

Severe Cerebral Vasospasm and Childhood Arterial Ischemic Stroke After Intrathecal Cytarabine

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We report on 2 patients who developed widespread cerebral vasospasm and arterial ischemic strokes (AIS) after application of intrathecal (IT) cytarabine. In a 3-year-old child with acute lymphoblastic leukemia (ALL), left leg weakness, hyperreflexia, and clonus were noted 4 days after her first dose of IT cytarabine during the induction phase of her chemotherapy. Cerebral MRI revealed multiple acute cerebral ischemic infarcts and widespread cerebral vasospasm. A 5-year-old girl complained of right arm and leg pain and began limping 11 days after IT cytarabine. Symptoms progressed to right dense hemiplegia, left gaze deviation, headache, and speech arrest. MRI revealed 2 large cortical areas of diffusion restriction in the right frontal and left parietal lobes. Cerebral magnetic resonance angiography (MRA) showed irregular narrowing affecting much of the intracranial arterial circulation. Although the first child fully recovered from her neurologic symptoms, the second patient had persistent hemiplegia on follow-up. Including this report, there are now 4 pediatric ALL cases of severe cerebral vasospasm and AIS in the context of IT cytarabine administration, strongly suggesting a true association. Differential diagnosis and management issues are discussed. Along with the more widespread use of MRI and MRA, the true frequency of this severe adverse effect will become clearer in future. For any child with neurologic symptoms within hours or days of receiving IT cytarabine, a low threshold for cerebral imaging with MRI and MRA is recommended.

Neurologic adverse effects of chemotherapy drugs are relatively common. Stroke has been related to chemotherapy both in children and adults.¹

We report on 2 children diagnosed with precursor B-cell acute lymphoblastic leukemia (ALL) who developed acute ischemic strokes (AIS) after intrathecal cytarabine.

CASE REPORTS

Case 1

A previously healthy 3-year-old girl presented with a 1-week history

of cervical lymphadenopathy and pallor. On admission, the remainder of her physical examination including neurologic examination was normal. Pancytopenia was found; hemoglobin 23 g/L, platelet count $41 \times 10^9/L$, white blood cell count $13.1 \times 10^9/L$, absolute neutrophil count $1.18 \times 10^9/L$, and blast cell count $7.73 \times 10^9/L$. A peripheral blood smear, flow cytometry, and bone marrow examination showed evidence of precursor B-cell ALL. Cerebrospinal fluid was normal with no evidence of blast cells. Coagulation testing was normal. She was diagnosed with standard-risk ALL.

abstract

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Treatment was initiated according to the Children's Oncology Group AALL 0932 protocol, including oral dexamethasone 2 mg oral twice daily for 28 days (started on day 1 of the protocol); 70 mg of intrathecal (IT) cytarabine on day 1; intravenous (IV) vincristine 0.9 mg on days 1, 8, 15, and 21; and IV peg-asparaginase (PEG-ASP) 1700 U on day 4. Four days after her IT cytarabine, she refused to walk, reporting a "funny feeling" in her left foot. Left leg weakness, hyperreflexia, and clonus were noted. She was afebrile, and no seizures had been observed. Arterial hypertension was found, with a maximum blood pressure of 130 mm Hg (systolic, >95 percentile) for systolic and 88 mm Hg (diastolic, >95 percentile). Hypertension was treated with nifedipine.

A cerebral MRI and magnetic resonance angiography (MRA) revealed multiple small acute infarcts in the right frontal and periorlandic region with multiple foci of narrowing and beaded appearance involving the large cerebral arteries (Fig 1).

Echocardiography, renal ultrasound, ophthalmologic examination, and electroencephalography all revealed normal findings. No evidence for systemic vasculitis was found. There was no family history of migraine or thrombosis.

Treatment with unfractionated heparin was initiated, and her IT cytarabine was omitted. She was discharged 8 days after stroke onset with low molecular weight heparin (LMWH). However, she developed lower gastrointestinal bleeding. LMWH was stopped, and protamine sulfate was administered. Due to a thrombocytopenia at $66 \times 10^9/L$, low fibrinogen circulating level at 0.3 g/L, prolonged international normalized ratio at 2.2, and activated partial thromboplastin time at 44 seconds, she required replacement therapy with multiple blood products.

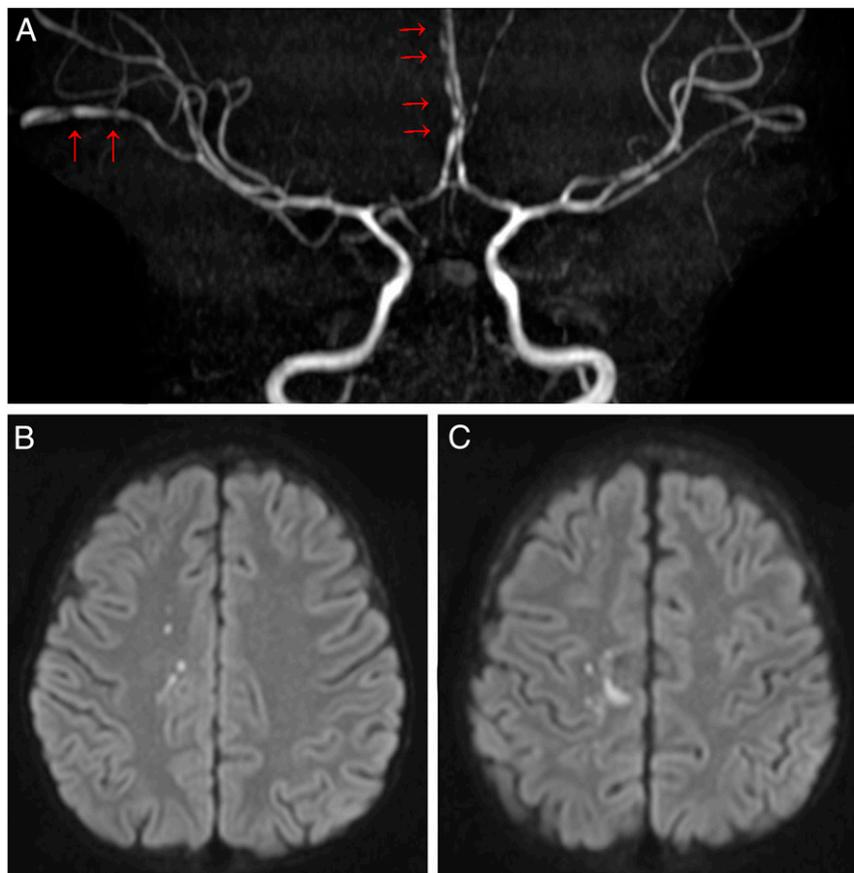


FIGURE 1

Case 1. A, Time-of-flight MRA with multiple foci of stenoses with beaded appearance of the A2 segment of the anterior cerebral artery and branches of the middle cerebral arteries (red arrows). B and C, Acute small infarcts indicated by diffusion-weighted imaging–positive foci around the right precentral gyrus and cingulate gyrus.

No source of bleeding could be identified. Gastrointestinal bleeding eventually stopped, and she resumed her chemotherapy protocol.

A follow-up MRA 5 weeks after stroke onset showed marked improvement of her arterial narrowing. She was discharged without focal neurologic deficit.

Case 2

A 5-year-old previously healthy girl presented with fatigue, fever, and bilateral leg pain. On presentation, neurologic examination was normal. Complete blood count revealed peripheral blasts, and bone marrow biopsy was diagnostic for standard-risk precursor B-cell ALL. Induction chemotherapy per protocol Children's Oncology Group ALL 0932

was initiated. The patient received oral dexamethasone 2 mg twice daily for 28 days (started on day 1 of the protocol); IT cytarabine 70 mg on day 1; IV vincristine 1 mg on days 1, 8, 15, and 21; IV PEG-ASP 1725 U on day 4; and IT methotrexate 12 mg on day 8. On day 11 of induction, she complained of right arm and leg pain and began limping. Symptoms progressed to include dense right hemiplegia, left gaze deviation, speech arrest, and lethargy. On arrival in the emergency department, blood pressure was 109/73 mm Hg (90 percentile/95 percentile). Forced gaze deviation to the left was noted. Motor testing revealed 1/5 strength in the right arm and leg, whereas left hemibody strength was full. Right-sided hyperreflexia and upgoing right toe were noted. MRI at that time

(12 days after cytarabine application) revealed 2 large cortical areas of diffusion restriction in the right frontal and left parietal lobes. MRA showed irregular narrowing affecting much of the intracranial arterial circulation (Fig 2).

Echocardiogram was normal. Laboratory studies, including hypercoagulability panel, erythrocyte sedimentation rate, antinuclear antibody, antineutrophil cytoplasmic antibody, and myeloperoxidase, were negative. The patient has no family history of hypercoagulability or migraine.

No further IT cytarabine was given. PEG-ASP was held until repeated MRA showed resolution of vasculopathy. She missed 1 dose but has been receiving further PEG-ASP doses without any problems.

She was started on gabapentin for pain and aspirin 81 mg daily for stroke prophylaxis.

Follow-up MRA on day 36 of induction showed significant improvement in the vasculopathy, although arterial irregularities were still noted with some areas of progression (Fig 2). Postcontrast 3-dimensional high-resolution black blood MRI² demonstrated no abnormal enhancement of the vessel wall at sites of luminal narrowing, consistent with vasospasm and not with vasculitis.³ At that time, the patient was beginning to make some motor recovery. Nimodipine was initiated 30 days after stroke onset for vasospasm prophylaxis and continued for 49 days. At follow-up 2.5 months poststroke, substantial clinical recovery was noted, although mild persistent hemiparesis was evident.

DISCUSSION

We report 2 pediatric cases of diffuse cerebral vasospasm complicated

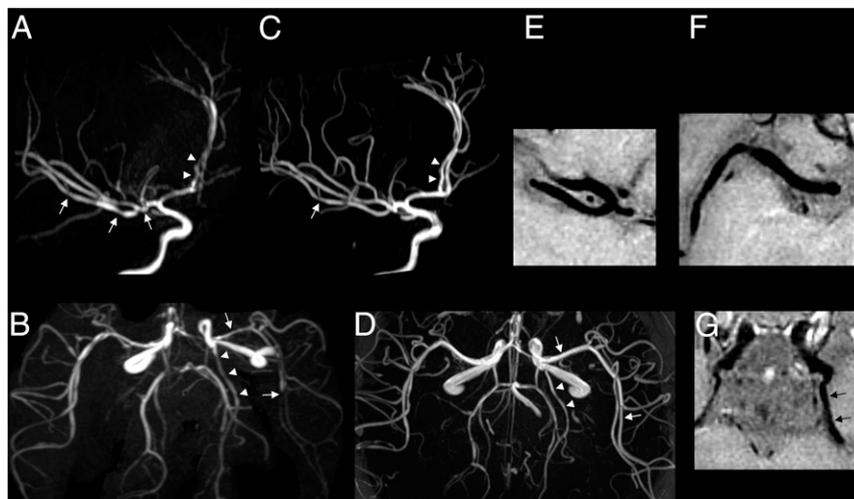


FIGURE 2

Case 2: maximum intensity projection (MIP) images from three-dimensional time-of-flight MRAs acquired on day 12 (A and B) and day 36 of induction (C and D) in anterior-posterior oblique and axial views, respectively. Partial improvement in luminal irregularity involving the right middle cerebral artery (A and C, arrows) and anterior cerebral artery (A and C, arrowheads) vessels and improvement of left middle cerebral artery stenosis (B and D, arrows) and of left accessory posterior cerebral artery irregularity (B and D, arrowheads) was observed. The improved appearance was exaggerated by the higher resolution used on follow-up imaging ($0.63 \times 1.25 \times 1.4 \text{ mm}^3$ at 1.5T vs $0.52 \times 0.54 \times 0.55 \text{ mm}^3$ at 3T). Three-dimensional high isotropic resolution black blood MRIs demonstrated no abnormal vessel wall enhancement seen on long-axis reconstructions of the right MCA (E and F; anterior-posterior oblique and axial views, respectively) and the left duplicated posterior cerebral artery (G, arrows), supporting vasospasm rather than an inflammatory vasculopathy.

by AIS related to IT cytarabine treatment. Both cases show striking similarities to 2 previous pediatric reports (Table 1). A 7-year-old girl with precursor B-cell ALL developed acute encephalopathy, aphasia, incontinence, visual hallucinations, and right-sided weakness.⁴ MRA showed diffuse cerebral vasospasm and ischemic lesions in both frontal lobes extending to the left parietal lobe. The patient fully recovered without anticoagulation. MRA abnormalities had resolved after 4 months. A 7-year-old boy with precursor B-cell ALL complained of intermittent visual loss on day 2 after IT cytarabine, toe pain on day 7, and persistent right-sided leg weakness on day 10. Diffusion-weighted imaging changes were not reported, but MRA showed diffuse cerebral vasospasm involving the anterior and posterior circulation. In addition, T1-weighted images showed “multifocal acute leukoencephalopathy,” and follow-up imaging revealed multifocal lacunar

infarcts.⁵ A comparable adult case was published previously.⁶ A 54-year-old woman undergoing induction therapy for ALL treatment developed an encephalopathy after receiving IT cytarabine. MRI showed abnormalities consistent with posterior reversible encephalopathy syndrome (PRES) associated with prominent vasospasm on MRA.

Different chemotherapeutic drugs are related to stroke and cerebrovascular events. Our patients had been exposed to PEG-ASP, dexamethasone, vincristine, and IT cytarabine at the time of symptom onset. Cerebral sinus venous thrombosis has been frequently associated with PEG-ASP, especially if combined with steroids, cerebral hemorrhages, and PRES.^{1,7,8} Cerebral vasospasm has never been reported in the context of PEG-ASP. Vincristine is mainly related to peripheral neuropathies. AIS or cerebral sinus venous thrombosis secondary to vincristine treatment have not been published.

TABLE 1 Summary of Known Cases of Cytarabine Induced Cerebral Vasospasm and Acute Ischemic Stroke

	Pound et al ⁴ (Ottawa, Canada)	Yoon et al ⁵ (Goyang, South Korea)	This report	
			(Toronto, Canada)	(Baltimore, USA)
Age at stroke onset, y	7	7	3	5
Type of leukemia	Precursor B-cell ALL	Precursor B-cell ALL	Precursor B-cell ALL	Precursor B cell ALL
Chemotherapy protocol	COG AALL 0331	not stated	COG AALL 0932	COG ALL 0932
Dose of IT cytarabine	70 mg	70 mg	70 mg	70 mg
Symptoms	Aphasia, incontinence, visual hallucinations, right-side weakness	Headache, visual loss, right-side weakness	Left leg weakness, dysaesthesia left leg	Right-side limb pain, right hemiplegia, left-gaze deviation, headache, speech arrest
Symptom onset after IT cytarabine application	3 d	10 d	4 d	11 d
MRA	diffuse vasospasm	diffuse vasospasm	diffuse vasospasm	diffuse vasospasm
Stroke pattern	bilateral, subcortical frontal white matter	multifocal cortical and subcortical white matter	multifocal cortical	bilateral cortical
Management	no medication	nimodipine, LMWH, citicoline, antithrombin, fresh-frozen plasma	LMWH	Nimodipine, aspirin, gabapentin,
Neurologic outcome	Full recovery	Full recovery	Full recovery	Persistent hemiplegia
MRA brain follow-up of vasospasm	Improvement after 10 d, complete resolution after 4 mo	Marked improvement after 25 d	Marked improvement after 4 wk	Marked improvement after 36 d

COG, Children's Oncology Group.

High-dose IV cytarabine has been reported to cause central nervous system toxicity, including seizures, encephalopathy, and acute cerebellar syndrome.^{1,9} Apart from the aforementioned pediatric cases, stroke has not been previously reported. Interestingly, diffuse brain hypoperfusion was found in a study of children who underwent single photon emission computed topography scan during high-dose cytarabine IV administration.¹⁰

In our cases as well as those previously published, the MRA pattern was characterized by widespread cerebral vasospasm resembling reversible cerebral vasoconstriction syndrome (RCVS). However, the clinical histories in our cases are not typical for RCVS, which is extremely rare in early childhood.¹¹ Neither the clinical history nor laboratory and MRI results in our patients were suggestive of meningitis or a primary angiitis of the central nervous system. In the absence of headache and presence of a negative family

history, migraine was not considered a differential diagnosis.

The location, conformation, and persistence of the parenchymal lesions indicate that these were consistent with vaso-occlusive infarcts and not hypertensive encephalopathy or PRES. Thus, even though the exact pathomechanism leading to the development of cerebral vasospasms and consecutive AIS is difficult to be finally proved, we propose that toxic effects of IT cytarabine are the most plausible explanation in our patients. Arterial hypertension was a potential cofactor in case 1 but not case 2.

Our first patient was treated with anticoagulation. Aspirin was used in case 2. Both heparin and aspirin are treatment options for secondary stroke prevention in children.^{12,13} The rationale for the treatment decision in our cases was based on a severe, widespread vasculopathy combined with multifocal strokes of different age. Heparin was also administered in the most recently published case.⁵ Meanwhile, whereas LMWH had to be stopped in our case

due to gastrointestinal bleeding, no LMWH related adverse events were reported by Yoon et al.⁵

The risk for stroke recurrence in the presence of cerebral vasospasms is basically unknown. The use of medication is controversial; anticoagulation is usually considered safe in children and is not contraindicated in oncologic patients unless additional bleeding risk factors (eg, recent surgery, active bleeding, low platelet count $<50 \times 10^9/L$, uncorrected disseminated intravascular coagulation, or uncontrolled severe malignant hypertension) are present.^{14,15}

However, primary management is symptomatic, including identification and elimination of any precipitating or aggravating factors. Additional treatment may include analgesics, antiepileptic drugs for seizures, and treatment of arterial hypertension. Hypotension in the setting of cerebral vasoconstriction and cerebral infarction is potentially dangerous. Nimodipine was administered in our second case as well as 1 published case.⁵ However, evidence for the risks

and benefits of any drugs targeted at vasospasm, including nimodipine is not even available for the much more common RCVS in adulthood.¹¹

Therefore, observation and symptomatic management may be reasonable after discontinuation of the precipitating drug. MRI/MRA and clinical follow-up is warranted to identify early signs of progression and persistence of vasospasm. Recovery is not always complete, as illustrated by our second case.

Including this report, there are now 4 pediatric cases of severe cerebral

vasospasm and AIS in the context of IT cytarabine administration in ALL patients, strongly suggesting a true association. Given the total number of patients treated with IT cytarabine, the overall incidence is probably low. However, this complication may be underdiagnosed. With more widespread use of MRI and MRA the true frequency of this severe adverse effect of cytarabine will become clearer in future. For any child with neurologic symptoms within hours or days of receiving IT cytarabine, a low threshold for cerebral imaging with MRI and MRA is recommended.

ABBREVIATIONS

AIS: arterial ischemic stroke
ALL: acute lymphoblastic leukemia
IV: intravenous
IT: intrathecal
LMWH: low molecular weight heparin
MRA: magnetic resonance angiography
PEG-ASP: peg-asparaginase
PRES: posterior reversible encephalopathy syndrome
RCVS: reversible cerebral vasospasm syndrome

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