


# Parents' perception of treatment-related toxicity in children treated according to the NOPHO ALL2008 protocol for acute lymphoblastic leukemia

Nina Mogensen<sup>1,2</sup>  | Ulrika Kreicbergs<sup>1,3,4</sup> | Birgitte K. Albertsen<sup>5,6</sup> |  
Päivi M. Lähteenmäki<sup>7,8</sup> | Mats Heyman<sup>1,2</sup> | Arja Harila<sup>9</sup>

Correspondence: Nina Mogensen ([nina.mogensen@ki.se](mailto:nina.mogensen@ki.se))

## Abstract

This study aimed to assess how parents perceived treatment-related side effects during acute lymphoblastic leukemia (ALL) treatment. Parents of children 1–17.9 years at diagnosis in Sweden, Finland, and Denmark who were alive and in first remission  $\geq 6$  months after end of ALL treatment were asked to respond on specific items regarding how their child was affected by side effects related to vincristine (VCR), corticosteroids, peg-asparaginase (ASP), and maintenance therapy, as well as overall impact of these treatments, complications in general, and their perception of impact on their child in comparison with other children with ALL. Parents of 307 children responded. More than a third reported that their child had been affected to a high extent by VCR (39.7%) and corticosteroids (35.8%), with walking difficulties, muscular weakness, pain, changes in appetite, and mood swings as the most common and severe symptoms. Reporting of these toxicities was lacking from the NOPHO ALL2008 database, except for peripheral paralysis (12.1%). For distinct toxicities reported in the NOPHO ALL2008 database, for example, thrombosis and pancreatitis, parent reports were similar to the database. Although a high overall negative impact during treatment was reported, parents generally rated the impact on their child as less, or similar, to other children with ALL. Parents perceived VCR and corticosteroid therapy, in particular, to have a negative impact on their child during ALL treatment, which was not captured in the NOPHO ALL2008 toxicity reporting. Our results highlight the importance of including patient/parent-reported outcomes in toxicity reporting.

## INTRODUCTION

As acute lymphoblastic leukemia (ALL) survival has steadily improved over the last decades, the focus has shifted from leukemia survival to also assessing long- and short-term side effects and quality of life during and following intensive treatment. Serious side effects may be caused by the different chemotherapeutic agents used in ALL therapy, but the incidence and severity of toxicities are also influenced by host factors such as age and sex.<sup>1,2</sup> The treatment period may also be

complicated by infections, psychosocial challenges, and nutritional problems. While most study consortiums aim at actively assessing major toxicities during ALL treatment, data on minor side effects and the impact of side effects from the family's perspective are often lacking. Studies over the past few years indicate that adding patient-reported outcome measures (PROM) may result in more comprehensive clinical data<sup>3–6</sup> and increased patient satisfaction, supportive care,<sup>7,8</sup> and clinical outcomes.<sup>9,10</sup> Hence, instruments for patient-reported adverse events (AEs), such as PRO-CTCAE, and the pediatric

<sup>1</sup>Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>2</sup>Department of Pediatric Oncology, Karolinska University Hospital, Stockholm, Sweden

<sup>3</sup>Department of Health Care Sciences, Palliative Research Centre, Marie Cederschiöld University, Stockholm, Sweden

<sup>4</sup>Louis Dundas Centre for Children's Palliative Care, Great Ormond Street Institute of Child Health, Population, Policy & Practice Department, University College London, London, UK

<sup>5</sup>Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark

<sup>6</sup>Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

<sup>7</sup>Department of Clinical Medicine, Turku University Hospital, University of Turku, and FICAN-West, Turku, Finland

<sup>8</sup>Swedish Childhood Cancer Registry, Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>9</sup>Department of Women's and Children's Health, Uppsala University and Pediatric Oncology, Uppsala University Hospital, Uppsala, Sweden

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ped-PRO-CTCAE, have been developed<sup>11–13</sup> for assessing adverse effects during treatment. This study aimed to assess parents' experiences retrospectively regarding how their child was affected by different treatment-related specific and overall side effects during ALL treatments, with a focus on side effects caused by corticosteroids, vincristine (VCR), asparaginase, and the long oral maintenance treatment. We also investigated how parental experiences aligned with the registered toxicity data reported by clinicians.

## METHODS

### Study design and population

The study design and population have been described in detail elsewhere.<sup>14</sup> Briefly, families of children aged 1–<18 years old at diagnosis in Denmark, Finland, and Sweden who were treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL 2008 protocol and were alive in first remission without any secondary malignancy at the time of data collection (2013–2019) were invited to participate (Figure 1). Patients with Down syndrome, mixed phenotype acute leukemia (MPAL), and patients who had undergone allogeneic stem cell transplantation (SCT) were excluded. An invitational letter, informed consent forms, and a packet of questionnaires were sent by mail to potential participants (children and their parents) at least 6 months after the end of ALL therapy.<sup>14</sup>

### NOPHO ALL2008 treatment protocol

The NOPHO ALL2008 protocol was used in Sweden, Finland, and Denmark from 2008 to 2019 and recruited all children older than 1 year of age except patients with mature B-cell or t(9;22) (BCR::ABL1) translocations. The protocol started with 1 month of induction, where treatment consisted of either prednisolone (PRED—patients with B-cell

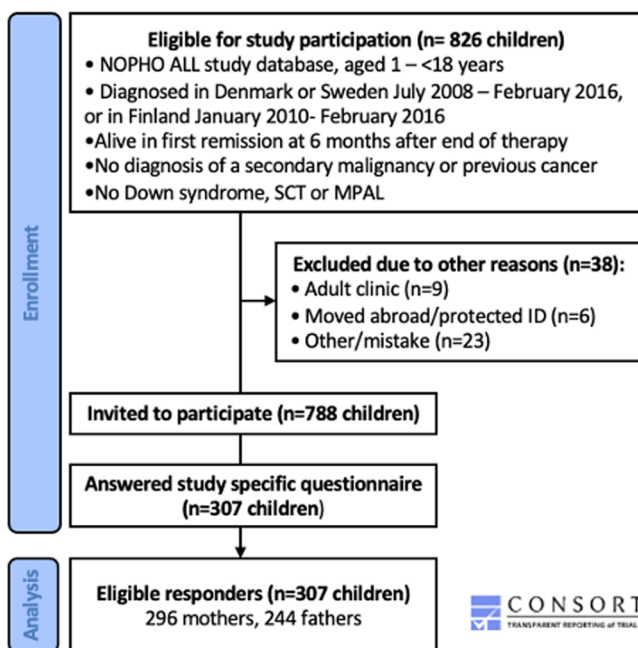
precursor (BCP) ALL with a white blood cell count at diagnosis  $<100 \times 10^9/L$  or dexamethasone (DEX; patients with BCP ALL with leukocyte count  $\geq 100 \times 10^9/L$  at diagnosis or T-cell ALL), together with VCR and doxorubicin. Then, according to treatment response and leukemic characteristics, patients were assigned to standard- (SR), intermediate- (IR), or high-risk (HR) treatment arms. After an initial consolidation phase (containing three high-dose [HD] methotrexate [MTX] blocks together with pegylated asparaginase [ASP], VCR, and 6-mercaptopurine [6MP]), the subsequent treatment intensity differed between treatment arms. The SR and IR arms included one or two delayed intensifications, respectively, while the HR arm consisted of 7–9 very intensive chemotherapy blocks followed by delayed intensification. Maintenance therapy (MT) consisted of oral 6MP and MTX interspersed with HD-MTX blocks (five for SR and IR patients, three for HR patients) and VCR-DEX pulses (four for SR and five for IR patients). A final phase of oral MT concluded the protocol for all patients.<sup>15</sup>

Each VCR dose was  $2.0 \text{ mg/m}^2$  (capped at 2.5 mg if under 18 years), which was higher than in many contemporary treatment protocols. ASP was given as an intramuscular injection in this protocol starting from Day 30 and then every second week (for IR and SR arms) unless participating in a randomized clinical trial in which ASP was given every sixth week after five injections in the experimental arm, resulting in eight instead of 15 injections. For HR patients, ASP was given at every chemotherapy block. Intrathecal injections and intravenous HD-MTX were used as the central nervous system (CNS)-directed treatment. The protocol has been described in detail earlier.<sup>15</sup>

### Study-specific questionnaire and NOPHO ALL2008 database data

The authors developed a study-specific questionnaire with input from families of pediatric patients previously treated for ALL. Questions on treatment-related toxicity were focused on well-known and/or common side effects from VCR, corticosteroids, ASP, and MT, as some of their potential side effects were deemed to be identifiable by parents and may also have a major impact on the child's well-being in daily life. Parents were asked to grade specific symptoms (e.g., walking difficulties due to VCR) from “no symptoms” to “mild symptoms,” “moderate symptoms,” or “severe and disabling symptoms.” Examples were sometimes provided for the different grades (e.g., moderate symptoms included “pain that required significant extra medication, assistance needed to walk, constipation difficult to treat,” while severe and disabling symptoms included “lost ability to walk, severe pain despite treatment, severe or life-threatening consequences of constipation such as severe infection or paralytic bowel”) and differentiation between grades was encouraged depending on the level of interference with daily life (e.g., symptoms with no interference were considered “mild”). There was also one question on whether the side effects had resulted in any dose adjustments, switch to crisantaspase (for ASP), or longer interruptions (for MT), one question on overall negative impact from that treatment element (grading from “not at all” to “a high extent”), one question regarding the extent to which the child was affected by complications overall during treatment, and finally one question to estimate the extent to which the child was affected by complications overall compared to the parent's perception of difficulties for other children with ALL. Furthermore, respondents were given the possibility to provide additional comments in free text.

Clinical information, including baseline demographic characteristics of the patients (age, sex, and birth year) as well as treatment-related factors, such as treatment intensity (categorized as SR, IR, or HR) and data on the 19 predefined reported toxicities were retrieved from the NOPHO ALL2008 database.<sup>16</sup>



**FIGURE 1** Consort diagram of the study population. MPAL, mixed phenotype leukemia; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SCT, stem cell transplant.

## RESULTS

Parent reports representing the experience of 307 children (296 mothers, 244 fathers) were included (Figure 1). In cases with two answering parents, the mother's response was used, as more mothers than fathers had responded. There were no significant differences between mothers' and fathers' symptom grading (Supporting Information S1: Figure S1). A total of 162 patients were males (52.8%), 81.5% were between 1 and 7 years old at diagnosis, and most of the children were treated within the SR or IR arm (Table 1). Frequencies of the 19 toxicities reported in the NOPHO database were rather similar in our study population compared to that reported overall in the NOPHO ALL2008 cohort for age 1–9 years (Supporting Information S1: Table S2), with allergic reactions (15.0%) being the most commonly reported toxicity, followed by peripheral paralysis (12.1%) and intensive care (11.4%), in our cohort. It should be noted that our study, in contrast to the total NOPHO ALL2008 cohort, did not include patients with SCT in first remission. Some toxicities (e.g., allergy, pancreatitis, thrombosis, and osteonecrosis) in the NOPHO database were also specifically addressed in the questionnaire (Table 2).

### VCR-related toxicity

Almost all children (98.4%) had at least one parent-reported symptom related to VCR. The most prominent of the eight VCR-related symptoms was walking difficulties, with more than a third of parents describing their child as having had severe and disabling symptoms (39.7%, Figure 2, Supporting Information S1: Table S3), followed by muscular weakness (30.9%). A majority of the children were reported to have had some level of muscular or jaw pain, stomach pain, or constipation, mostly at a moderate level (ranging from 35.6% to 37.0%), although 25.4% reported pain at a severe level. Side effects leading to reduced doses of VCR were reported in 16.3% (Supporting Information S1: Table S4) of cases, and more than a third (35.8%)

reported a high negative impact on the child overall from VCR (Figure 3 and Supporting Information S1: Table S5). Free-text comments included: "Drop foot/walking difficulties became permanent and now requires surgical procedure," "... lost the walking ability for 8 months and had impaired walking ability for a long time after," "as long as it helped cure her, it was OK" and "incredibly difficult mentally to see your child suffer from pain."

### Corticosteroid-related toxicity

Over 99% of all children were reported having had at least one symptom of corticosteroid-related toxicity. The most prominent reported symptom was a change in appetite. Over half (54.2%) reported moderate and more than a third (34.9%) severe symptoms, followed by mood swings (52.0% and 29.1% for moderate and severe, respectively) and aggressivity (38.7% and 18.0% for moderate and severe, respectively). Sleep disturbances were common but were mostly reported as mild or moderate (31.9% and 34.9%, respectively), although severe in some (13.0%) cases. Weight gain (approximately 20% or more) was reported in three-quarters of cases and mostly caused mild (26.5%) or moderate (29.5%) symptoms. High blood glucose and steroid-induced diabetes were reported by parents of 61 (19.9%) and 16 (5.2%) children, respectively, but in most cases reported to have only mild symptoms (13.2% and 2.3%, respectively). Skeletal complications with osteonecrosis were reported in 32 cases, as compared with nine cases in the NOPHO ALL 2008 database, and fractures in 42 cases. More than a third (34.5%) of parents had rated any of the psychological/mood symptoms as severe. Parents reported a high negative impact overall from corticosteroid treatment in 39.7% of cases. Some comments from parents included: "... To see your child dampened and apathic is devastating as a parent. Food situation was hysterical," "Terrible. Our child tried to harm itself and us..." and "The positive thing was that she ate more."

### ASP-related toxicity

For ASP, most parents rated the overall negative impact as none or low (39.7% not at all, 19.5% low extent). The parents of 20 patients reported pancreatitis (17 in the NOPHO ALL-2008 database), and 64.7% of those reported in the database graded the symptoms as severe. Allergy was reported in 70 cases (46 with allergy in the database, of which 42 cases overlapped with parent reports, and in addition, three cases with allergy noted as the reason for truncation, without any allergy registered in the toxicity part of the database). Thrombosis was reported in 15 cases (of which 10 were also reported in the database) (Table 2). Of the 57 children reported to be severely affected overall by ASP treatment, 38 (66.7%) had either pancreatitis, thrombosis, or allergy reported in the NOPHO database. Twelve of the remaining 19 cases had any toxicity reported (hyperlipidemia  $n=4$ , fungal infection  $n=4$ , pneumocystis infection  $n=1$ , liver dysfunction  $n=1$ , venoocclusive disease (VOD)  $n=2$ , intensive care  $n=2$ ), and for three patients ASP was truncated (hyperlipidemia  $n=2$ , allergy  $n=1$ ). Those with a severe overall impact of ASP without reported toxicity in the database ( $n=7$ ) described general nausea and vomiting ( $n=2$ ), and some ( $n=2$ ) found it very traumatizing with the intramuscular injections, which was also reported by several other parents ( $n=26$ ) in the free comments section. Of the 66 parents who reported that the ASP dose had been modified or switched to cristaspase, 58 were congruent with data in the NOPHO database. Of the remaining eight cases, three had been randomized to the experimental arm in the ASP clinical trial (eight instead of 15 doses), one had an allergic reaction but received all remaining doses after

**TABLE 1** Baseline characteristics of children.

	Total ( $n = 307$ children)	
	$n$	%
Sex		
Male	162	52.8
Female	145	47.2
Age at diagnosis, years, mean (SD)	5.3 (3.7)	
Age group at diagnosis, years		
1–7	250	81.4
8–12	37	12.1
13–18	20	6.5
Country of residence		
Sweden	157	51.1
Denmark	72	23.5
Finland	78	25.4
Treatment arm		
Standard risk	163	53.1
Intermediate risk	118	38.4
High risk	26	8.5

Abbreviation: SD, standard deviation.

**TABLE 2** Toxicities in NOPHO ALL2008 database and parent-reported toxicity.

Toxicities in the NOPHO research database	Reported in database		Parent-reported		Graded severe <sup>a</sup> n database (n parent-reported)	% reported (% all children)	Cases in database also reported by parents	
	n	%	n	%			n	%
Allergy	46	15.0	70	22.8	29 (37)	63.0 (12.1)	42	91.3
Peripheral paralysis	37	12.1	291 <sup>b</sup>	94.8	29 (134)	78.4 (43.6)	37	100
Pancreatitis	17	5.5	20	6.5	11 (13)	64.7 (4.2)	15	88.2
Thrombosis	15	4.9	15	4.9	8 (10)	61.5 (3.3)	10	66.7
Osteonecrosis	9	2.9	32	10.4	3 (11)	33.3 (3.5)	7	77.8

Note: Reported incidence in the database compared with parent-reported incidence.

<sup>a</sup>N database refers to the number of children with severe symptoms reported in the NOPHO ALL2008 trial database. In parentheses is the number of children with severe symptoms reported by parents. % reported refers to the percentage of children with severe symptoms over all children with symptoms of any severity reported in the NOPHO ALL2008 trial database, while (% of all children) is the percent of children with severe symptoms over all children included in the study.

<sup>b</sup>If a parent rated any symptom of muscular weakness, clumsiness, drooping eyelid, drop foot, or walking difficulties. "Severe" if any of these are rated severe by a parent.

premedication, one had comments on ASP delays but received all doses, and the last three had no remarks.

### Toxicity during MT

Most parents reported an overall negative effect of MT to some (42.7%) or to a moderate (29.6%) extent. Susceptibility to infections was the most prominent symptom, with over two-thirds reporting mild (33.2%) or moderate (38.2%) symptoms. The questionnaire included two additional MT symptoms: low blood glucose (with examples given, if not measured) and liver toxicity, for which about half reported no symptoms of either of these and otherwise reported generally mild-to-moderate symptoms. Parental comments on MT included: "We changed tablet intake from evening to morning, then it improved a lot," ... were not told nausea in the morning could be a side effect, often vomited, and then unnecessarily had to be home from daycare for 48 hours," and "We first felt the effect of maintenance after it stopped. Relative to treatment, this was easier. However, many infections occurred after the end of maintenance."

### Parent-reported overall toxicity

Most parents reported that their child had been affected by complications during treatment, including infections and nutritional problems, to some (37.1%) or to a moderate (24.1%) extent, although almost a third (31.3%) reported that their child had been affected to a high extent. When asked to compare their impression of the effect on other children with ALL, a majority of parents rated their child to have been affected to a similar (23.8%), lower (24.4%), or considerably lower (16.9%) extent.

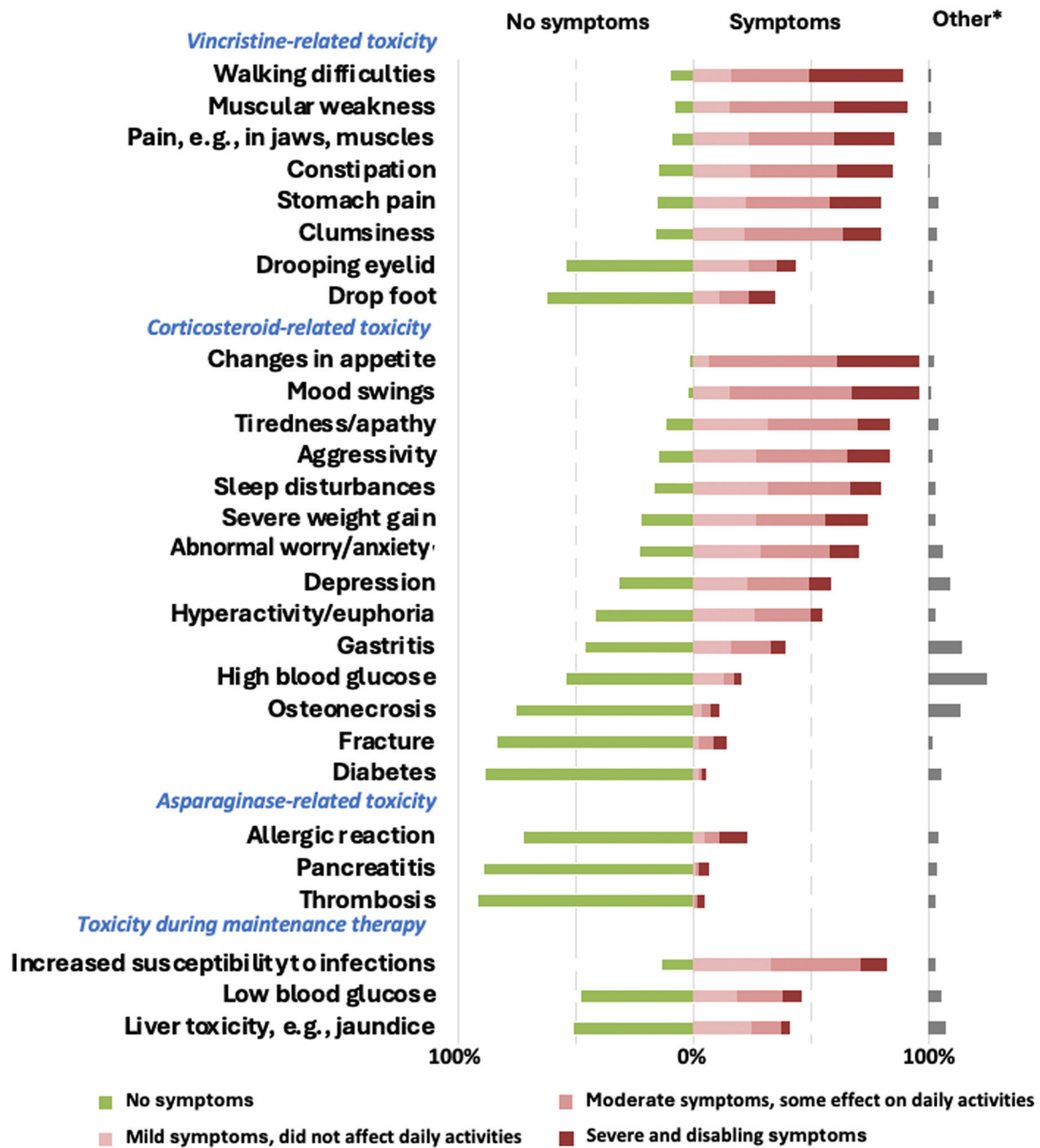
## DISCUSSION

This questionnaire study analyzed parent-reported toxicity related to treatment elements commonly causing side effects in a population-based cohort of 307 children from the NOPHO ALL2008 protocol. The results showed that almost all parents reported their child as having had VCR- and corticosteroid-related toxicity, and over one-third of them reported severe or disabling symptoms related to these medications. In contrast, toxicity related to ASP and MT was significantly lower, and only up to 12.2% reported any severe or disabling toxicity. Despite reporting severe symptoms, parents in

general rated their child as having been affected to a lower, or similar, extent when compared to other children with ALL. VCR- and corticosteroid-related toxicities were lacking from the NOPHO ALL2008 protocol toxicity reporting, except peripheral paresis leading to modification of VCR treatment (12.1%). Parents' reporting of the distinct severe toxicities (e.g., pancreatitis and thrombosis) were well congruent with the protocol database.

Toxicities caused by VCR and corticosteroids are often overlooked in the toxicity reporting for ALL protocols, probably because they are common and rather difficult to measure objectively since grading is based on subjective symptoms. Rather, toxicity registration has focused on distinct severe adverse events, for example, pancreatitis, thrombosis, diabetes, or osteonecrosis, which is understandable since they may be life-threatening and/or cause permanent long-term sequelae. However, our data highlight the importance of the inclusion of these more subjective toxicities when we aim to improve patients' quality of life and develop new ALL protocols.

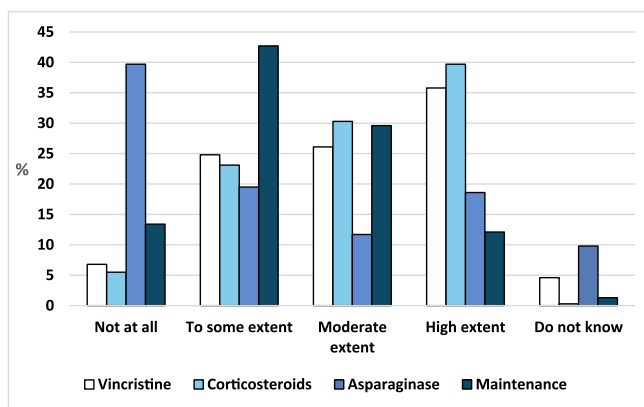
For VCR, parents reported walking difficulties and muscular weakness as the most severe and disabling symptoms, with over 70% rating these symptoms to have been either severe or moderate. It is known that VCR-induced peripheral neuropathy (VIPN) frequently occurs during ALL treatment,<sup>17,18</sup> although reported prevalence of VIPN have depended on definition, method of assessment (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE),<sup>19</sup> Total Neuropathy Score©-Pediatric Vincristine (TNS©-PV),<sup>20</sup> electrophysiological tests<sup>21</sup> or scoring of subjective symptoms<sup>22</sup>), concomitant medication and doses, as reviewed by Velde.<sup>23</sup> Motor symptoms seem to be more prominent in children,<sup>17,24,25</sup> and the high prevalence of motor deficits in our study is similar to that presented by Arzian et al.<sup>26</sup> (70% muscle weakness) and Courtemanche et al.,<sup>24</sup> who reported walking difficulties in 13/17 (76.5%) children with VIPN, being their most common clinical finding, followed by neuropathic pain in 70.6%. Some walking difficulties during therapy seem to persist, and walking impairment was recently found in two-thirds of ALL survivors 12 months posttherapy,<sup>18</sup> and VIPN in general has been found in 16%–41% of children after ALL treatment.<sup>27–29</sup> Pain was reported in a majority of children in our study (moderate or severe pain in 61.5%), which was higher than previously reported by Angheliescu et al.<sup>30</sup> (34.9%, retrospective data from medical records), Lavoie Smith<sup>17</sup> (44%, FACES pain scale), and Verstappen<sup>22</sup> (62% in "high dose cohort," subjective symptoms, adults). Constipation was common, in most cases reported at a mild to moderate level (although severe in a fifth of cases), which is in line with



**FIGURE 2** Parent-reported symptoms, incidence, and severity. \*Other refers to "Other reasons, including the parent noting that they cannot answer."

some previous studies,<sup>31</sup> although studies are few with widely shifting prevalence (6%–82%).<sup>24,26,31–33</sup> The overall high incidence and severity of symptoms could be due to the higher VCR dose and treatment intensity during induction and consolidation in the NOPHO ALL2008 protocol. This high VCR dose has been associated with a higher incidence of VIPN and led to the premature closure of a COG study using this dose.<sup>34</sup> Another explanation for the high reported incidence of motor symptoms could be that steroids, with known side effects of myopathy,<sup>35</sup> were often given concomitantly during the treatment. However, some studies have indicated that this does not seem to impact VIPN.<sup>17,19</sup> One previous study indicates that parents can identify motor VIPN during treatment in their child fairly accurately, while the assessments are less accurate for sensory symptoms compared to physio-/occupational therapist assessment.<sup>36</sup>

For corticosteroids, parents reported changes in appetite as the most severe symptom, followed by mood swings (81.1% moderate or severe). Eating/changes in appetite, along with mood changes, has previously been reported as a concerning problem for parents,<sup>37</sup> and previous studies assessing adverse psychological reactions (APR) have found APR in 5%–75% as reviewed by van Hulst,<sup>38</sup> but high-quality data and standardized measurements are generally lacking. Sleep disturbance<sup>39,40</sup> is a known side effect of corticosteroids<sup>41</sup> and was frequently reported in a majority of children in our study, but mostly at mild or moderate levels. Skeletal complications such as osteonecrosis, were reported more often by parents than in the NOPHO database, which in part could be due to missing cases in the database, for example if diagnosed after the end of treatment, but warrants further attention. Fractures (which are not addressed in the



**FIGURE 3** Parent-reported negative impact from treatment.

database) were reported in 42 (14.0%) cases, some of which parents commented that their child had vertebral compression fractures already at diagnosis, which is in line with the known risks of skeletal complications of the disease but also reflects osteoporosis during and after treatment.<sup>42</sup>

For ASP, the parent-reported incidence of side effects correlated quite well with the reported toxicity in the database and was generally reported to have had none, or low, overall negative impact among the children who presented with no ASP complications, for example, pancreatitis. MT-related side effects were generally reported to have had some, or moderate, negative impact, with parents commenting on general tiredness, infections, nausea, and, in some cases, serious episodes of low blood glucose.

Interestingly, parent reports covered 66%–100% of the toxicities also reported in the NOPHO ALL2008 database (thrombosis, pancreatitis, allergy, osteonecrosis, and peripheral paralysis) and was, to a large extent, congruent with database reports on thrombosis and pancreatitis. These are both medically distinct conditions that usually occur during treatment and require intervention and/or specific assessment and, hence, are probably readily identifiable for both healthcare professionals and parents. For allergy, osteonecrosis, and peripheral paralysis, parent reports exceeded those in the database. This could be due to underreporting in the database, which is probably true for at least some cases of allergy (as reflected by being stated as the reason for ASP truncation but not registered as toxicity), or to different interpretations. For example, to report peripheral paralysis in the database, the symptoms had to motivate a dose adjustment of VCR, which was often not done even with quite severe symptoms. Notably, parents reported VCR dose adjustment in 16.3% of children, which is more similar to the clinician-reported toxicity in the database, “peripheral paralysis” requiring VCR dose adjustment, at 12.1%. As indicated in previous studies, clinicians may miss or underreport common toxicities with subjective symptoms.<sup>6</sup> Higher rates of toxicities reported by parents than clinicians could also, in some cases, be due to conditions diagnosed or causing symptoms after the end of therapy.

This study gives a comprehensive overview of how parents perceived different common or severe side effects during ALL treatment in 307 children. Study strengths include the large number of participants and our approach to addressing the recorded incidence as well as the parent-perceived impact of several different side effects. Most previous studies have focused on separate side effects (e.g., only VIPN, sleep disturbances, etc.), while our study enables comparisons between side effects and treatment elements

from the families' perspective as well as a global assessment of how affected the child was by the treatment.

Although this questionnaire study's retrospective design may lead to recall bias, it also has some advantages, as stated by parents themselves (e.g., not realizing how tired their child was from MT until it was over or how severe the impact of steroids was until they resolved quickly after use, etc.).

In summary, our study shows that the negative impact of VCR and corticosteroids was high, with severe and disabling levels reported on several symptoms, which is not reflected in routine toxicity reporting. It also shows that parents, in general, can give accurate reports of their child's toxicities and may add to a more comprehensive toxicity reporting. It is striking how severely the parents rated their child's symptoms and overall impact from treatment, especially from VCR and steroids, while giving relatively accurate reports of toxicities that were also in the database. Parents also tended to estimate their child to be less or similarly affected by complications compared to other children with ALL. Taken together, these results may reflect the massive psychological and medical strain ALL and its treatment puts on children and families in their daily lives, especially during the first intensive treatment phases, which may not be fully recognized by healthcare professionals. Our study highlights the importance of including PROM in toxicity reporting to capture the complexity of the impact of treatment-related toxicity on children and families, as well as to get a comprehensive picture of the treatment-related side effects, which is especially important for toxicities manifesting with subjective symptoms.

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#### AUTHOR CONTRIBUTIONS

Nina Mogensen, Arja Harila, Mats Heyman, and Ulrika Kreicberg designed the study and interpreted the data. Birgitte Klug Albertsen and Päivi M. Lähteenmäki contributed to the conception, design, and data collection. Nina Mogensen analyzed the data and wrote the draft of the paper. All authors drafted and revised the paper critically and accepted the final version.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

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

#### ETHICS STATEMENT

Ethical approval was obtained by the Ethical Review Board of Stockholm (reference number 2013/1470-31) and the Ethical Committee of the South-West Finland Hospital District (reference number ETMK:17/1801/2015). In Denmark, the ethical approval for participation in the clinical study, NOPHO ALL2008 (EudraCT 2008-003 235-20), also applied for this part of the study. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participating families.

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## ORCID

Nina Mogensen  <http://orcid.org/0000-0001-7666-8611>

## SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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