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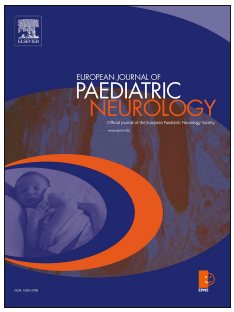

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Seizures during treatment of childhood acute lymphoblastic leukemia: a population-based cohort study

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Abstract

Background: Seizures are common in children with acute lymphoblastic leukemia (ALL). As ALL survival rates are improving, the challenge to minimize treatment related side effects and late sequelae rises. Here, we studied the frequency, timing, etiology and risk factors of seizures in ALL patients.

Methods: The study included children aged 1-17.9 years at diagnosis of B-cell-precursor and T cell ALL who were treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol between 2008 and 2015. Detailed patient data were acquired from the NOPHO ALL2008 registry and by review of medical records.

Results: Seizures occurred in 81/1464 (5.5%) patients. The cumulative incidence of seizures at one months was 1.7% (95% CI: 1.2-2.5) and at one year 5.3% (95% CI 4.2-6.5%). Patients aged 10-17.9 years, those with T cell immunophenotype, CNS involvement, or high-risk induction with dexamethasone had higher risk for seizures in univariable analyses. Only age remained a risk factor in multivariable analyses (the cumulative incidence of seizures for patients 10-17.9 years old at one year was 9.0% (95% CI: 6.2-12.9)). Of the 81 patients with seizures, 43 had posterior reversible encephalopathy syndrome (PRES), 15 had isolated seizures, nine had sinus venous thrombosis (SVT), three had stroke-like syndrome, and 11 had other neurotoxicities. Epilepsy diagnosis was reported in totally 11 ALL survivors at last follow up.

Conclusion: Seizures are relatively common in ALL patients and occur most often in patients with PRES, SVT, or as an isolated symptom. Older children have higher risk of seizures.

Keywords: epilepsy, ALL, neurotoxicity

Abbreviations

Abbreviation	*Meaning*
CNS	Central Nervous System
ALL	Acute Lymphoblastic Leukemia
PRES	Posterior Reversible Encephalopathy Syndrome
SVT	Sinus Venous Thrombosis
SLS	Stroke-Like Syndrome
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
BCP	B Cell-Precursor
NOPHO	Nordic Society of Paediatric Haematology and Oncology
SCT	Stem Cell Transplantation
ADHD	Attention Deficit Hyperactivity Disorder
EEG	Electroencephalogram
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
ICU	Intensive Care Unit
ILAE	International League Against Epilepsy
AED	Antiepileptic Drug
NMDA	N-Methyl-d-Aspartate

1. Introduction

Acute neurological side effects in the central nervous system (CNS) are reported in up to 13% of children with acute lymphoblastic leukemia (ALL)[1-4]. Seizures occur both as isolated CNS toxicity and as a symptom of systemic conditions[2, 5, 6]. The most frequently described neurotoxicities or systemic conditions that predispose patients to seizures are posterior reversible encephalopathy syndrome (PRES), cerebral sinus venous thrombosis (SVT), methotrexate-related stroke-like syndrome (SLS), methotrexate-related leukoencephalopathy, CNS infections, encephalopathy defined as altered mental status, and electrolyte disturbances including the syndrome of inappropriate antidiuretic hormone secretion (SIADH)[1, 2, 5-8]. Several chemotherapeutic agents used in ALL treatment are also associated with neurotoxicities and seizures[9-16]. Treatment of seizures is symptomatic but awareness of possible etiologies, such as PRES, infections or SVT, is important for timely diagnosis and optimal treatment [8, 17, 18]. The aim of this study was to explore the frequency, timing, etiology and risk factors for seizures in children with ALL as well as possible long-term effects.

2. Materials and methods

2.1 Subjects and study design

Children aged 1-17.9 years, diagnosed with B cell-precursor (BCP) or T cell ALL between July 1, 2008 and December 31, 2015 in twenty-two pediatric oncology centers in Sweden, Norway, Denmark, Finland, Iceland, Estonia, and Lithuania were included in the study. All of these centers had a common treatment protocol for childhood ALL, the Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 protocol[19-21]. This protocol included an on-line toxicity registration system covering 18 toxicities (including severe neurotoxicity) with a high compliance of 95%[19]. Patients treated with other protocols than

NOPHO ALL2008, such as patients diagnosed with bilineage ALL, Philadelphia positive ALL, and Down syndrome were excluded. Patients with suspected or verified neurotoxicity were retrospectively identified from the registry. Detailed data on neurological symptoms, laboratory parameters within 2 weeks prior to seizures, neuroimaging, treatment strategies, and outcome including epilepsy diagnosis at last follow-up of the patients with neurotoxicity was subsequently acquired by a questionnaire completed by the participating centers after review of medical records. NOPHO-ALL 2008 protocol provides definitions of acute CNS toxicities including seizures, PRES and methotrexate related neurotoxicity[19-21]. Further, Ponte Di Legno criteria classification of CNS toxicities in childhood ALL were applied in this study[6]. The questionnaires were reviewed by a child neurologist (SA). Semiology of seizures was assessed by SA according to current International League Against Epilepsy (ILAE) recommendations[22].

2.2 Ethics

The NOPHO-ALL 2008 study was approved by the national Competent Authority (EudraCT 2008-003235-20 and 2011-000908-18 (Lithuania)) and the scientific Ethical Review Boards and National Medical Products Agencies in the respective countries. The families have consented to registration of ALL and treatment related toxicities for research purposes. This study is a sub-study of the ALL2008 protocol and has been approved by the NOPHO scientific board.

2.3 Statistical analyses

The follow-up period began with the diagnosis of ALL and continued until relapse, stem cell transplantation (SCT), secondary malignancy, death, or last follow-up date, whichever occurred first. Time to seizure was defined as days from the start of ALL treatment to the day

of seizure, with censoring for relapse, secondary malignancy, SCT, death, other neurotoxicity, or last follow-up, whichever occurred first. Cox proportional hazards models were used for evaluating the association between possible risk factors and seizure incidence. Age group, immunophenotype, sex, CNS status at diagnosis, and risk group at diagnosis were included in the multivariable model. SPSS Version 25.0 for Windows (SPSS Inc., Chicago, IL), and R version 3.5.0, R Core Team (2019)[23], were used for all analyses and data processing. The method of Gray[24] was used for visualizing and calculating cumulative incidence of seizures, using the function *cuminc* from the R package *cmprsk*. Two-sided p-values below 0.05 were considered significant.

3. Results

3.1 Patient population

The study group included 1464 children; 1274 with BCP and 190 with T cell ALL. The median follow-up time for survivors was 5.0 years (range, 0.0-9.3 years, n=1351) with interquartile range 3.4-6.9 years. Acute severe CNS toxicities were reported in 135/1464 patients (9.4%). PRES, SVT, and isolated seizures were the most common neurotoxicities; seizures independently of etiology were reported in 81/135 with CNS toxicities respectively 81/1464 children with ALL.

3.2 Incidence and risk factors for seizures

The overall incidence of seizures under ALL treatment was 5.5% (81/1464 patients). Two patients with seizures during ALL treatment had had previous history of febrile seizures: one patient had had generalized epilepsy but was treatment free three years prior to ALL diagnosis and one patient had been diagnosed with rolandic epilepsy with no AED treatment four years prior to ALL diagnosis. The cumulative incidence of seizures was 1.7% (95% CI: 1.2-2.5) at

one month and 5.3% (95% CI: 4.2-6.5) at one year from ALL diagnosis. Most seizures occurred during the first 20 weeks of treatment (induction to delayed intensification) but sporadic cases occurred throughout treatment period (**Figure 1**). Isolated seizures without a clearly defined cause were present in 15 cases; in 13 cases isolated seizures occurred within 3 weeks of intrathecal methotrexate administration, alone or combined with intravenous methotrexate (data missing for one patient) and they might reflect methotrexate toxicity[(9)]. The underlying causes of seizures in the remaining 66 patients included PRES, SVT, SLS, possible PRES (defined as a course of symptoms compatible to PRES but lacking respective neuroimaging findings), CNS infection and systemic conditions with seizures namely hyponatremia, hypoglycemia, and multiorgan failure. The clinical characteristics of all patients, with and without seizures, in this cohort are shown in **Table 1**. The seizures were generalized (n=42), focal (n=21), and focal to bilateral tonic-clonic (n=8); data on semiology of seizures were not available in 10 cases (**Supplementary Table 1**).

Older age (10-17 years compared to 1-9 years), T cell immunophenotype, CNS involvement at diagnosis, and high-risk induction with dexamethasone treatment showed higher risk for seizures in univariable analyses (**Table 1**). Older age remained as risk a factor for seizures after applying multivariable analyses (**Table 1 and Figure 2**). The cumulative incidence of seizures in the 1-9 years group was 1.5% (95% CI: 1.0-2.4) at one month and 4.3% (95% CI: 3.2-5.6) at one year. The cumulative incidence of seizures in the 10-17.9 years group was 2.3% (95% CI: 1.1-4.8) at one month and 9.0% (95% CI: 6.2-12.9) at one year.

3.3 Other symptoms and signs in patients with seizures

Apart from seizures, some patients also displayed signs or symptoms of encephalopathy, headache, paresis, nausea, dysphasia, dyspraxia, visual field defects, sensory disturbances,

psychosis, fever, constipation, abdominal pain in various combinations and frequencies. See **Supplementary Figure 1** for the distribution of various symptoms among patients according to underlying CNS toxicity.

3.4 Work-up

Electroencephalogram (EEG) recordings were performed in 52 patients with seizures and were pathological in 43/51 cases (EEG data is missing for one patient). The EEG findings, as described, include slow activity with no closer specification (n=16), focal epileptiform or suspect epileptiform activity (n=11), encephalopathy (n=6), seizure activity including epilepsia partialis continua (n=3), status epilepticus (n=3), postictal status (n=1), suspect generalized epileptiform activity (n=1), and drug-induced abnormal activity (n=1); pathological EEG result is missing for one patient.

Of the 81 patients with seizures, neuroimaging was performed at least once in 75 cases. Sixty-six patients were examined with brain magnetic resonance imaging (MRI), median days to MRI: 1 day (range: 0-20 days, data missing for 1 patient; abnormalities were observed in 58 cases). Forty-four patients were examined with brain computed tomography (CT), median days to CT: 0 days (range: 0-8 days; abnormalities were observed in 31 cases). Thirty-seven patients underwent both brain MRI and CT, median days to MRI or CT: 0 day (range: 0-16 days; abnormal findings in both examinations were present in 27 cases, only in MRI in 7 cases and only in CT in 0 cases). Neuroimaging was not performed in six patients with seizures; two of whom had isolated seizures, one had hyponatremia, one had hypoglycemia, one had possible PRES, and one had multiorgan failure. Follow up brain MRI was performed in 47 patients (data missing for three patients); median time from neurotoxicity to follow-up MRI was 5 weeks (range: 0-179 weeks; abnormalities were observed in 23 cases). Follow up

brain CT was performed in eight patients (data missing for four patients); median time to follow up CT from neurotoxicity was12 weeks (range: 4-52 weeks, data missing for 1 patient; abnormalities were observed in five cases).

3.5 Treatment

Antiepileptic drugs (AEDs) were administered to 57 patients with seizures, along with other treatments for the underlying conditions. The most frequently administered benzodiazepine was diazepam followed by midazolam, clonazepam, and clobazam. The most frequently administered AED, other than benzodiazepines, was levetiracetam followed by phenytoin, valproate, phenobarbital, topiramate, lamotrigine, and oxcarbazepine. The median duration of treatment with AEDs was 4.4 weeks (range: 0.1-177.7 weeks), data missing for 34 cases.

For the treatment of underlying neurotoxicities, 34 patients received antihypertensives, six patients received dextromethorphan (three with PRES, two with SLS and one with isolated seizures), two patients received intravenous immunoglobulins, one patient received aminophylline, and one patient received magnesium. Patients with SVT received anticoagulants and patients with bacterial or viral infections received respective treatments. Forty-two patients were admitted to the ICU during the course of their seizures and underlying causes. Modifications of chemotherapy including postponement of treatment and dose reduction were reported in 38 patients (most frequently methotrexate but also vincristine, asparaginase, mercaptopurine, high-risk block-treatment, cyclophosphamide, dexamethasone, daunorubicin, and cytarabine).

3.6 Recurrent seizures during ALL treatment and outcome at last follow up

At the acute phase of CNS toxicity two patients had multiple seizures lasting more than one week, seven patients had multiple seizures lasting one to seven days, 33 patients had multiple seizures lasting up to 24 hours and 24 patients had single seizures with various duration (data are missing for 15 patients).

Seven patients had repeated seizures during ALL treatment after first CNS toxicity episode occurrence (median 6 months; range 2-26 months). One of these patients had ongoing prophylactic AED medication. Recurrence of seizures was related to methotrexate treatment in two cases and recurrence of PRES in one case; no triggering factor was described in four cases. We do not have data for recurrence of seizures after the end of ALL treatment for all patients.

At the last follow-up 74/81 patients were alive, (median 5.1 years; range 1.7-9.2 years). Totally 11 ALL survivors who displayed seizures had an epilepsy diagnosis. Epilepsy diagnosis for these 11 patients was made at acute phase, reccurence of seizures or after the end of ALL-treatment (median 12 days; range 0-1535 days). Three patients had ongoing epilepsy diagnosis and AED treatment at last follow up whereas AED treatment was successfully withdrawn in eight patients after 18-40 months, median 24 months.

Nine of the 11 patients with epilepsy were initially evaluated with brain MRI. Seven patients had MRI changes typical of PRES, one patient had possible PRES with unspecific cortical ischemic lesions in the occipital lobe and in pons, and one patient had isolated seizures with discreet increased T2 signal in the right temporal lobe. A follow-up MRI was performed in eight patients and in three of them signal abnormalities remained ‑ all previous PRES cases. Although the majority of patients with epilepsy had abnormal MRI findings and PRES as

underlying neurotoxicity, neither pathological initial MRI findings, pathological follow-up MRI findings or PRES were statistically significant risk factors for epilepsy diagnosis (data not shown).

See **Table 2** for underlying causes, work-up, treatment strategies, and outcome in patients with seizures.

4. Discussion

In this study, of patients with ALL treated according to the NOPHO ALL2008 protocol, 5.5% had seizures, most commonly as a manifestation of PRES or SVT or as isolated seizures. Children with ALL treated with various protocols have had an incidence of seizures between 1.5% and 13%[1-4, 25]. Epilepsy has previously been described as outcome of ALL patients with seizures, but the reported frequency varies presumingly due to different treatment protocols, use of neurotoxic cranial irradiation in previous studies and different length of follow up of patients[1, 25, 26]. Likewise, reports on recurrence of seizures under chemotherapy after first manifestation of neurotoxicity vary[25, 26]. The most common underlying etiologies for seizures reported by now have been leukoencephalopathy, cerebral infarction, hypertension, or metabolic disturbances[25, 27-29]. Here, PRES was the predominating underlying neurotoxicity under childhood ALL treatment in patients with seizures [5, 17, 30-32] which might reflect higher awareness of PRES and difficulties in differential diagnoses among neurotoxicities under ALL treatment[17, 33]. Interestingly PRES seems to be related to epilepsy diagnosis among ALL patients, as shown even previously[32], even though this relation did not reach statistical significance in this study. Seizures are often related to antileukemic agents [3, 18, 25, 29, 34]. The NOPHO ALL2008 protocol[19-21] includes dexamethasone in high-risk induction and high doses of methotrexate, vincristine and

asparaginase, which might contribute to the risk of neurotoxicity[3, 5, 25, 34, 35]. In contrast to an earlier study we did not find that females had a higher risk for seizures[25].

Older age as risk factor for seizures in ALL pediatric patients was not a surprising result as older age has previously been related to a higher risk for further toxicities including thrombosis, pancreatitis, and osteonecrosis[36-38]. Adolescents with ALL have worse overall outcomes, which could be due to a higher frequency of T cell leukemia, KMT2A rearrangement in leukemic cells, and higher post-induction minimal residual disease[36, 37]. T-cell leukemia, CNS involvement at diagnosis and induction with dexamethasone showed higher risk for seizures in univariate analyses but not in multivariable analyses. Another previous study on pediatric ALL and seizures showed a trend for association between more intensive ALL treatment and seizures without reaching statistical significance[4].

The association of chemotherapeutic agents with distinct neurotoxicities should be considered in differential diagnoses. PRES was the most common underlying syndrome in patients with seizures in our study and is more frequent in the NOPHO protocols compared to other reports, possibly due to the high intensity of vincristine treatment during the first three months of treatment[19-21]. SLS is related to and occurs within three weeks of administration of methotrexate[39, 40]. Most isolated seizures occurred within 3 weeks after methotrexate administration and could be attributed to methotrexate toxicity[9]. Methotrexate is administrated at least every three weeks during the first months of NOPHO ALL2008 treatment. Asparaginase and glucocorticosteroids are related to thromboses, including SVT[8, 41]. Electrolyte disturbances, hypoglycemia, CNS infections, and multiorgan failure should also be considered at the onset of seizures. MRI is the most important diagnostic examination and modern MRI techniques can be beneficial in differentiating SLS and PRES[42, 43].

Administration of AEDs and supporting of vital bodily functions are the cornerstones for treatment of seizures. AEDs are used in the treatment of prolonged or relapsing seizures regardless of underlying etiology[44]. According to the present study, use of enzyme inducing AEDs phenytoin, phenobarbital and oxcarbazepine was common in ALL patients. However clinicians should be aware that concomitant use of liver enzyme inducers and chemotherapy should be discouraged due to diverse interactions and therefore alternative AEDs should be recommended[45]. The decision to use prophylactic AED treatment should be grounded on the presence of risk factors for relapse, namely abnormal EEG findings and abnormal neuroimaging findings[46]. According to guidelines on withdrawal of AEDs in epilepsy, discontinuation of AEDs should be considered after 2 seizure-free years as soon as seizures are controlled with respect to clinical development and possible persistence of abnormalities in EEGs or other documented etiology[47]. There are no closer established guidelines for this patient group, but it is reasonable to consider withdrawal of AEDs earlier than 2 seizures-free years in cases where the triggering factors are removed and the patients show good recovery clinically and radiologically. Furthermore, it is important to treat the underlying cause of neurological symptoms[46].

The retrospective nature of this study, missing data, lack of neuroimaging and EEG reviews and unclear proportion of child neurologist evaluation of seizures and details on how epilepsy diagnosis was established are limitations of our study that might have unclear impact on classification of seizures and epilepsy diagnosis. Still, the results reflect the clinical praxis and should encourage cooperation between child oncologists and child neurologists for optimal assessment of seizures and follow up of epilepsy.

5. Conclusions

Seizures are a common adverse effect during the treatment of ALL. Older pediatric patients have higher risk of seizures. Seizures are most often reported in patients with PRES during ALL treatment. Epilepsy diagnosis after seizures has been reported in more than every tenth ALL survivors but the frequency of long-term epilepsy has been lower.

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Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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413 **Figure legends**

414

415 **Figure 1.** Distribution of seizures according to underlying cause during the treatment period.
416 PRES=posterior reversible encephalopathy syndrome, SVT=sinus venous thrombosis,
417 SLS=stroke like syndrome. “Other” includes possible PRES, hyponatremia, hypoglycemia,
418 central nervous system infection, and multiorgan failure.

419

420 **Figure 2.** Cumulative incidence of seizures.

421

422 **Supplementary Figure 1.** Clinical symptoms of underlying causes of seizures in pediatric
423 ALL patients. PRES=posterior reversible encephalopathy syndrome, SVT=sinus venous
424 thrombosis, SLS=stroke like syndrome.

425

Table 1. Clinical characteristics of patients with seizures and risk factors for seizures.

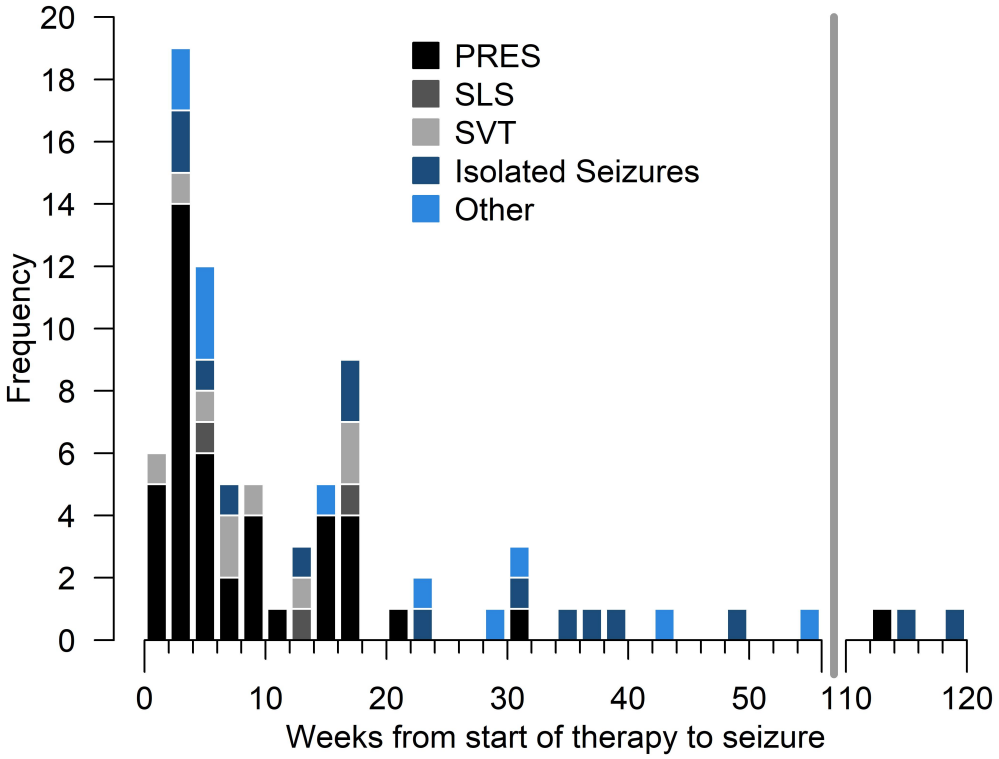
	Controls (n=1383)	Seizure (n=81)	Univariable HR (95% CI; p)	Multivariable HR (95% CI; p)**
Age in years (median, IQR, range)	4.5 (2.8-8.3; 1.0-18.0)	7.8 (4.4-11.3; 1.7-17.0)	1.09 (1.04 - 1.13; <0.001)	-
Age group, n (%)				
1-9 years	1111 (80.3)	53 (65.4)	Ref	Ref
10-17 years, n (%)	272 (19.7)	328 (34.6)	2.15 (1.36 - 3.41; 0.001)	1.95 (1.21 - 3.13; 0.01)
Sex				
Female	632 (45.7)	40 (49.4)	Ref	Ref
Male	751 (54.3)	41 (50.6)	0.86 (0.56 - 1.33; 0.50)	0.78 (0.50 - 1.22; 0.28)
Immunophenotype, n (%)				
BCP ALL	1213 (87.7)	61 (75.3)	Ref	Ref
T cell ALL	170 (12.3)	20 (24.7)	2.35 (1.42 - 3.90; <0.001)	1.60 (0.64 - 4.05; 0.32)
CNS status*, n (%)				
CNS 1	1205 (87.1)	64 (79.0)	Ref	Ref
CNS 2 or 3	174 (12.6)	17 (21.0)	1.83 (1.07 - 3.13; 0.03)	1.62 (0.93 - 2.781; 0.09)
Induction therapy, n (%)				
Prednisolone	1120 (81.0)	56 (69.1)	Ref	Ref
Dexamethasone	251 (18.1)	25 (30.9)	2.00 (1.25 - 3.21; <0.001)	1.09 (0.45 - 2.65; 0.85)

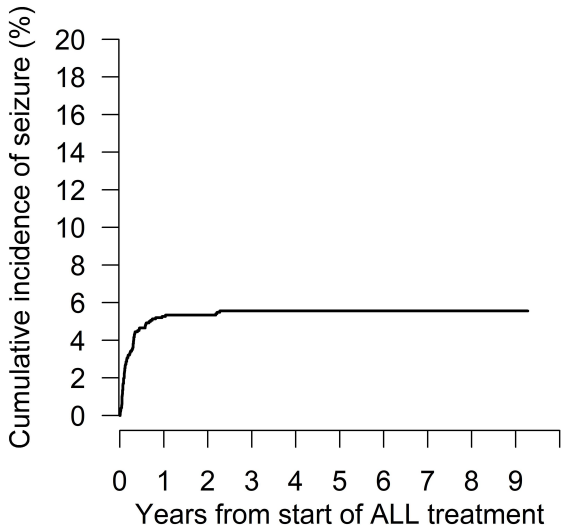
*4 missing values for the controls ** Including Age group, sex, immunophenotype, CNS status, induction therapy. HR=hazart ratio, CI=confidence interval, IQR= interquartile range, CNS=central nervous system.

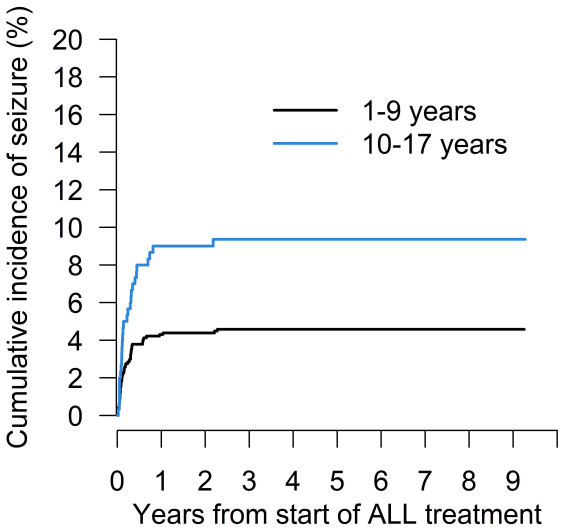
Table 2. Underlying causes to seizures, work up, treatment strategies and outcome in patients with seizures.

Underlying CNS toxicity	**Number of patients (%)**
PRES	43/81 (53.0)
SVT	9/81 (11.1)
Isolated seizures	15/81 (18.5)
SLS	3/81 (3.7)
Possible PRES	3/81 (3.7)
Hyponatremia	3/81 (3.7)
Hypoglycemia	2/81 (2.5)
CNS infection	2/81 (2.5)
Multiorgan failure	1/81 (1.2)
Neuroimaging studies	
Brain-MRI performed	66/79 (83.5)
Abnormal brain-MRI	58/66 (87.9)
Brain-CT performed	44/79 (55.7)
Abnormal brain-CT	31/44 (70.5)
Both brain-MRI and brain-CT performed	37/79 (46.8)
Both brain-MRI and brain-CT abnormal	27/37 (73.0)
EEG	
EEG performed	52/77 (67.5)
Abnormal EEG	43/51 (84.3)
Treatment strategies	
Anticonvulsants/antiepileptics	57/73 (78.1)
ICU support	42/78 (53.8)
Temporary adjustment of chemotherapy	38/78 (48.7)
Antihypertensives	34/73 (46.6)
Steroids	18/71 (25.4)
Intravenous immunoglobulin	2/73 (2.7)
Magnesium	1/68 (1.5)
Aminophylline	1/67 (1.5)
Outcome	
Survivors	74/81 (91.4)
Epilepsy	11/70 (15.7)

Denominator <81 indicates that data were not available for all patients regarding the respective title. CNS=central nervous system, PRES=posterior reversible encephalopathy syndrome, SVT=sinus venous thrombosis, SLS=stroke like syndrome, MRI=magnetic resonance imaging, CT=computed tomography, EEG=electroencephalographem, ICU=intensive care unit.







Seizures during treatment of childhood acute lymphoblastic leukemia: a population-based cohort study

Highlights

- Seizures are common in pediatric acute lymphoblastic leukemia (ALL) patients.
- Particularly posterior reversible encephalopathy syndrome (PRES), but also sinus venous thrombosis, methotrexate related stroke-like syndrome, methotrexate, vincristine and diverse cytostatica toxicity, central nervous system infections, electrolyte disturbances were underlying causes of seizures in ALL.
- Older age was an independent risk factor for seizures in pediatric ALL.
- Epilepsy was common sequelae after seizures and was most common in ALL patients having displayed PRES.

Seizures during treatment of childhood acute lymphoblastic leukemia: a population-based cohort study

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.