Motor Performance and Functional Exercise Capacity in Survivors of Pediatric Acute Lymphoblastic Leukemia

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Background. Impaired motor performance and reduced maximum exercise capacity during and after treatment of acute lymphoblastic leukemia (ALL) has been shown. However, no longitudinal study monitoring motor performance after cessation of treatment has been published. Whether sub-maximal exercise capacity is reduced is unknown. ***Procedure.*** Motor performance of pediatric ALL survivors, treated with Dutch Childhood Oncology Group ALL-9 protocol was measured with the movement-ABC at stop treatment and ≥5 years later. At follow-up functional exercise capacity was also investigated using the 6-minute walk test (6MWT). Heart rate and oxygen saturation were measured with a portable pulse oximeter before and after the 6MWT. ***Results.*** Nineteen boys and 15 girls, median age 12.3 years (range: 9.0–18.7), median time since completion of chemotherapy 5.2 years (5.0–7.1), participated. Mean height/age and weight/age were within the norm, whereas mean BMI/age was significantly increased (mean SDS 0.38, SEM 0.17, $P = 0.04$). Motor performance had improved significantly ($P = 0.001$). In contrast, functional exercise capacity at follow-up was significantly impaired (mean SDS −2.05, SEM 0.13, $P < 0.001$). ***Conclusions.*** At ≥5 years after completion of ALL treatment motor performance had improved significantly, but functional exercise capacity was significantly impaired. The exact underlying cause of this late effect needs further study. Pediatr Blood Cancer

Key words: acute lymphoblastic leukemia; functional exercise capacity; motor performance

INTRODUCTION

The survival rate of acute lymphoblastic leukemia (ALL) in children has increased significantly in the last decennia. Therefore, side effects of treatment have gained importance. Late effects of chemotherapy may involve myopathy, muscle atrophy, osteoporosis [1,2], osteonecrosis [3], corticosteroid-related obesity [4], vincristine-induced polyneuropathy [5], and anthracycline-induced cardiomyopathy [6,7]. Children treated for ALL receive substantial dosages of corticosteroids and vincristine over a 2-year period.

Various studies have shown impairment of motor performance during [8–10] and after completion of treatment for ALL [5,11,12]. However, no longitudinal study monitoring motor performance from completion of treatment onwards has been published.

In addition exercise capacity may be affected by chemotherapy for ALL. Chemotherapy has an immunosuppressive effect, which may cause increased frequency of upper respiratory tract infections and has been suggested as a contributing factor to impaired exercise capacity [13]. In addition, obesity which has been repeatedly reported in survivors of ALL has an adverse effect on exercise capacity [14,15]. Furthermore, children who had received anthracyclines as part of their chemotherapy treatment for ALL, showed reduced exercise duration and maximum oxygen uptake ($VO_{2\ max}$) during graded exercise testing in various [7,16,17] but not all [18] studies. Even survivors who had not received anthracyclines were also found to have impaired exercise capacity on anaerobic as well as aerobic exercise tests [19]. The aforementioned studies all used maximum exercise tests where patients are encouraged to perform until reaching exhaustion. However, in everyday life maximum exertion is seldom required and functional everyday exercise capacity is better reflected by a sub-maximal exercise test [20]. One study found an impaired sub-maximal response associated with obesity in 55 survivors of ALL and other malignancies. However, the ALL survivors had all received cranial radiation [21]. Another study showed reduced cardiac function during sub-maximum cycling tests in 13 children treated with anthracyclines for malignancies, but no details regarding the exact diagnoses were provided [22]. More importantly, neither study used a standardized exercise testing protocol. The 6-minute walk test (6MWT) is currently the most widely used standardized exercise test in both adult and pediatric clinical populations [23]. The 6MWT is a self-paced, sub-maximal exercise test used to assess functional exercise capacity and is considered as the test of choice when using a functional walking test for clinical or research purposes.

Therefore, the aim of our study was to study motor performance and functional exercise capacity in children who had completed treatment for ALL more than 5 years ago.

METHODS

Patients

The study was conducted at the outpatient clinic of the Department of Pediatric Oncology/Hematology of the Erasmus MC-Sophia Children's Hospital Rotterdam, the Netherlands. Survivors of childhood ALL, who completed chemotherapy more than 5 years ago, who participated in a previous study [8] and were in first complete continuous remission, were eligible to take part. Survivors aged ≥19 years were excluded, as were

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survivors diagnosed with another condition that could affect motor performance. Clinical data (i.e., treatment regimen, fractures, symptomatic osteonecrosis, weight and height at onset, and at completion of chemotherapy) were obtained from the medical records. Height (cm) and weight (kg) were measured. Body mass index (BMI) was calculated with the formula weight (kg)/height^2 (m). Height and weight were expressed as standard deviations scores (SDS) based on normative values for Dutch children [24]. Information regarding participation in physical education classes and sports was collected from children and their parents in a semi-structured interview. The Medical Ethical Committee approved the study. Written informed consent according to the Helsinki agreement was obtained from all parents and from patients aged $\geq$12 years [25].

Chemotherapy Treatment

Patients (>1 and <19 years) were treated according to the dexamethasone-based ALL-9 protocol of the Dutch Childhood Oncology Group (DCOG) [26]. The ALL-9 non-high risk (NHR) protocol started with induction therapy, including dexamethasone, asparaginase, and vincristine, followed by high-dose MTX courses and maintenance therapy with 6-mercaptopurine/MTX plus vincristine/dexamethasone pulses. Patients were treated according to the high risk (HR) protocol when they met one of the following criteria: white blood cell count at diagnosis $\geq 50 \times 10^9$, T-cell immunophenotype, mediastinal mass, involvement of the central nervous system (CNS), infiltration of the testes, *t*(9;22) or BCR-ABL gene rearrangement, *t*(4;11) or translocations involving 11q23 with *MLL* gene-rearrangements. HR ALL patients received additional anthracyclines during induction treatment, higher doses of MTX during CNS prophylaxis and received two additional intensification courses before starting maintenance therapy (total cumulative anthracycline dose 175 mg/m^2). None of the patients included in this study received CNS irradiation. For doses of vincristine and dexamethasone, see Table I.

Motor Performance

At follow-up motor performance was measured using the Movement Assessment Battery for Children, version 2 (movement-ABC 2), suitable for children aged 3–16 years [27]. Motor performance at cessation of treatment had been measured with the movement-ABC 1 [28]. Although not identical, both versions consist of eight standardized tasks, divided into three sub-sections: hand function, ball skills, and balance skills. Age-related norm scores are provided in percentiles and are interpreted as follows: $\leq$P5 equals impairment, P6–P15 equals at risk for impairment, and >P15 equals score within the norm.

TABLE I. Vincristine and Dexamethasone Schedules by Regimen

	NHR	HR
Number of doses vincristine	34	31
Dose (mg/m^2)	2.0	2.0
Maximum vincristine dose per administration (mg)	2.5	2.5
Cumulative dose (mg/m^2)	68	62
Cumulative dexamethasone dose (mg/m^2)	1,370	1,244

NHR, non-high risk; HR, high risk.

Functional Exercise Capacity

Functional exercise capacity was measured with a sub-maximal test: the 6MWT. Children were instructed to cover as much distance as possible during a period of 6 minutes. The distance between turning points was 10 m. Running was not permitted. The phrases used to instruct and to encourage the children were standardized according to the Guideline of the American Thoracic Society [29]. Heart rate and oxygen saturation were measured with a finger pulse oximeter (Beijing Choice Electronic Technology Co. Ltd, Beijing, China), at the start and on completion of the test. The distance covered was measured and expressed as SDS using normative values of the population-based sample aged 3–18 years from the study by Geiger et al. [30]. The 6MWT is considered a suitable test to assess sub-maximal level of functional exercise capacity [31]. Validity and reliability of the 6MWT are good [32].

In order to determine the physiological demand during the 6MWT we calculated the percentage of heart rate reserve (HRR) they were exercising, based on the following assumptions [33]. HRR was calculated as the difference between maximal heart rate and heart rate at rest. Average heart rate during maximal exercise reaches 197 beats/minute in Dutch children during treadmill exercise testing [34]. We calculated HRR = 197 − heart rate at rest. Percentage of HRR was calculated as: (heart rate on completion of the 6MWT − heart rate at rest)/heart rate reserve) × 100.

Ankle Dorsiflexion

Reduction of passive ankle dorsiflexion as a result of vincristine neuropathy is a known side effect during and after treatment for ALL [35,36]. It was relevant to ascertain whether passive ankle dorsiflexion was impaired because this might affect gait pattern and therefore the 6MWT score. Passive ankle dorsiflexion was measured in supine position with the knee extended. A range of motion past the neutral had a positive notation and less than neutral was negative. The lower of the two passive ankle dorsiflexion values—left and right side—determines the level of impairment and was therefore used for analysis. Passive ankle dorsiflexion needs to reach at least 5° past the neutral position for the ankle to move normally [37]. We therefore defined $\leq$5°of passive dorsiflexion as ''impaired.''

Statistical Analysis

All continuous data were assessed for normality using the Shapiro–Wilk test. Normally distributed data are reported as mean ± standard deviation (SD) or indicated otherwise. One sample *t*-tests were used to determine whether mean SDS differed from 0. A paired *t*-test was used to examine changes in motor performance between cessation of treatment and follow-up. The Mann–Whitney *U*-test was used to analyze differences between groups. Spearman's rho (r_s) was calculated to examine the relationship between motor performance and 6MWT performance. The statistical package SPSS 18 was used to analyze the data. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patients

The single center pediatric ALL survivor cohort of a previous study (n = 41) was invited to participate [8]. Since completion of chemotherapy one child had developed severe epilepsy. Five children were over the age of 18 years and one child declined participation. The remaining 34 children, 19 boys and 15 girls participated in the study. Median age was 12.3 years (range: 9.0–18.7), median age at diagnosis 4.7 years (range: 1.3–11.5), and median time since completion of chemotherapy 5.2 years (range: 5.0–7.1). Twenty-four children (71%) had been treated with the ALL-9 NHR protocol and 10 children (29%) with the ALL-9 HR protocol. Children treated with HR regimen were significantly older than those treated with NHR regimen ($P = 0.049$). During treatment five participants had developed symptomatic avascular necrosis (AVN), which was treated conservatively. At the time of the study, two of them still had complaints of feeling stiff after prolonged standing or after playing sports. Eight children had sustained fractures: four children had a fracture during treatment and two children after treatment was completed. Two other children had fractures during as well as after treatment. One of the latter two children was subsequently diagnosed with osteogenesis imperfect (OI) type 1. The OI only manifested itself in hyperlaxity and not in skeletal abnormalities. None of the children were excluded from the study. There were no children with pulmonary or cardiac compromise (Table II).

Height and Weight

Mean height for age did not differ from the norm (mean SDS −0.22, SEM 0.13, $P = 0.11$), nor did mean weight for age (mean SDS 0.19, SEM 0.15, $P = 0.24$). However, mean BMI for age was significantly increased (mean SDS 0.38, SEM 0.17, $P = 0.04$). Using the cut-off points as proposed by Cole et al. [38] four children (12%) were obese, 12 (35%) were overweight, and 18 (53%) had normal weight at stop treatment. At follow-up none were obese, one child had become overweight, and seven had remained so (24%). The other 26 children (76%) had normal weight (Table II).

TABLE II. Overview of Patient Characteristics

Case	Sex	Age at diagnosis	Age at study	Risk group	AVN	#	BMI SDS at study
1	M	4.3	13.1	NHR	—	—	1.92
2	M	6.3	14.8	NHR	—	—	−0.69
3	F	5.3	14.1	NHR	—	—	1.32
4	F	1.7	10.4	HR	—	—	0.08
5	F	9.3	18.2	HR	X	—	−1.59
6	M	1.3	10.3	NHR	—	—	1.27
7	F	2.6	10.8	HR	X	—	−0.77
8	M	2.8	11.4	NHR	—	—	0.53
9	F	4.2	13.0	NHR	—	—	−1.34
10	M	8.2	16.9	NHR	—	X	0.71
11	M	1.6	9.8	NHR	—	—	1.06
12	M	4.4	12.9	NHR	X	X	0.61
13	F	3.2	11.3	NHR	—	—	1.21
14	F	6.4	14.8	NHR	—	—	1.30
15	F	11.5	18.7	HR	X	—	0.18
16	M	10.2	17.8	HR	X	—	1.14
17	M	5.3	12.5	NHR	—	—	−1.90
18	F	5.4	12.8	HR	—	X	1.62
19	F	4.0	11.3	NHR	—	—	1.35
20	F	9.4	16.4	HR	—	—	−1.19
21	M	3.4	10.6	HR	—	—	0.57
22	M	10.1	17.2	HR	—	—	0.88
23	M	4.3	11.4	NHR	—	X	0.60
24	F	3.8	11.0	NHR	—	—	0.17
25	F	7.1	14.3	NHR	—	X	2.16
26	F	1.6	9.0	NHR	—	—	0.54
27	M	9.3	16.6	NHR	—	—	0.46
28	M	2.5	9.8	NHR	—	—	0.31
29	M	11.0	18.2	HR	X	—	1.41
30	F	4.6	11.8	NHR	—	—	−0.42
31	M	4.7	11.8	NHR	—	X	−0.20
32	M	4.7	11.9	NHR	—	X	−1.07
33	M	3.2	10.3	NHR	—	—	0.58
34	M	5.0	12.1	NHR	—	—	−0.01

M, male; F, female; NHR, non-high risk; HR, high risk; AVN, avascular necrosis; #, fracture during or after treatment; BMI SDS, body mass index SD scores; X, present, —, absent.

Motor Performance

At cessation of treatment three participants had been too young (<4 years) too be tested with the motor performance test. Median percentile score of the remaining 31 children was 19.0 (1–93). At follow-up five participants were too old. Median percentile score of the remaining 29 children was 50.0 (5–98). Motor performance scores both at cessation and at follow-up were obtained from 26 children. Their scores had changed significantly over time ($P = 0.001$). Fifteen of the 26 children (58%) who had achieved normal scores at cessation of treatment continued to do so at follow-up. Ten children (38%) who had been ''at risk for impairment'' at cessation of treatment, achieved normal scores at follow-up. One child (4%) had been ''at risk'' at cessation of treatment, which did not change over time (Fig. 1). Gender did not affect motor performance at cessation of treatment ($P = 0.54$) or at follow-up ($P = 0.86$). Treatment regimen had no effect on motor performance at cessation of treatment ($P = 0.69$). However, at follow-up children who had been treated with HR regimen performed significantly better than those treated with NHR regimen ($P = 0.01$).

Functional Exercise Capacity

The 6MWT was performed by 34 children. The mean distance covered during the 6MWT was 558.4 m (±43.3). Standard deviation scores on the 6MWT (6MWT SDS) were significantly lower than normative values (mean SDS −2.05, SEM 0.13, $P < 0.001$; Fig. 2). Median oxygen saturation at the start of the 6MWT was 98% (96–99) and 97% (96–98) immediately after completion of the test ($P = 0.4$). The mean HRR on completion of the test was 48% (±32). There was no relationship between increase in heart rate during the test and 6MWT SDS ($r_s = 0.04$, $P = 0.85$). Gender did not affect 6MWT SDS or HRR ($P = 0.47$, $P = 0.17$) nor did treatment regimen ($P = 0.99$, $P = 0.94$). There was a weak negative trend between BMI SDS and 6MWT SDS ($r_p = -0.34$, $P = 0.053$). There was a weak positive trend between 6MWT SDS and motor performance ($r_s = 0.33$, $P = 0.051$).

Ankle Dorsiflexion

At completion of chemotherapy 23 of the 34 children (68%) had impaired ankle mobility. At follow-up ankle mobility had remained limited in six children and had become limited in one child (21%). Mean passive ankle dorsiflexion on the left was 10.7° (±5.2) and on the right 11.0° (±5.6). Impairment of ankle mobility in these survivors had no significant effect motor performance score ($P = 0.8$) or on 6MWT SDS ($P = 0.86$).

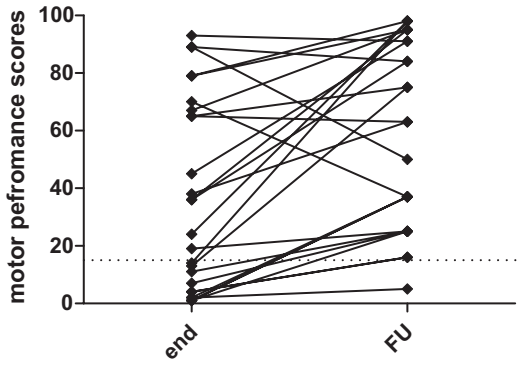

Fig. 1. Movement-ABC scores of 26 survivors of acute lymphoblastic leukemia at end of treatment showing a significant increase at median follow-up of 5.2 years ($P = 0.001$). Scores above the dotted line are within the norm. FU = follow-up.

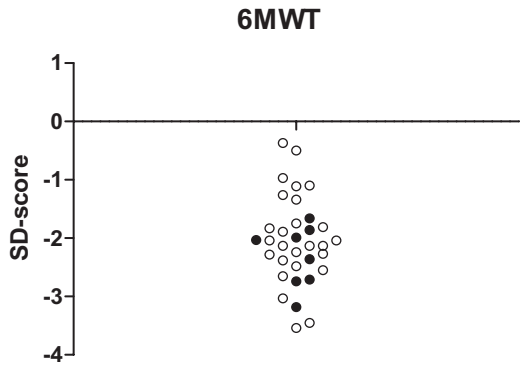

Fig. 2. Standard deviation scores on the 6-minute walk test of 34 survivors of acute lymphoblastic leukemia showing significant impairment at median follow-up of 5.2 years ($P < 0.001$). Open circles indicate normal body weight, solid circles indicate overweight. Horizontal line indicates the norm mean.

Physical Education and Sports Participation

Physical education classes were attended by 29 of the 34 children (85%); four children (12%) did not have physical education at their school and from one child (3%) the information was not collected. Twenty-two children (65%) played sports at club level after school. There was no difference in 6MWT SDS between children who did or did not participate in sports ($P = 0.41$).

DISCUSSION

The aim of our study was to investigate motor performance and functional exercise capacity after 5 years follow-up in pediatric ALL patients, treated according to DCOG ALL-9. We observed significantly higher motor performance levels 5 years after treatment compared to directly after treatment. Motor performance improved over time and at 5 years follow-up it was comparable to healthy peers. This progress may be due to normal physiological recovery after withdrawal of chemotherapy. As energy levels improve, children may increasingly participate in physical activities thus providing their own rehabilitation. In addition, the importance of physical activity is routinely explained to children and parents at the time of diagnosis. The children in the current study had motor performance evaluations regularly throughout the 2-year chemotherapy treatment and the benefits of physical activity were reinforced at each evaluation. This may have been a contributing factor to their physical recovery. At follow-up children treated with the more intensive HR regimen performed better than children treated with the NHR regimen, which was a surprising finding. The HR regimen has a slightly lower cumulative vincristine dose but the difference is minimal. Moreover, we would expect motor performance at cessation of

treatment to be affected similarly, which was not the case. At follow-up children treated with HR regimen were significantly older than those treated with NHR regimen. Relatively older children may have a better understanding of the benefit of regular exercise, which may have influenced outcome variables.

In contrast, functional exercise capacity scores of the ALL survivors were significantly below the norm. This was an unexpected finding in a group of children who appeared to have a reasonable level of sports participation. A number of factors need to be taken into account. The distance between 6MWT turning points in the normative study by Geiger et al. was 20 m, whereas in our study we used only 10 m. Children therefore had to negotiate more turns to cover the same distance as the children in the normative study. However, it has been shown that course length does not affect the outcome of the 6MWT [39,40]. Therefore it is unlikely that this would explain the low 6MWT scores we found in the ALL survivors.

Motivation and understanding the purpose of performing the 6MWT affect results [30]. This applies particularly to children. They tend to start out enthusiastically, but can find it difficult to maintain the same pace for the duration of six minutes, as the task is simple. We used the standardized encouragements repeated every minute, irrespective of the actual level of performance and children were not given any feedback regarding the distance they had covered. In contrast, the children in the study by Geiger et al. [30] were continuously informed of their progress by a measuring wheel displaying the distance. This is potentially more motivating than the standardized encouragements that we used. To verify our 6MWT scores we therefore compared them to Asian normative values (n = 1,445) as well [41]. With the Asian norm values the ALL survivors also scored poorly, with scores of 82% of the participants below the 10th percentile.

Geiger et al. found a mean increase in physiological demand during the 6MWT of 48% and 56% of HRR in healthy boys and girls, respectively. We found considerable lower increase in HRR and more variability, with a mean increase in HRR of 30% ± 20%. This shows that the 6MWT is quite demanding for some children. Moreover, a number of children had only a very low heart rate response. The reduced heart rate response in some of our subjects needs further study.

Body weight affects 6MWT scores. Overweight and obesity are recognized problems in children receiving chemotherapy for ALL [15,42]. In our cohort 24% of the children (n = 8) were overweight, but the majority of children (76%) had normal body weight. This indicates that weight is by no means the only explanation for impaired functional exercise capacity. Moreover, a recent study showed that overweight children covered the same distance during the 6MWT compared to normal weight age- and sex-matched controls [43]. In our sample, BMI was borderline significantly related to 6MWT performance, indicating that increased body mass may contribute to impaired functional exercise capacity. The sample (n = 34) may have been too small to demonstrate significance in this matter.

In addition to overweight, pulmonary and cardiac impairments might influence exercise capacity [16]. In the current study, this was not evaluated because none of the drugs used in the ALL-9 protocol are known to cause pulmonary toxicity. Furthermore, anthracycline treatment was restricted to the HR patients and total cumulative dose <180 mg/m^2, which makes late cardiac toxic effects unlikely [44].

Musculoskeletal factors are related to exercise capacity. Decrease in strength of knee extensors and foot dorsiflexors has been demonstrated in ALL survivors [19,35]. Both these muscle groups play a major role in walking at a fast pace. Their strength was not tested in the present study. However, it is not unlikely that the cumulative doses of vincristine and corticosteroids used in the DCOG ALL-9 protocol have caused a reduction in muscle strength. Particularly in a motor task of prolonged duration, such as walking for a duration of 6 minutes, reduced muscle strength in the lower limbs may have contributed to the reduced 6MWT SDS. Future studies should address the relationship between lower extremity muscle strength and 6MWT performance.

A sedentary life style has also been suggested to contribute to reduced exercise capacity in this patient group [45]. Total daily energy expenditure has found to be less in children who survived ALL compared to healthy children, particularly in girls [46,47]. We did not measure daily energy expenditure, but activity levels of the ALL survivors appeared to be normal. The majority (65%) of children played sports at club level. A Dutch survey of 2004 showed that in general 80% of children and adolescents are involved in sports [48].

In summary, motor performance scores significantly improved in children who completed treatment for ALL more than 5 years ago and resembled the normal population. In contrast, functional exercise capacity was markedly reduced. No single underlying cause for the impairment of functional exercise capacity could be identified. Further prospective studies, using Dutch healthy controls, are needed to determine whether cardiopulmonary factors or long-term reduction in muscle strength are underlying causes for impaired functional exercise capacity in ALL survivors or whether differences in methodology affecting motivation were the main determinants of these low scores. On the basis of those results, we consider incorporating the 6MWT to the yearly scheduled follow-up appointments for ALL survivors in order to monitor functional exercise capacity at an early stage.

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