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Symptomatic Epilepsy Associated With Intracranial Calcifications in Children With Acute Lymphoblastic Leukemia (ALL)

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A B S T R A C T

Acute and long-term sequels of central nervous system (CNS) prophylaxis with irradiation and intrathecal chemotherapy in children suffering from acute lymphoblastic leukemia (ALL) include vasculopathies, leucoencephalopathies, intracranial calcifications, intellectual and neurological impairment. We report two children at the age 5 and 8 years who manifested partial motor or complex seizures and intracranial calcifications 2–4 years after the diagnosis of ALL had been established. The occurrence of these disorders was much earlier than reported in the literature. Both children received prophylactic CNS treatment with irradiation and intrathecal methotrexate (MTX). Their brain CT scans and EEG had been normal before the first epileptic seizure was registered. Children are now seizure free on carbamazepine, and a boy with complex partial and myoclonic seizures is also on valproate and vigabatrine. Symptomatic epilepsy associated with intracranial calcifications and persisting EEG changes might occur as side effects of ALL treatment.

Introduction

Acute and long-term sequels of the central nervous system (CNS) prophylaxis with irradiation and intrathecal chemotherapy in children include leucoencephalopathy and necrotising encephalopathy or microangiopathy associated with different intellectual and neurological impairment[1–4]. Areas of demyelinisation, axonal swelling, necrosis and calcifications are found on brain autopsy[5].

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Although the doses used in prophylactic cranial irradiation are much below the doses causing morphological injury[5,6], even low doses are able to produce EEG changes[7]. Methotrexate is the folic acid antagonist interfering with myelin metabolism constituents. Chronic methotrexate encephalopathy presents occasionally with epileptic seizures and intracranial calcifications[8]. No correlation could be established between neurological abnormalities and CT findings that are found in 53% of ALL children after prophylactic CNS treatment with irradiation and intrathecal chemotherapy[1,3]. Post irradiation syndrome might be a predictor of the development of late neurological sequels in children with ALL. We report two children who manifested recurrent epileptic seizures and intracranial calcifications 2–4 years after the diagnosis of ALL had been established.

Case 1

S.I., is a boy who was at the age of 5.5 years admitted to hospital because of his first epileptic seizure associated with right hemiparesis postictally. He was born after pregnancy during which his mother had been operated for cerebral aneurysm, and her CT scans had been performed in the 7th month of gestational age. The diagnosis of acute lymphoblastic leukemia was established at the age of 2.5 years. He was treated with intrathecal methotrexate (MTX 8 mg 10 on days 1, 14, 16, 18, 20, 22 and four times during maintenance therapy every three months) + cytosine arabinoside (30 mg/m^2). The Vehicle used for intrathecal therapy was 0.9% NaCl. Three months prior to the admission he had been in complete hematological and clinical remission and his first EEG had been normal. On admission he was somnolent, with right

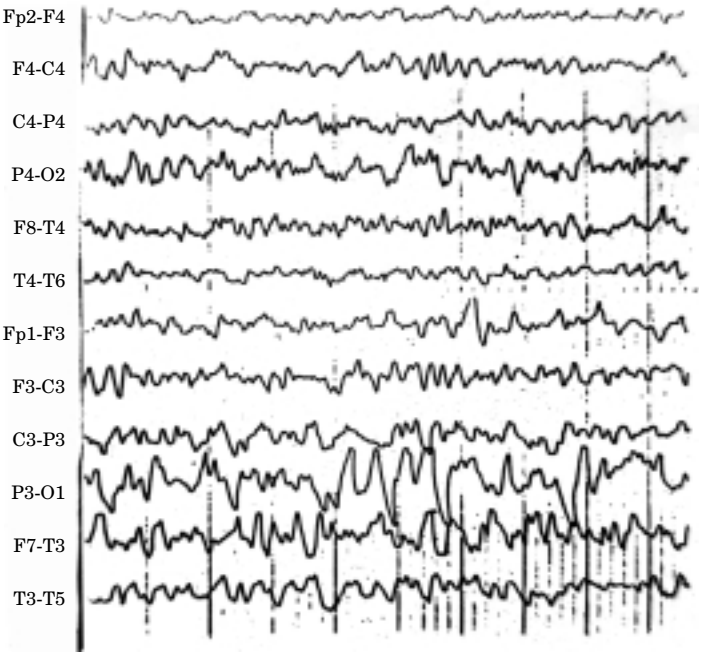

Fig. 1. S.I., 5.5 yrs.; Asymmetrical abnormality with continuous slow activity above the left hemisphere.

spastic hemiparesis which resolved after two days. His EEG showed asymmetrical abnormality with continuous slow activity above the left hemisphere (Figure 1). His brain CT-scan was normal at that time. One month later he developed clinical and radiological signs of CNS leukemia. Relapses in CNS were treated with systemic chemotherapy, intrathecal MTX (8 12 mg MTX) and CNS irradiation (the brain and cervical spine were irradiated with 2000 cGy divided in 14 daily doses). He manifested recurrent epileptic seizures at the age of 6.6 years. Control brain CT-scans at the age of 7.5 years showed intracerebral calcifications in the periventricular white matter (Figure 2). He is now seizure free on carbamazepine treatment, exhibiting normal psychomotor development.

Case 2

S.D., an 8-year-old boy, was admitted to hospital because of 2 partial complex seizures. Diagnosis of ALL was established at the age of 1.5 years and he received CNS irradiation (the brain and three upper parts of cervical spine were irradiated with 2000 cGy divided in 14 daily doses). Intrathecal methotrexate was given 9 times (MTX 8 mg on days 1, 14, 16, 18, 20, 22 and three times during maintenance therapy every three months). The vehicle used for intrathecal therapy was 0.9% NaCl. He had been in complete clinical and hematological remission two years prior to the seizures. His first EEG, made before the first seizures occurred, had been normal as well as the EEG made one year afterwards on follow-up. His CT scan had revealed gyriform intracerebral calcifications, which remained unchanged on the recently performed control brain CT-scan. He was treated with valproic acid, and carbamazepine. Besides complex partial seizures, he also manifested complex absence of seizures. His EEG at the time of therapy with valproate and carbamazepine showed intensive focal as well as extensive paroxysmal discharges (Figure 3). Ethosuximide in combination with valproic acid was introduced without positive therapeutic effects. Vigabatrine (Sabril) was introduced together with valproic acid at the age of 11 years. He is seizure free for the last 3 years and he has normal mental development. EEG recording for the last two years is completely normal.

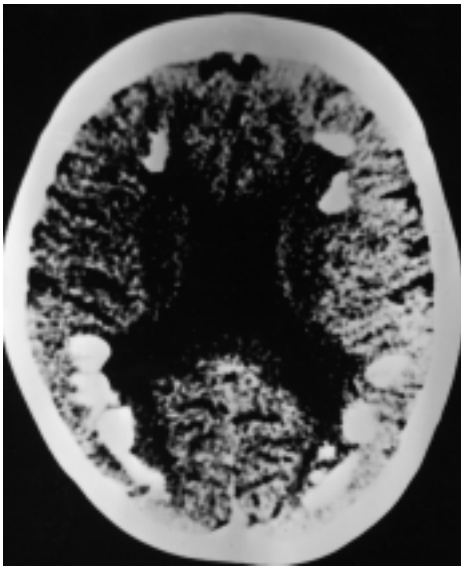

Fig. 2. S.I., 5.5 yrs.; Brain CT-scan shows intracranial calcifications in the periventricular white matter.

Discussion

We observed persistent EEG abnormalities 2–4 years after induction of clinical and hematological remission in two children with ALL who received CNS irradiation/MTX treatment. CT scan and EEG were normal in both of them during the ALL treatment Diffuse EEG changes during induction/reinduction treatment or CNS irradiation are usually transient. They are mostly associated with acute neurotoxic side effects of chemotherape-

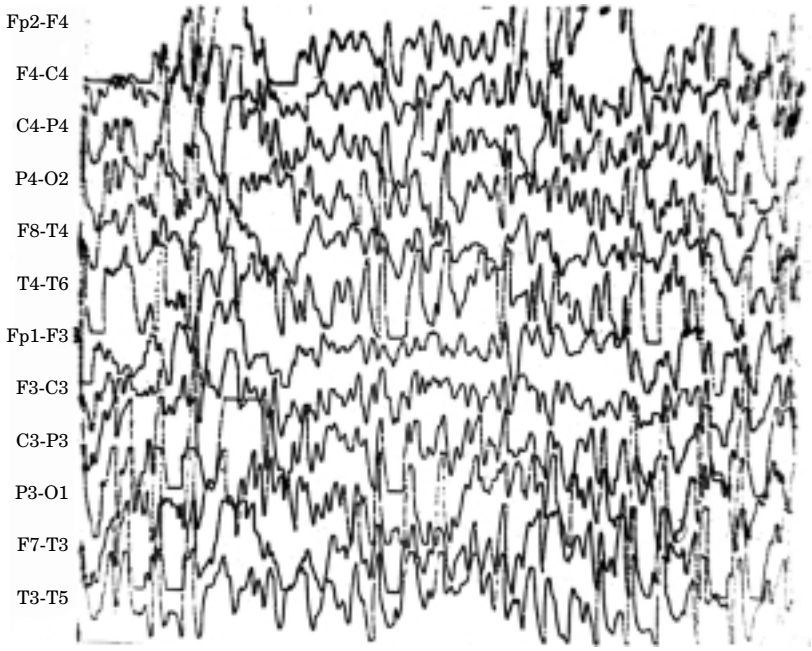

Fig. 3. S.D., 8 yrs.; EEG shows focal or multifocal as well as extensive paroxysmal discharges.

utics or radiotherapy. Focal or diffuse EEG abnormalities with or without seizures are usually associated with CNS leukaemia[9]. Majority of patients with ALL have normal EEG in hematological remission prior to prophylactic cranial irradiation[6]. Patients receiving MTX parenterally very frequently revealed recurrent EEG abnormalities and less frequently seizures as compared to the patients who were treated with CNS irradiation[10]. Improvement in EEG occurred in 37% of ALL children 2 months after introduction of chemotherapeutic treatment, while EEG normalization was observed in 65% of children after 1–1.5 years. Severe persistent EEG abnormalities were not registered in long-term follow up of ALL children[9]. We observed persistent EEG abnormalities 2–4 years after induction of clinical and hematological remission in children with ALL who received CNS irradiation/methotrexate treatment.

Follow-up CT scans of reported children revealed calcifications associated with recurrent epileptic seizures and persistent EEG abnormalities. According to *Medline* there are no reports in the literature of intracranial calcifications associated with symptomatic epilepsy in ALL children occurring in such a short period after CNS irradiation and MTX treatment. Ochs et al. studied 1,289 patients with ALL, of whom 132 (10%) experienced one or more seizures. CT scans showed brain calcifications in 13 patients. But the period between irradiation and MTX therapy and calcification in brain was much longer than in our patients. Patients who received intrathecal MTX repeatedly with or without MTX intravenously or prior to prophylactic cranial irradiation had 20-fold higher seizure risk during the 6^{th} to 12^{th} month of therapy than those who received irradiation and only five intrathecal injections of

MTX early in the course of treatment[11]. The lowest risk for seizure occurrence was reported in patients with cranial radiation with 2400 cGy and 5 MTX doses according to the same protocol that was applied in one of our patients (Case 1)[11]. Seizures incidence is highest during induction of antileukemic treatment, CNS intensification and reinduction period. Seizures were associated with cerebral lesions in 47% of ALL children[12]. Some authors suggest the possibility that MTX and CNS irradiation are primarily responsible for CNS abnormalities [1]. Most recently intracranial calcifications were described in patients treated exclusively with chemotherapy[12,13]. Parenteral application of MTX or its vehicle may play an important role in occurrence of seizures. MTX interfere with folate and tetrahydrobiopterin metabolites causing a decrease in brain gamma-aminobutyric acid (GABA) levels. Disruption of monoamine metabolism on the rodent model has been proposed as a cause of brain dysfunction during MTX therapy. Seizure recurrence was registered after multiple MTX injections correlating with high MTX doses which might also be one of the reasons for the development of late neurological sequels[14,15]. CNS irradiation damages the blood brain barrier permitting MTX to penetrate in the brain in larger amounts. Especially high MTX levels are present in patients with CNS leukemia (Case 1). We did not observe intracranial calcifications in children who received MTX without CNS irradiation.

Conclusion

Intracranial calcifications associated with symptomatic epilepsy might occur as a late morphological and functional sequel of CNS leukemia itself or prophylactic CNS irradiation together with intrathecal methotrexate treatment. EEG is mostly normal in all children with ALL in hematological and clinical remission, showing transient abnormalities after CNS irradiation. Longitudinal EEG assessment of children with ALL treated with intrathecal methotrexate and CNS irradiation showed persistent abnormalities clinically associated with epilepsy. Combined prophylactic therapy of CNS (MTX/irradiation), rather than MTX treatment only, might be responsible for development of brain calcifications resulting in seizures. However, the number of our patients is far too small to make definite conclusions.

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SIMPTOMATSKA EPILEPSIJA POVEZANA S INTRAKRANIJALNIM KALCIFIKACIJAMA U DJECE S AKUTNOM LIMFOBLASTIČNOM LEUKEMIJOM (ALL)

S A Ž E T A K

Akutne i dugotrajne posljedice profilakse središnjeg živčanog sustava (SŽS) s iradijacijom i intratekalnom kemoterapijom u djece koja boluju od akutne limfoblastične leukemije (ALL) uključuju: vaskulopatije, leukoencefalopatije, intrakranijalne kalcifikacije, te intelektualne i neurološke ispade. Izvješće je dano za dvoje djece, dobi 5 i 8 godina, kod kojih su se manifestirali djelomični motorni ili kompleksni epileptički napadi te intrakranijalne kalcifikacije 2–4 godine nakon što je dijagnoza ALL utvrđena. Ovi poremećaji javili su se mnogo ranije nego što se može naći u literaturi. Oboje djece primilo je profilaktičku SŽS terapiju s iradijacijom i intratekalnim metotrexatom (MTX). Njihov CT pregled mozga i EEG bili su normalni prije nego što je prvi epileptički napad zabilježen. Djeca su sada bez napada, na karbamazepinu, a dječak koji je imao kompleksne djelomične i miokloničke napade prima još i valproat i vigabatrin. Simptomatska epislepsija povezana s intrakranijalnim kalcifikacijama i postojanim EEG promjenama može se javiti kao uzgredna pojava liječenja ALL.