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ORIGINAL PAPER

Paediatrics

Severe steroid-related neuropsychiatric symptoms during paediatric acute lymphoblastic leukaemia therapy—An observational Ponte di Legno Toxicity Working Group Study

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on behalf of the Ponte Di Legno Neurotoxicity Working Group

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Summary

Steroids are a mainstay in the treatment of acute lymphoblastic leukaemia (ALL) in children and adolescents; however, their use can cause clinically significant steroid-related neuropsychiatric symptoms (SRNS). As current knowledge on SRNS during ALL treatment is limited, we mapped the phenotypes, occurrence and treatment strategies using a database created by the international Ponte di Legno Neurotoxicity Working Group including data on toxicity in the central nervous system (CNS) in patients treated with frontline ALL protocols between 2000 and 2017. Ninety-four of 1813 patients in the CNS toxicity database (5.2%) experienced clinically significant SRNS with two peaks: one during induction and one during intensification phase. Dexamethasone was implicated in 86% of SRNS episodes. The most common symptoms were psychosis (52%), agitation (44%) and aggression (31%). Pharmacological treatment, mainly antipsychotics and benzodiazepines, was given to 87% of patients while 38% were hospitalised due to their symptoms. Recurrence of symptoms was reported in 29% of patients and two previously healthy patients required ongoing pharmacological treatment at the last follow up. Awareness of SRNS during ALL treatment and recommendation on treatment strategies merit further studies and consensus.

KEYWORDS
ALL, children, neuropsychiatric symptoms, steroids

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For affiliations refer to page 1457.

INTRODUCTION

Advances in the treatment of paediatric acute lymphoblastic leukaemia (ALL) have led to a current survival of more than 90% for children and adolescents in developed countries.[1] However, patients remain at high risk of significant acute, subacute and chronic side effects related to treatment.[2] One of the most burdensome side effects for patients and families is the nearly universal occurrence of adverse behavioural symptoms associated with steroid administration, while a subset suffers from disabling steroid-related neuropsychiatric symptoms (SRNS).[2–7]

Steroids, in the form of the glucocorticoids prednisolone and dexamethasone, were introduced in the treatment of ALL in the early 1950s and remain a mainstay in the backbone of ALL chemotherapy regimens. They are administered during multiple phases of therapy including induction, delayed intensification/re-induction and continuation/maintenance, and are important for systemic and central nervous system (CNS) leukaemia control. Dexamethasone, which penetrates the blood–brain barrier more effectively, has been related not only to enhanced antileukaemic effect but also increased toxicity.[8–10] Some variation is noted regarding the type of steroid, dose and duration of exposure across protocols.[5,10,11] The antileukaemic effect of steroids is derived from their receptor-induced apoptosis of cancer cells as well as anti-inflammatory properties.[10,12–14] The toxicity of steroids is also receptor-mediated through inhibition of cytokine production, alterations of oncogene expression, cell cycle arrest and apoptosis.[10,15] Moreover, steroids have been reported to affect the hypothalamic–pituitary–adrenal axis and hippocampus, as well as the neurotransmitters serotonin and dopamine, which may contribute to the risk of developing SRNS.[14,16]

Treatment-related adverse effects in ALL related to steroids alone or in combination with other chemotherapy agents include osteopathy, hyperglycaemia, hypertension, thrombosis and posterior reversible encephalopathy syndrome. Most of these steroid side effects are well described, but data concerning SRNS are scarce.[2,5,10,14,16–18] The most common SRNS in paediatric ALL patients are reported to be euphoria, aggression, anxiety, insomnia, obsessive thoughts, hyperactivity, pressured speech, loss of emotional control and psychosis.[5,14,16,19–23] A proposed SRNS severity grading refers to subtle symptoms such as slight or moderate euphoria as well as increased joviality and optimism as Grade 1. Grade 2 SRNS include profound mood uplift including restlessness, insomnia and accelerated mental activity. Grade 3 SRNS include severe anxiety and obsessive symptoms. Grade 4 SRNS include the most severe symptoms such as hallucinations and delusions.[6] There is however no Common Terminology Criteria for Adverse Events (CTCAE) classification of SRNS severity and therefore different definitions prevail in diverse reviews.[6,7,24,25]

Studies on adult and paediatric patients with diverse underlying conditions suggest that psychiatric adverse effects are dose-dependent and may respond well to steroid dose-reduction, switch to alternate steroid or discontinuation.[14,16,20] When dose-reduction or discontinuation of steroids is not an option, administration of antipsychotics or benzodiazepines, antidepressants or neuroleptics may provide some symptom relief.[14,16]

As studies on SRNS in paediatric ALL are infrequent, our goal is to map the phenotypes and course of clinically significant SRNS as part of a large international effort to better understand the predisposing factors, clinical course and outcomes of chemotherapy-related CNS toxicity in children and adolescents with ALL.

METHODS

Patients with SRNS were identified from a CNS toxicity database which included 1813 children and young people, aged 1–25 years, treated according to frontline ALL protocols. The database was created by the Ponte di Legno (PdL) Toxicity Working Group across 14 study groups representing 23 countries using different treatment protocols between 2000 and 2017 who reported CNS toxicities, including SRNS.[26,27] The total intended cumulative dose of dexamethasone and prednisone/prednisolone differed among protocols as well as between arms of each protocol. Data capture was performed retrospectively and included demographics, leukaemic phenotype and risk grouping, neurotoxicity symptoms, steroid type and dose and outcome data. For the purpose of this study, clinically significant SRNS were defined as severe neurobehavioural symptoms that occurred from initiation of steroid therapy up to 2 weeks post cessation, which required hospitalisation, prolongation of current hospitalisation, alteration in steroid dose, change in steroid or use of medication(s) for management of neuropsychiatric symptoms. Patients with less severe or subtle symptoms were not included. Results refer to the first SRNS in patients and not recurrent episodes. Patients with SRNS after haematopoietic stem cell transplantation, or with simultaneous other CNS or metabolic toxicity, were excluded. Classification of ALL risk for children with B-ALL at diagnosis was defined as per National Cancer Institute (NCI).[28] Descriptive statistics were applied to present results; analyses were performed by SPSS version 26 for Windows (SPSS Inc., Chicago, IL). Source data varied from case notes to central trial adverse event reports, in some cases data fields were missing: a denominator <94 implies available data, when relevant.

RESULTS

Epidemiological features of patients

Ninety-four of 1813 patients in the PdL database met the inclusion criteria for clinically significant SRNS (5.2% of reported CNS toxicities) as reported by 10 study groups (Table S1).

Median time from ALL diagnosis to last follow-up was 6.0 (interquartile range [IQR]: 3.0–8.0; data not available in four cases) years and median time from SRNS to last follow-up was 5.0 (IQR: 2.25–7.0; data not available in six cases) years. Median age of patients at time of ALL diagnosis was 6.7 (IQR: 3.0–13.7; data not available in one case) years. One patient had a prior attention-deficit hyperactivity disorder diagnosis and two patients had trisomy 21, without any previously reported neuropsychiatric symptoms.

Of patients with SRNS, 56/93 were males (60.2%, data not available in one case). Dexamethasone was the most common steroid administered to patients at the time of SRNS (85.5%), (data not available for 32 patients). At diagnosis, 18.3% of patients had T-cell immunophenotype, 16.0% had $>50\times10^9$ white blood cells, 37% of patients with B-ALL ($n=76$, data not available in one case) were NCI high risk, and 3.4% had CNS3 status; these patients would normally be allocated increased CNS-directed therapy (all clinical features are presented in Table 1).

Clinical course of SRNS

Median time to SRNS from ALL diagnosis was 5.0 (IQR range: 1.0–7.0) months ($N=90$). SRNS occurrence showed two clear peaks: one during the first month of treatment and one during fifth and sixth months (Figure 1). Occurrence of SRNS was most common during intensification phases defined here as consolidation/delayed intensification/re-induction (63.8%), followed by induction (24.5%) and maintenance (11.7%). Details on specific symptoms were available for 93/94 patients with SRNS with psychosis, agitation and aggression predominating. Symptoms of insomnia, emotional lability, hallucinations and disorganised speech were over-represented during intensification compared to induction (Table S2). Of patients with SRNS during intensification with available data on steroid type (46/60) 44 received dexamethasone: 34 of them received ≥10 mg/m^2/day and three received <10 mg/m^2/day (data on dose were not available in seven cases), while two patients received prednisone/prednisolone one of whom received 60 mg/m^2/day (dose was not available in the other case). Among patients with SRNS during induction with available data on steroid type (11/23) six received 60 mg/m^2/day prednisone/prednisolone, one received <10 mg/m^2/day and another ≥10 mg/m^2/day dexamethasone (data on dexamethasone dose were not available in three cases).

The most commonly reported symptom was psychosis, followed by agitation and aggression, also known as 'positive' symptoms. These symptoms showed no sex variation, but insomnia appeared more common among girls and suicidal/homicidal ideation and somnolence in boys (Table 2; Figure 2). Symptoms by age group and sex are shown in File S1, although small numbers of girls in the older age groups makes interpretation of sex differences in adolescents difficult. Most patients ($n=48$) had a single symptom, but there was considerable variation with 45 patients having two or

TABLE 1 Demographic and clinical features of patients with severe SRNS ($N=94$).[a]

Demographic and clinical features	*n*/*N* (%)
Age at leukaemia diagnosis	
<10 years	60/93 (64.5)
10–15 years	16/93 (17.2)
>15 years	17/93 (18.3)
Sex	
Male	56/93 (60.2)
Female	37/93 (39.8)
Immunophenotype	
B-lineage	76/93 (81.7)
T-lineage	17/93 (18.3)
Cytogenetics	
t(12:21) Tel-AML1	12/47 (25.5)
High hyperdiploidy	6/47 (12.8)
MLL rearrangement	1/47 (2.1)
Other[b]	22/47 (46.8)
WBC ($\times10^9$) at diagnosis	
<50	79 (84.0)
>50	16 (16.0)
CNS status[c]	
CNS1	76/89 (85.4)
CNS2	10/89 (11.2)
CNS3 by CM or FCI	3/89 (3.4)
NCI risk arm at diagnosis ($n=75$), B-ALL[d]	
Standard risk	47/75 (62.7)
High risk	28/75 (37.3)
Treatment phase	
Induction	23/94 (24.5)
Consolidation/delayed intensification/ re-induction	60/94 (63.8)
Maintenance	11/94 (11.7)
Steroid type associated with episode of SRNS	
Dexamethasone	53/62 (85.5)
Prednisone/prednisolone	9/62 (14.5)
Steroid dose	
Dexamethasone ($n=40$)	
≥10 mg/m^2/day	36/40 (90.0%)
<10 mg/m^2/day	4/40 (10.0%)
Prednisone/prednisolone ($n=8$)	
60 mg/m^2/day	7/8 (87.5%)
40 mg/m^2/day	1/8 (12.5%)

Abbreviations: ALL, acute lymphoblastic leukaemia; CM, cytomorphology; CNS, central nervous system; FCI, flow cytometric immunophenotyping; NCI, National Cancer Institute; SRNS, steroid-related neuropsychiatric symptoms; WBC, white blood cells.

[a]Denominator <94 implies missing data.

[b]Other included t(7;9), del 12p, t(9;18), and complex cytogenetics of uncertain origin and 'good risk' (not otherwise specified, $n=6$).

[c]CNS1: no CNS leukaemia, CNS2: ≤5/μL cells in the cerebrospinal fluid and blasts on cytospin, CNS3: >5/μL cells in the CSF and leukaemic blasts by CM, or clinical/radiological signs of CNS leukaemia.

[d]Standard risk: children younger than 10 years with WBC $<50\times10^9$/L, high risk: children aged ≥10 years and/or children who have WBC $\geq50\times10^9$/L.

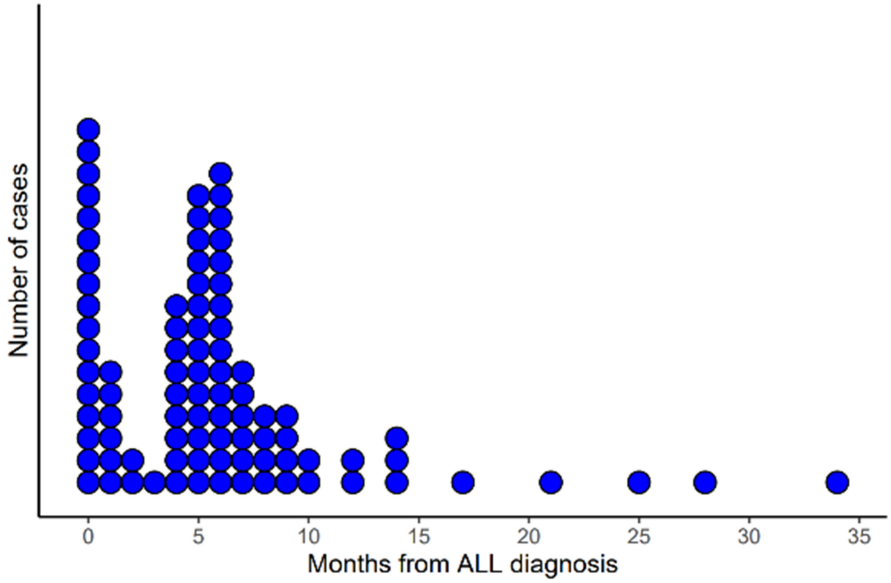


FIGURE 1 Distribution of cases with severe steroid-related neuropsychiatric symptoms during the treatment period.

TABLE 2 Frequency of reported symptoms in 93 patients with SRNS of whom 56 were males and 36 females.[a]

Symptoms	All patients, *n* (%)	Males, *n* (%)	Females, *n* (%)
Psychosis	48 (51.6)	30 (53.6)	18 (50.0)
Agitation	41 (44.1)	24 (42.3)	16 (44.4)
Aggression	29 (31.2)	18 (32.1)	10 (27.8)
Insomnia	20 (21.5)	9 (16.1)	10 (27.8)
Emotional lability	16 (17.2)	9 (16.1)	6 (16.7)
Hallucinations	14 (15.1)	8 (14.3)	6 (16.7)
Disorganised speech	10 (11.1)	7 (12.5)	3 (8.3)
Suicidal ideation	9 (10.0)	8 (14.3)	1 (2.8)
Somnolence	7 (7.5)	7 (12.5)	0 (0.0)
Personality changes	5 (5.4)	3 (5.4)	2 (5.6)
Catatonia	3 (3.2)	2 (3.6)	0 (0.0)
Homicidal ideation	3 (3.2)	3 (5.4)	0 (0.0)
Mood changes	1 (1.1)	0 (0.0)	1 (2.8)
Depression	2 (2.1)	1 (1.8)	1 (2.8)
Mania	1 (1.1)	1 (1.8)	0 (0.0)
Delirium	1 (1.1)	1 (1.8)	0 (0.0)
Logorrhoea	1 (1.1)	1 (1.8)	0 (0.0)
Dystonic movements	1 (1.1)	0 (0.0)	1 (2.8)

Abbreviation: SRNS, steroid-related neuropsychiatric symptoms.
[a]Data on sex not available for one patient.

more symptoms. In most cases, symptoms lasted 1 week to 1 month and 12/32 patients with available data (37.5%) required hospitalisation for their symptoms. Psychopharmacological treatment was administered in a total of 52/60 (86.7%) patients with available data. It should be noted that need for medication was among the inclusion criteria for our study which may explain the high proportion of patients reported here. Most patients required a single medication ($n = 37$), but a combination of 2–3 medications ($n = 13$) or combination of more than three medications ($n = 2$) were also reported. Antipsychotics and benzodiazepines were the most frequent medications (Figure 3). The median duration of pharmacological treatment was 16 (IQR range: 9.3–90.0) days. Other interventions included the discontinuation of steroids (11.8%) (four cases in maintenance, one in induction and one in re-induction), dose reduction of steroids (11.8%) (two cases in induction, two cases in maintenance and one case in delayed intensification) or change in steroid type from dexamethasone to prednisone/prednisolone (11.8%) (five cases in delayed intensification/re-induction, and one in induction); nevertheless, in the majority of cases steroid treatment was continued as planned (64.7%), (Table 3).

Outcome

Of 81 patients with follow-up data, 79 (97.5%) with SRNS were alive, and the two deaths were unrelated to SRNS (sepsis and relapsed ALL). Recurrence of symptoms was reported in 12/41 patients (29.3%). Data for time to recurrent symptoms were available for 7/12 patients with the median time to recurrence of symptoms of 3 (IQR: 1.0–3.0) months. Management of steroid treatment in patients with recurrent symptoms were available for eight patients: four of them had continued with steroid treatment as planned despite their first episode of SRNS, in two cases dexamethasone was switched to prednisone/prednisolone, in one case steroid dose was reduced and in one case steroid treatment was discontinued. Two previously healthy patients, with no known family history of neuropsychiatric disorder, had ongoing SRNS symptoms at last follow-up (17 and 34 months after debut of SRNS); both of them also had ongoing pharmacological treatment for SRNS.

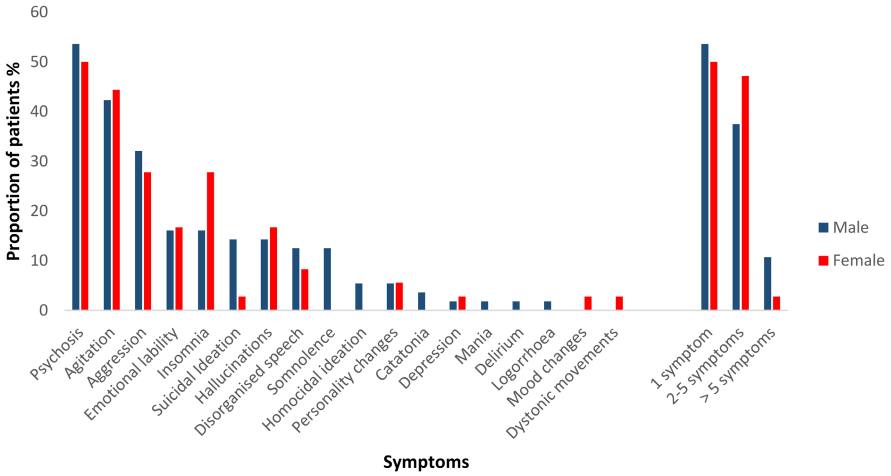
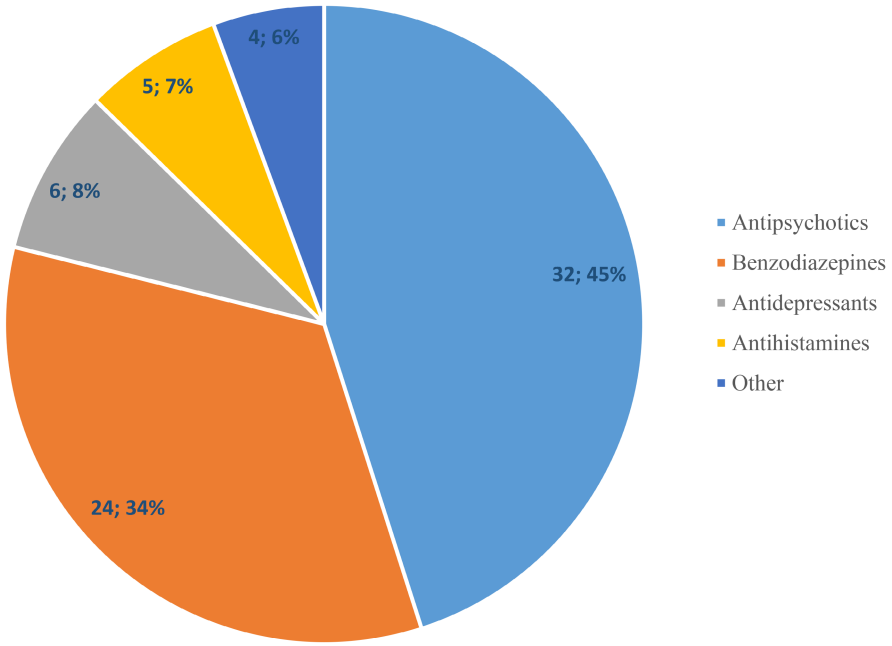


FIGURE 2 Distribution of symptoms in patients according to sex and number of cases with 1, 2−5 and >5 symptoms. Data on sex missing for one patient with five symptoms.



Category of medication				
Antipsychotics (n)	**Benzodiazepines (n)**	**Antidepressants (n)**	**Antihistamines (n)**	**Others (n)**
Risperidone (11)	Lorazepam (11)	Sertraline (3)	Promethazine (3)	Anti-seizure medication (valproate) (1)
Haloperidol (7)	Clonazepam (5)	Fluvoxamine (1)	Chlorpheniramine (1)	Hormone (melatonin) (1)
Olanzapine (9)	Benzodiazepines NOS (2)	Citalopram (1)	Diphenhydramine (1)	Neuroleptic (levomepromazin) (1)
Aripiprazole (2)	Diazepam (2)	Trimipramine (1)		Sedative (zolpidem) (1)
Chlorpromazine (2)	Midazolam (2)			
Quetiapine (1)	Oxazepam (1)			
	Delorazepam (1)			

FIGURE 3 Medications used to treat SRNS (*n*; %). NOS, not otherwise specified; SRNS, steroid-related neuropsychiatric symptoms.

TABLE 3 Duration of symptoms and treatment strategies in patients with SRNS ($n = 94$).[a]

Duration of symptoms	
<1 week	8/29 (27.6)
1 week to 1 month	13/29 (44.8)
1 month to 1 year	8/29 (27.6)
Ongoing symptoms	2/39 (5.1)
Hospitalisation	
Hospitalisation due to symptoms	12/32 (37.5)
Treatment strategies	
Continuation of steroids as planned	33/51 (64.7)
Discontinuation of steroids	6/51 (11.8)
Dose reduction of steroids	6/51 (11.8)
Change in steroid type	6/51 (11.8)
Medications for the symptoms	52/60 (86.7)
Recurrence of symptoms	
Recurrent symptoms	12/41 (29.3)

Abbreviation: SRNS, steroid-related neuropsychiatric symptoms.

[a]Denominator <94 implies missing data.

DISCUSSION

This is the largest case series of severe steroid-related neuropsychiatric side effects occurring on frontline ALL therapy. SRNS accounted for 5.2% of CNS toxicities in this international CNS toxicity database of paediatric patients with ALL. Prior data suggest no statistical or clinically significant difference in SRNS caused by dexamethasone compared to prednisone/prednisolone; however, a more negative effect of dexamethasone was noted in older children (>6 years).[5,29–31] In this cohort, use of high dose dexamethasone ≥10 mg/m^2/day was more common than use of lower dose dexamethasone or prednisone/prednisolone in patients who displayed SRNS at all ages; however, as the use and dose of dexamethasone varied between protocols, one cannot assume causality from steroid type and dose intensity. SRNS occurrence had two peaks: one during the first month and one during the fifth and sixth months of treatment—reflective of treatment periods (induction, delayed intensification/re-induction) which commonly involve prolonged high-dose steroid use. This is similar to timing in a longitudinal study on the emotional impact of dexamethasone during ALL treatment, which was notably more severe during re-induction/consolidation (with the caveat that the sample size of that cohort was small).[32] Moreover, during these two treatment periods, patients also often receive asparaginase that may aggravate the side effects of dexamethasone through hypoalbuminaemia.[33]

The prevalence of SRNS in this cohort was higher in boys – especially in children aged >10 years. There is a slightly higher incidence of ALL in boys; incidence in males versus females in the USA: 45 cases per million children versus 39 cases per million children per year, respectively.[34] However, this difference in ALL incidence between boys versus girls is less pronounced than the difference in prevalence of SRNS in boys versus girls (60.2% vs. 39.8%, respectively)—suggesting that SRNS is more prevalent in boys. Both girls and boys presented with a similar symptom profile—dominated by 'positive' symptoms of psychosis, agitation and aggression. We examined whether symptom presentation changed with age and sex in response to the potential impact of sex hormones on the hypothalamic–pituitary–adrenal axis which controls mood.[35] When comparing younger children (<10 years) with peri-pubertal (10–15 years) and post-pubertal (>15 years) patients, emotional lability, sleep disturbance and disorganised speech peaked in peri-pubertal patients, while both peri- and post-pubertal patients presented with more psychosis than younger children. In contrast, with the exception of psychosis, the symptom profile of pre- and post-pubertal patients was approximately the same. The low case numbers of peri- and post-pubertal girls make clear conclusions about the impact of female versus male puberty in SRNS occurrence impossible. It has previously been suggested that SRNS are more common in girls, and that there was a trend for boys to display aggression and girls depression, but data supporting this suggestion are less robust.[5,14,36] Future studies which include large patient numbers and a control population of patients without SRNS, may illuminate potential sex differences in incidence and manifestations of SRNS as well as impact of puberty on their occurrence.

A significant majority of patients (87%) required pharmacological intervention to manage their symptoms. Additionally, 38% of patients needed hospitalisation or prolongation of hospitalisation and 35% required a modification in their steroid treatment course (either discontinuation, dose reduction or change in steroid type). These interventions are in line with limited previous reports and recommendations on patients treated with steroids due to diverse underlying diseases who displayed similar SRNS.[14,16,19,20]

Most available studies on steroids' effect on patients behaviour, mood, sleep and quality of life focus on maintenance chemotherapy at a time when the acuity of the illness and intensity of chemotherapy is decreased and patients spend more time in day-care settings or home, compared to induction and delayed intensification/re-induction periods.[21,31,37–41] In our study, the prevalence of severe SRNS during maintenance is relatively low, probably because symptoms during maintenance did not meet the severity threshold for inclusion in the study. Awareness of less severe steroid treatment-related adverse effects during maintenance is also important, in order to provide anticipatory guidance and psychological support as these are distressing symptoms for patients and families.[21,37,39] There is no established intervention to prevent steroid-related neuropsychiatric adverse effects. In a recent randomised trial, the authors tested the hypothesis that the adverse neurobehavioral effects of dexamethasone depend on suboptimal activation of mineralocorticoid receptors (MR) as previously suggested.[42] Activation of both MR and glucocorticoid receptors (GR) by endogenous and exogenous glucocorticoids is

implicated in normal function of mood, behaviour and sleep. Dexamethasone has a greater affinity for GR than MR while suppressing endogenous cortisol production. The addition of a physiological dose of the MR agonist hydrocortisone in the trial failed to demonstrate benefit of this intervention to ameliorate neurobehavioural problems and support this hypothesis.[43] Another study explored potential predictive markers of dexamethasone adverse events during maintenance chemotherapy and indicated that glucocorticoid hypersensitivity may signal increased risk for dexamethasone-induced depression in patients. Further studies should examine potential predictive markers for dexamethasone toxicity before they can be applied to clinical practice.[44]

The prevalence of SRNS during paediatric ALL treatment is not yet fully elucidated; reported data vary among available studies. Most reports on SRNS in children with ALL are derived from case reports, cases series or few randomised trials comparing dexamethasone and prednisone/prednisolone.[14,36,45,46] One study in the UK, which explored the effectiveness of dexamethasone compared to prednisolone, reported findings on steroid toxicity including SRNS in 6% of patients treated with dexamethasone and in 1% of patients treated with prednisone/prednisolone.[36] Another study in the USA which also compared dexamethasone and prednisone/prednisolone, described that 1.1% (6/530) of patients treated with dexamethasone displayed SRNS; in all cases, steroids were finally switched to prednisone/prednisolone.[46] A third study of the Nordic Association of Pediatric Hematology and Oncology described that one in 1464 patients (0.07%) displayed steroid psychosis; however, it is possible that in this study all patients with SRNS were not included among reported CNS toxicities.[3] In the light of our finding that severe SRNS constitute 5.2% of reported CNS toxicity, further studies on the prevalence of SRNS, standardisation of definitions and recommendations on treatment strategies are merited.

The occurrence of SRNS can be attributed to their molecular biochemical properties; however, a recent study on steroid-related affective disorders identified family history of psychiatric disease, and not exposure to steroids, as risk factor.[9] Only three patients in our study were reported as having a family history of psychiatric disorder and the two patients with persistent SRNS symptoms at last follow-up had no known heredity to psychiatric disease. Since the prevalence of SRNS during paediatric ALL treatment is unclear and probably low, genetic studies to further illuminate the pathogenesis of SRNS may be challenging. International collaborations may support large cohorts and genome wide analysis (GWAS) may map potential genetic background of SRNS. In order to proceed to GWAS a consensus regarding phenotypes and severity grading of SRNS during the treatment of ALL is needed. Systematic comparisons of children with ALL suffering from SRNS with children treated with steroids for asthma, neurological, inflammatory or rheumatological diseases, also suffering from SRNS, may also contribute to identification of risk factors and appropriate management.

Limitations

We acknowledge limitations related to use of different treatment protocols as well as missing data since data were abstracted from various sources in this international study. In particular, the lack of a control population (matched patients treated on the same protocols but not experiencing an episode of SRNS) limits our ability to fully understand predisposing factors for development of SRNS. Another limitation of our study is that case capture varied cross protocols and trial groups. In some cases, SRNS was an adverse event of special interest but the definition may have varied from that used in this study. For example, one working group (Berlin-Frankfurt-Munich) only captured patients requiring medications for their SRNS, thus enriching the cohort for medication use. Despite this, as the largest study of SRNS in children and adolescents with ALL it increases insights into potential risk factors, current treatment and natural history of severe SRNS occurring during paediatric ALL therapy.

CONCLUSION

Severe SRNS affect treatment of patients with ALL and increase hospitalisation. Steroids are crucial in ALL treatment and cannot be easily omitted, but early identification of symptoms, prompt assessment and treatment, and proactive information to families, should ease the course of the adverse event.

AUTHOR CONTRIBUTIONS

Stavroula Anastasopoulou provided data on patients from the NOPHO group, reviewed patients' phenotypes and comorbidities, performed data analysis and drafted the paper. Gemma Swann identified all patients with SRNS, with or without other CNS toxicity, and performed data analysis. Liv Andres-Jensen played a coordinating role in the PTWG activities and critically reviewed the paper. Andishe Attarbaschi contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Shlomit Barzilai contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Daniel J. Erdelyi contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Gabriele Escherich contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Lina Hamadeh created the database, cleaned and analysed the data. Arja Harila contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Anja Moricke contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Sheena McGowan created the database, cleaned and analysed the data. Elixabet

Lopez-Lopez contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Caterina Putti contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Judit C. Sagi provided data on patients and critically reviewed the paper. Kjeld Schmiegelow contributed to the creation of the PdL database, provided data on, designed the research study and critically reviewed the paper. Nicole J. Ullrich contributed to the discussion and critically reviewed the paper. Inge M. van der Sluis contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Qurat-ul-Ain Wahid identified all patients with SRNS on the main PdL database, created the SRNS sub-database and co-supervised the sub-study. Naomi Winick contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Ester Zapotocka contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Deepa Bhojwani contributed to the creation of the PdL database, provided data on patients, designed the research study and critically reviewed the paper. Christina Halsey contributed to the creation of the PdL database, provided data on patients from the UKALL group, designed the research study and critically reviewed the paper.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for the Ponte Di Legno Neurotoxicity study was obtained by the London-Westminster Research Ethics Committee on (17/LO/1258) as well as by local ethical committees or institutional review boards in all participating countries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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