease. Since cerebrospinal fluid counts had returned to normal on day 6 of the induction phase and since cerebral CT scanning showed no abnormalities, it seems unlikely that sinus thrombosis was caused by CNS localisation of tumour cells. In the other four children, there was no evidence of CNS disease. These five children were treated by one of the published lymphoma protocols of the French Pediatric Oncology Society [12–14] or a subsequent protocol. All children had advanced disease, either stage IV lymphoblastic lymphoma or stage III Burkitt's lymphoma. None of them suffered from thrombocytopenia or thrombocytosis. Apart from the occurrence of DST, the treatment was tolerated well in all children. No patient had received L-asparaginase. They had all displayed a rapid disappearance of tumour and were in complete remission at time of onset of symptoms related to DST. Symptoms appeared early in the course of chemotherapy treatment. The median interval between start of chemotherapy and onset of symptoms was 19 days (range 8–40). The duration of symptoms was always short, with a maximum of five days. These patients all recovered completely, clinically as well as radiologically, from DST.

During the study period, 307 patients were treated for stage III or IV non-Hodgkin lymphoma in our centre and registered in one of the protocols of the French Pediatric Oncology Society. Amongst these were five patients with reported convulsions in the induction or consolidation phase in whom a diagnosis of DST was not made. In three of them, convulsions were attributed to another cause. One child had a cerebral abscess; in one child administration of high dose methotrexate was thought to have caused the convulsions and one child with fever was thought to have had a febrile convulsion. In two children, no cause was found. In one of them, DST was assumed to have caused the convulsions, but imaging studies failed to confirm this. In view of this information, the incidence of symptomatic DST during the induction and consolidation phase in patients with advanced stage non-Hodgkin lymphoma probably lies between 1% and 3%.

DISCUSSION

Dural sinus thrombosis in children is associated with multiple etiologies such as dehydration, infections, haematological diseases and disorders of coagulation [15–23]. In many cases the cause is unknown.

In adult series of patients suffering from DST, malignancy is a rare cause [24]. Obstruction of venous drainage can be due to invasion or compression of sinuses by the neoplasm [25]. Thrombosis as a "paraneoplastic" phenomenon is another possibility [1].

Thrombosis of the sagittal sinus has been reported in children with cancer [3–6,8,26,27]. The first observations were made in children with leukaemia [3–6]. This complication can be ascribed to hypercoagulability due to the asparaginase-induced antithrombin III deficiency [7]. Legrand et al. [8] reported four children in whom DST occurred early in the course of treatment for non-

Hodgkin lymphoma. Only two of these children had been treated with L-asparaginase.

The number of new patients with solid tumours seen in our centre is approximately 300 per year. In the present study, we have reviewed all cases of DST diagnosed in a 15-year period. We have established that DST is a very rare event. Six out of seven cases occurred in children who were treated for non-Hodgkin lymphoma; one child was treated because of relapsing neuroblastoma. The most important presenting problem was either a severe headache or sudden convulsions. Neurologic deficits, for instance, hemiplegia, also occurred regularly. Symptoms usually disappeared within a few days.

In our patients, diagnosis was usually confirmed by a cerebral CT scan. It must be noted that diagnosis could not be established on the initial scan in two cases, while repeat of the investigation after 2 weeks did. In fact, CT scanning was repeated because the symptoms were thought to be typical of DST, prompting the clinician to ask for a repeat investigation. Symptoms had by then usually disappeared. This implies that diagnosis may have been missed in some patients with a less clear symptomatology, in whom repeating a CT scan seemed unnecessary. In one patient with a positive angiography, CT scanning repeatedly failed to reveal DST. The poor quality of CT scans in the earlier years is probably partly responsible for this. An MRI was performed in two children only; in one of whom it seemed superior to CT scanning.

Radiological proof of DST can be obtained in a number of ways. The first choice method seems to be cerebral CT scanning. A spontaneous hyperdensity of the sinus can be observed, whereas the thrombus itself can be visualized as the so-called empty delta sign after contrast administration [10]. This is illustrated in Figure 1. Magnetic resonance imaging is said to be more sensitive than CT scanning [9]. Various abnormal signal intensities of the sinuses on either T1- or T2-weighted images can be seen, depending on the time relapsed between onset of thrombosis and imaging (see Fig. 2). Furthermore, absence of bloodflow in the sinuses results in loss of hypersignal on fast spin-echo images of occluded sinuses. With the improvement of the quality of CT scans and the increase in availability of MR angiography, the use of angiography will decrease in the future (see Fig. 3).

The etiology of DST is not evident in most of our patients. Although CNS localisation of the malignancy was the probable cause in one and dehydration in another, the reason was not known in the remaining five patients. These patients were all treated because of stage III or IV non-Hodgkin lymphoma. Even if it is taken into account that the diagnosis of DST is sometimes missed in patients with a short episode of convulsions, the incidence of DST in patients with advanced stage non-Hodgkin lymphoma during the induction or consolidation phase seems to be below 3%.

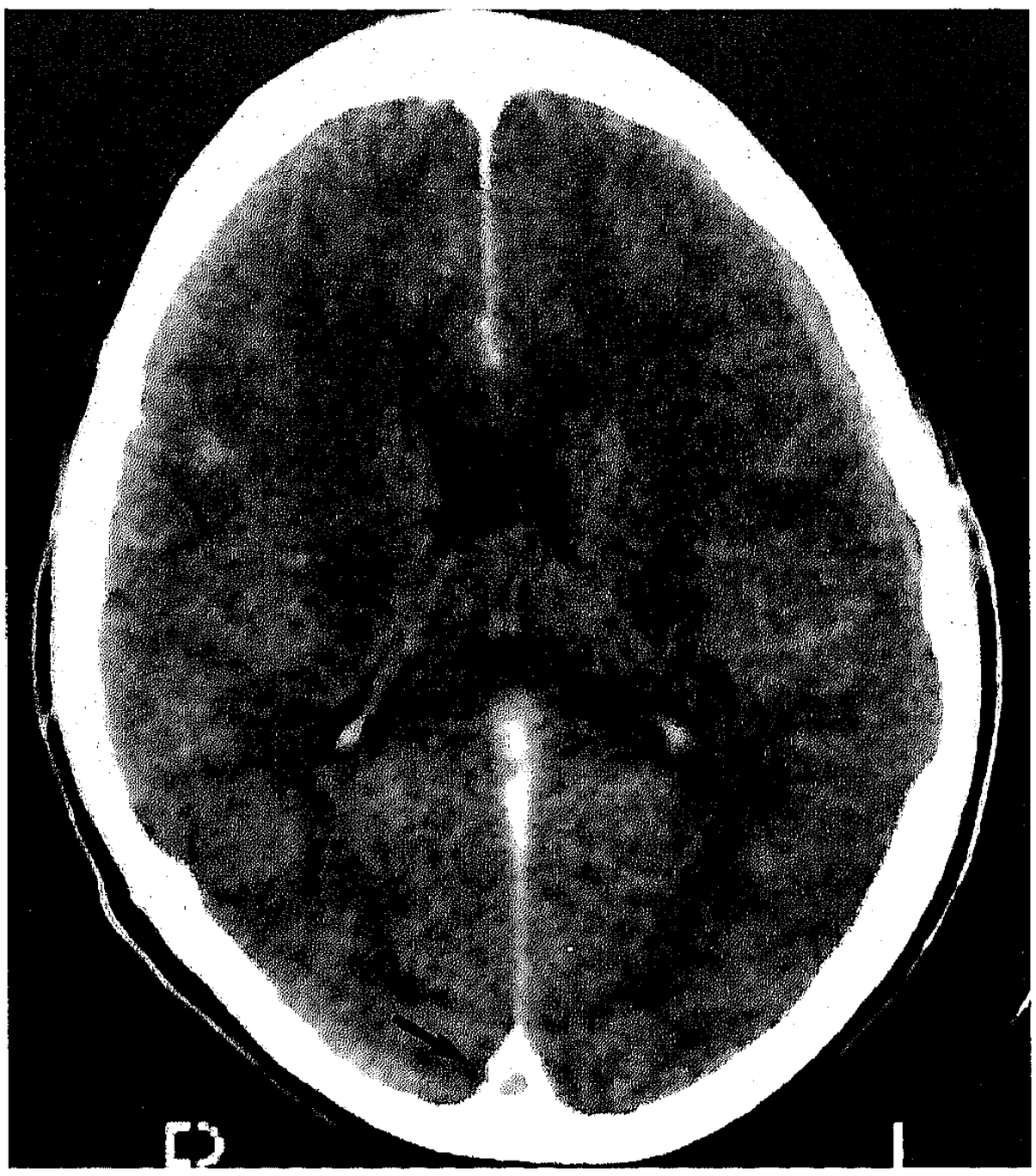

Fig. 1. CT scan of patient number 2, made 3 days after onset of symptoms, clearly showing the empty delta sign after contrast administration (arrow).

It does not seem likely that a specific chemotherapeutic drug was responsible for the event. None of the children in this study received L-asparaginase. Furthermore, the problems did not seem to occur following the administration of any other specific drug. Additionally, the drugs that were used are also used for the treatment of other malignancies, whereas the occurrence of DST seems to occur almost exclusively in patients treated for lymphoma. The occurrence of DST in children treated for lymphoma has previously been described by Legrand et al. [8]. Only two out of four children in their study had received L-asparaginase.

Hypercoagulation as a cause of DST remains a possibility. A "hypercoagulable state" has been described in children with leukaemia and solid tumours [28]. If not caused by L-asparaginase or another drug, it may be caused by some agent released by the tumour itself. In fact, initial tumour burden was relatively high, since all patients had advanced disease. Tumour lysis in the period preceding sinus thrombosis must have been extensive, since all patients were in remission when DST occurred within 40 days after start of therapy. Possibly procoagulant factors were released with the breakdown of tumour cells. In this case, one would also expect the occurrence of thrombotic events at other sites of the body in children

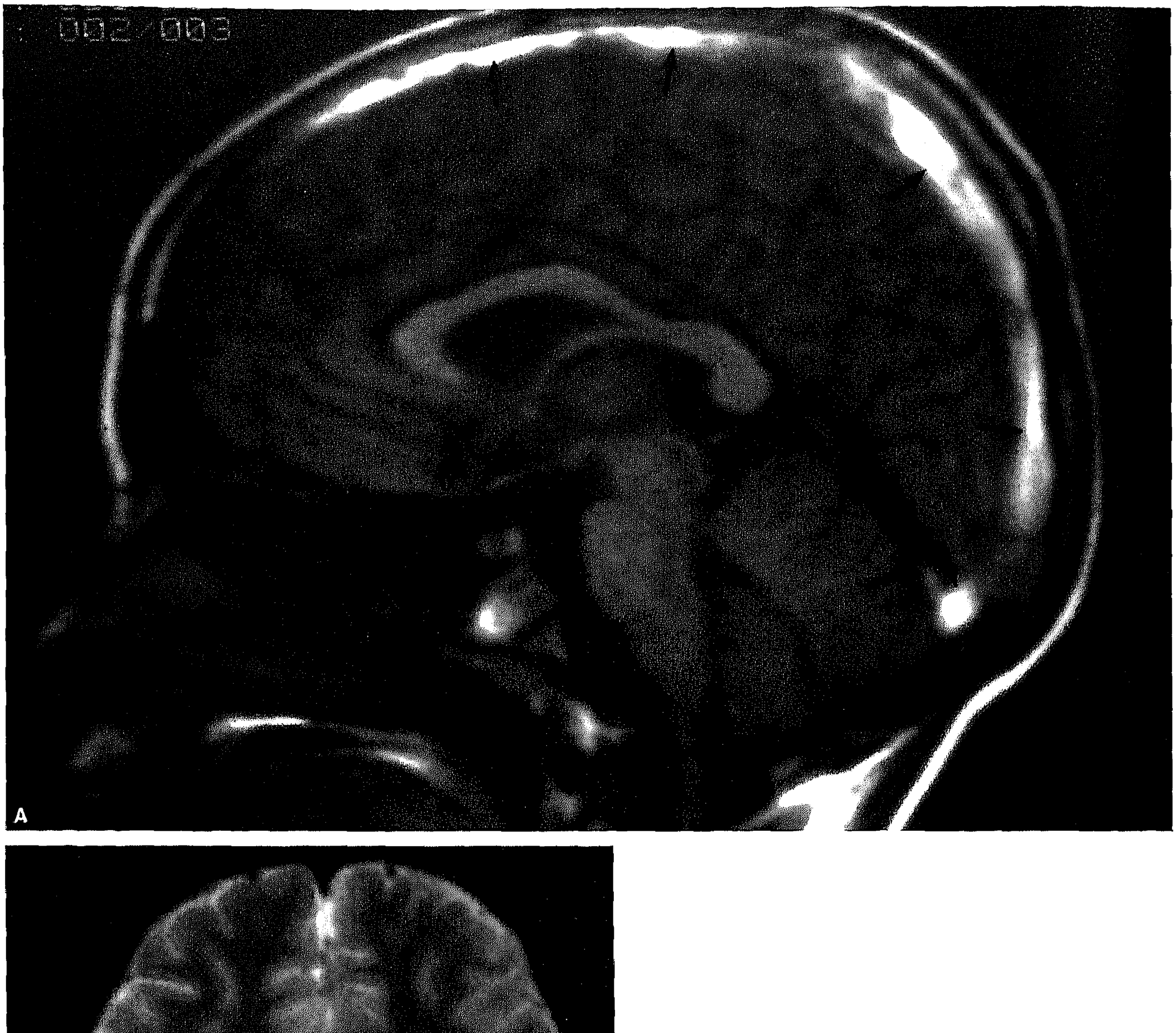

Fig. 2. MRI scan of patient number 3, made 9 days after onset of symptoms. **A:** Sagittal T1-weighted image, clearly showing extensive hyperintense signal of the entire sagittal sinus (arrows). **B:** Axial T2-weighted image showing hyperintense signal emerging from the thrombus in the sinus (arrow) and haemorrhage in the right parietal lobe (arrowhead).

treated for non-Hodgkin lymphoma. This, however, has not been observed by us. The simple haemostatic studies that were performed in most children in this study do not exclude abnormalities of coagulation. A hypofunction of the fibrinolytic system also remains possible, because studies in this direction were not performed in any patient.

It could also be hypothesized that local problems in or

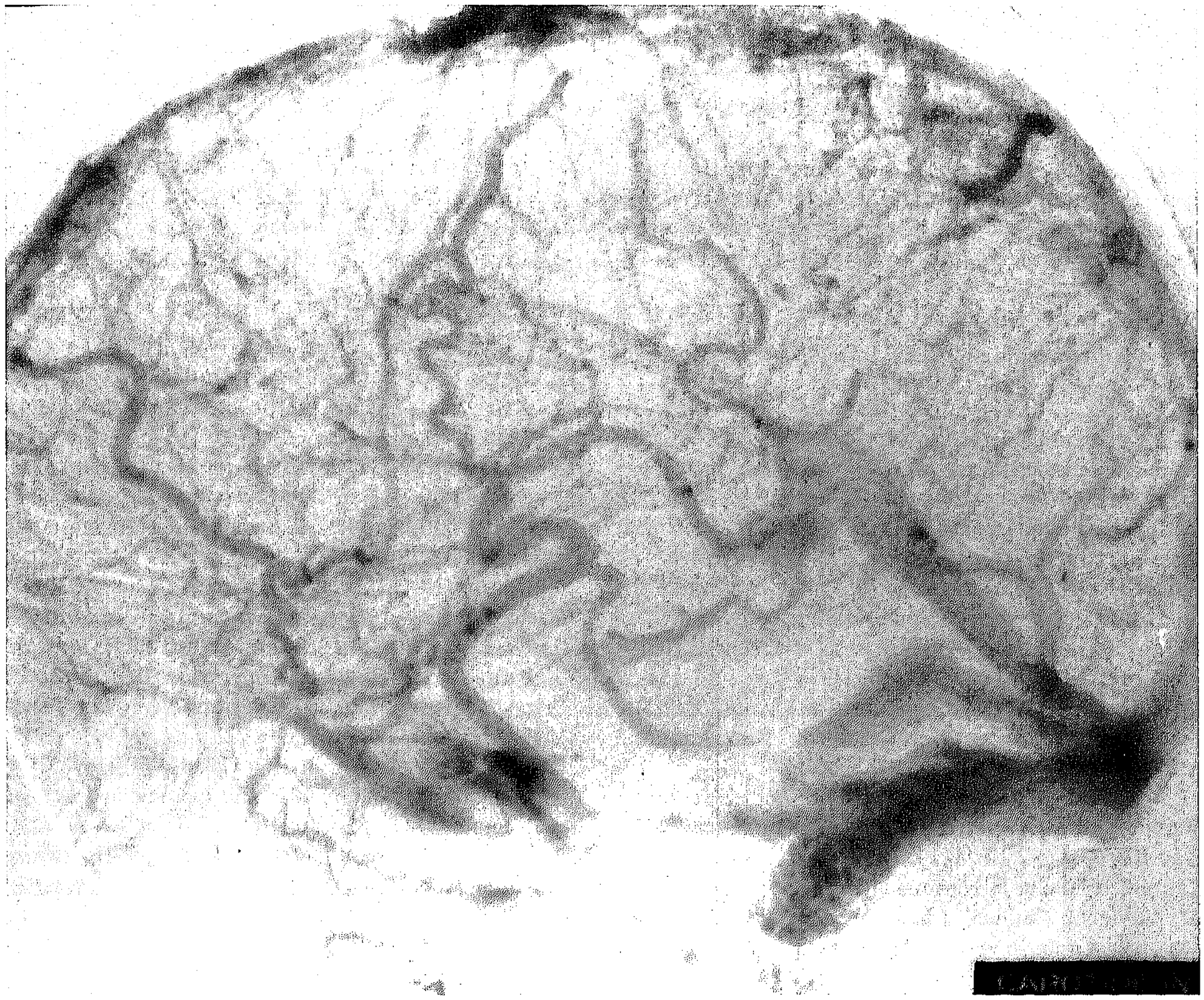

Fig. 3. Angiography of patient number 2, made 4 days after start of symptoms, establishing nonvisualisation of the entire sagittal sinus and formation of numerous collaterals.

close to the dural sinus were the cause. One could assume that small amounts of tumour cells were present in the sinuses of these patients at diagnosis. These cells could lead to sinus thrombosis, either directly or indirectly by inducing vascular effects. If small amounts of lymphoma cells could cause this, one would assume that dural sinus thrombosis would be a frequent event in children with proven CNS localisation. However, since only one of the patients suffered from initial CNS disease, initial CNS disease does not seem to be related to sinus thrombosis.

Some authors recommend treatment with heparin in patients with dural sinus thrombosis [6,24,29]. Systemic fibrinolysis and even local fibrinolysis have also been proposed [23,30–33]. Others advocate a conservative treatment [15,34]. Our data show that therapy is unnecessary and even potentially dangerous. In six of seven patients, prognosis of dural sinus thrombosis as such was favourable, without therapy. The only patient treated, was treated with systemic heparinisation. This patient, who also suffered from CNS localisation of lymphoma, died from intracerebral hemorrhage. Symptomatic treatment of convulsions seems to be the only justified treatment modality.

We conclude that DST is a rare event occurring in children with cancer. It almost exclusively occurs in children with advanced stage non-Hodgkin lymphoma, particularly within the first 2 months of therapy. Main symptoms are seizures with or without a transient neurologic deficit. These symptoms are often preceded by headaches. In the event of such signs in children treated for non-Hodgkin lymphoma, this diagnosis should be considered immediately after establishing the absence of metabolic disturbances. The cause is not known. The prognosis is good and no specific therapy is necessary. A detailed study of haemostasis and fibrinolysis in children treated for non-Hodgkin lymphoma could be performed in the future in the search for an explanation of this complication.

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