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Article

Comparing the developmental pathways of leukemic preschool children with their healthy peers: communicative and social sequelae one year after treatment

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Abstract: Early childhood is considered to be a period of rapid development, with the acquisition of abilities predicting future positive school competences. Motor, cognitive and social difficulties related to cancer therapies heavily impact the development of children with cancer. This study focused on two main aims: to assess the developmental pathways in preschool children with leukaemia one year post-treatment; and to compare these abilities with those of a control group of healthy peers.

Forty-eight children and their families, recruited through the Haematology-Oncologic Clinic of the Department of Child and Woman Health (University of Padua), agreed to participate in this study. The children's mean age was 4.36 years (SD = 1.07, range = 1.91-6 years), equally distributed by gender, most of whom were diagnosed with Acute Lymphoblastic Leukaemia (N = 44). Matched healthy peers were recruited through paediatricians' ambulatories. Each family was interviewed adopting the Vineland Adaptive Behaviour Scales.

Paired sample t-tests revealed that children, especially aged 42-72 months, were reported to have significantly more developmental difficulties than their healthy peers, particularly in verbal competence, social and coping skills and gross motor abilities. These findings suggest that the creation of specialized interventions for both parents and children may fill the possible delays in children's development due to toxic therapies and their associated hospitalisation.

Keywords: Preschool; leukaemia; adaptive behaviour; developmental skills; healthy peers

1. Introduction

The number of children and adolescents who have survived cancer has increased in recent years due to significant improvements in survival rates [(1)]. Three main areas crucial in overcoming children's main developmental tasks were investigated: the cognitive sequelae related to cancer treatments (methotrexate, vincristine, steroids, Hematopoietic Stem Cell Transplantation (HSCT) [(1);(2)], motor performance delays [(3); (4)] and the general social impairments related to the illness (academic achievements, interpersonal relationships and coping skills) [(5); (6); (7)].

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1.1 Cognitive sequelae related to the illness and its treatment

Children's cognitive functioning after being treated with anti-tumoral drugs was largely investigated by analysing their long-term effects on survivors [(8)] as deficits in neurocognitive functions may not appear in the immediate period following treatment; similarly, testing shortly after diagnosis is not feasible [(9)]. Verbal competence, main executive functions and complex visual-spatial tasks were impaired in childhood survivors of ALL [Acute Lymphoblastic Leukaemia; (10)], with a lower performance in measures of working memory than controls [(11)] and a decline in intelligence and academic achievement [(12)]. Language performance remained stable in ALL children following intrathecal chemotherapy (ITC) over a two-year period [(2)], even if this treatment may impact language skills in the long-term [(13)].

The main risk factors in possible developmental deficits in childhood cancer survivors were identified as: aged under five at diagnosis [(14)], higher intensity therapy and the number of years since the individual's first therapy [(15)]. Reduced working memory and nonverbal abilities may be present during the first year of treatment after ALL depending on the last methotrexate dose and/or infusion rate [(16)]. Additionally, attentional dysfunctions are found in survivors of childhood ALL, especially in cases of severe treatment dosages [(17)]. The cognitive sequelae in children with leukaemia can also be influenced by HSCT, with a decline in motor and mnemonic abilities within the first year post-HSCT [(1)] and in verbal skills, with arithmetic and motor scores attested below the norms by three years post-HSCT [(18)].

1.2 Motor performance delays

Motor performance has been recognized as a key element for children's healthy development, especially towards their future social life, and even more so in kindergarten children [(19)]. Motor competence in early childhood impacts future developmental steps throughout school, stressing an important association between academic and social functioning. Children with cancer showed reduced motor performance at the end of the acute treatment phase, specifically in muscular explosive strength, handgrip strength, leg fatigue, visual-motor coordination, balance, speed and flexibility [(4)]. These difficulties appeared to persist in varying degrees several years after the end of treatment [(20)], in addition to visual–motor deficits and associated difficulties in math and reading achievements [(21)]. Higher levels of fatigue and a lower general wellbeing were self-reported in adult and adolescent (AYA) cancer survivors who underwent HSCT [(6)]. A known complication of treatment with vincristine (VCR) was the development of polyneuropathy, which can result in the loss of peripheral muscle power in both the upper and lower extremities, with increased motor problems. However, there were significant improvements over time, as revealed by the lower prevalence of neuropathy at increasing intervals following VCR injections [(22)]; in other studies [i.e. (23)], no correlation was found between motor performance and the cumulative dose of chemotherapy drugs, age, and follow-up time.

Important delays in the motor abilities of preschool children with leukaemia during the maintenance phase of therapy were found, especially if children underwent HSCT [(24)]. These conditions could influence their general social wellbeing and academic achievement, as demonstrated in Section 1.3.

1.3 Social impairments and academic difficulties

The experience of illness and its related aspects – such as hospitalization and the overhaul of daily routines – may impact on social functioning as well. Coming back to or beginning schooling after strong medical treatment can be academically and socially difficult for children with cancer. The decline in intelligence and academic achievement appeared to be related to poor social functioning, especially in female children [(7)]. Peer socialization was reported as the main difficulty by survivors, whom displayed limited comprehension of simple social rules (i.e. turn taking) or with easy reported bounds with older children or teachers then with their peers [(25)]. Social skills were less developed due to reduced peer interaction [(26)] and the perceived social support from friends was lower than

healthy peers [(27)], with a reduced ability to maintain friendships and social competence, with survivors demonstrating a more compromised relationship with their best friend [(28)], in addition to increased self-esteem problems [(5)].

1.4 Aims

Little is known about the developmental trajectories of preschool patients with leukaemia, which allow them to have adequate functioning during acute cancer treatments. In this study, we will focus on the specific developmental domains of children with leukaemia and compare their adaptive functioning skills with those of a group of healthy peers. By identifying the possible developmental delays in paediatric oncologic patients, we could discover specific indications for what psychological and physiotherapist interventions should be focused on.

The research questions are:

1. Are there differences between the clinical and control groups in their developmental task performances?

2. Are there differences in developmental tasks throughout the different age groups (between ages three and five years)?

3. In which domains do children show more difficulties (communication abilities, daily living skills, socialization competence, motor performance)?

2. Materials and Methods

2.1 Procedure

Ethical approval was obtained from the University Hospital of Padua Ethical (code 1783P), following the rules of the Declaration of Helsinki of 1975. A clinical psychologist contacted families during the first hospitalization of their children, in the second week after diagnosis. The project aims were explained and informed consent was obtained. Approximately one year later, the clinical psychologist administered the Vineland Adaptive Behavior Scales (VABS) [(29)] at the day hospital of the clinic.

2.2 Participants

Participants were preschool children aged 1.91-6 years from an ample sample consisting of 75 children one-year post diagnosis. Of these, 15 exited the study due to death or a terminal diagnosis (N = 9), or otherwise dropped out (N = 6). The response rate attested to 92%, excluding the deceased patients.

Forty-eight healthy peers were matched with the remaining 60 patients for this study, so the study was run on 48 paediatric leukemic patients matched to 48 healthy controls paired for age and gender. Children's mean age was 4.36 years (SD = 1.07), equally distributed by gender, most of whom were diagnosed with ALL (N = 44), while four had Acute Myeloid Leukaemia (AML), with a mean hospitalization period of 56.13 days (SD = 49.36). All parents were Caucasian, aged 36.81 years on average (SD = 6.93) and had a mean of 12.33 years of schooling (SD = 3.61). Parents' perceived economic condition was mostly average (51.2%), equally distributed between high (24.4%) and low (24.4%) for Italian norms, but all were above poverty. Family were composed of either two (N = 32), one (N = 13) or three (N = 3) children.

The eligibility criteria for the control group participants (N = 48) was: absence of life-threatening or chronic illness and no presence of learning or sensory problems and other pathological aspects. The control group of healthy peers consisted of those enrolled at paediatricians' ambulatories.

The mean age of the clinical group was 4.36 years (SD = 1.06; range 1.91-6) and the mean age of the control group was 4.5 (SD = 1.06; range 2-5.91). After comparing the two groups based on their mothers' characteristics, we found that they were homogeneous on their mothers' age ($t_{47} = -.84$; $p>0.05$) and the number of sons in the family ($t_{47} = -.43$; $p>0.05$), whilst they differed on their mothers'

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schooling years (t47 = 3.85; p<.001), with mothers of the control group possessing more years of schooling (mean = 15.14; SD = 3.26) than the clinical group (mean = 12.33; SD = 3.61).

2.3 Instruments

The VABS is an interview administered to parents by a trained psychologist. This interview is psychometrically validated and scores several adaptive behaviours of children. The scoring was norm-referenced and referred to specific developmental levels between birth and adulthood along several domains. The 540 items that constituted this interview are organized around four adaptive behaviour domains (Communication, Daily Living Skills, Socialization and Motor Skills) and are grouped in clusters. These groupings are distributed in developmental order under sub-domains. The three Communication sub-domains are: Receptive, Expressive and Written Language. Personal, Domestic and Community make up the Daily Living Skills domain, while the Socialization sub-domains are Interpersonal, Play and Leisure and Coping Skills. Finally, Gross and Fine Motor Abilities make up the Motor Abilities domains. Each sub-domain contained a series of items grouped into their representative clusters. The clusters assessed in the clinical and control groups demonstrated a roofing effect, and obtained significantly different results in some specific clusters as shown in Table 1.

Table 1. Vineland Adaptive Behavior Scales organized by domains, subdomains, clusters and item content: significant items.

Domain	Subdomain	Cluster	Items content
Communication	Receptive	Attention	How and how long the individual listen to someone, pays attention to activities or stories and understand given information. (E1-E5)
	Expressive	Vocabulary	Number of words known and pronounced from the individual. (E1-E3)
		Language in sentences	Sentence composition in a progressive difficulty order (names, verbs, and negatives). (F1-F4)
		Use of proper names	Individual knows name, nicknames or surname of familiar people when requested. (G1-G4)
		Questions formulation	Individual is able to raise different type of questions to gather information. (H1-H6)
		Abstract concepts use	Individual is able to male generalizations and understand basic concepts. (I1-I4)
		Tell their own experiences	Individual can spontaneously talk about own experiences. (J1-J5)
		Use of connectors	Individual is able to use different connectors to build sentences. (L1-L5)
		Articulation	Quality and precision in speech articulation is evaluated. (M1-M4)
		Recitation	Ability to recites rhymes, songs, folk tales is assessed. (N1-N4)
		Use of plurals and verbs times	Individual uses verb forms correctly in different tenses. (O1-O6)

 doi:10.20944/preprints201905.0086.v1

		Provide information about yourself	Ability to answer correctly to questions referred to address, telephone number or other personal information is measured. (P1-P7)
		Expressing complex ideas	Individual is able to express complex ideas. (Q1-Q3)
Socialisation	Interpersonal Relationships	Recognition of emotions	Individual is able to recognize emotions and classify them. E1-E3)
		People identification	Individual know names of family members, and identifies them through features other than their name. (F1-F4)
		First forms of social communication	Individual is able to participate in conversation. (G1-G3)
		Friendships	Individual has friendships of the same of other sex. (H1-H5)
		Give presents	Individual creates or buys presents for others.
	Play and Leisure	Sharing and cooperation	Ability to share and cooperate with others without beeing reminded to do so. (I1-I4)
		Watching TV	Individual knows channel and names properly favourite TV programme. (E1-E4)
		Following play rules	How individual plays games, respect turns and is able to follow rules are measured. (F1-F3)
		Games participation	Participation to different types of games (i.e. cards, hazard based board) is assessed. (G1-G4)
		Go out with friends	Individual is able to meet friends outside home in the afternoon or evening. (H1-H4)
	Coping skills	Respect for the rules	Individual respects rules in community and social situations. (A1-A4)
		Good education in conversation	Individual is able to have conversations with others showing good education. (C1-C3)
		Responsible time management	Individual shows ability in managing time limits and making projects along time. (D1-D2)
Motor abilities	Gross	To gamble	Jumping and balancing are assessed. (H1-H3)
		To catch and throw a ball	Individual's ability to catch and throw balls of various dimensions are measured. (I1-I5)
		To ride a tricycle and bicycle	Individual displays ability to ride a two or three wheeled vehicle. (J1-J4)
Motor abilities	Fine	To gather objects and make models	Individual's use of hands and fingers to reach and manipulate objects are measured. (B1-B4)
		To draw	Ability to draw with drawing implements and write properly is assessed. (D1-D7)

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To open drawers and doors	Individual displays ability to pull and push doors and open locks. (E1-E4)

The scoring of the items is as follows: "2" stands for behaviours usually or habitually performed; "1" represents behaviours sometimes/partly performed or when the parent does not know if the child performs the activity or if the child has never had the opportunity to do so; while "0" stands for behaviour never performed.

Furthermore, medical and socio-demographic information were collected.

2.4 Statistical methods

Descriptive statistics were run to show the child's developmental skills scores one year post-diagnosis; specifically, their global score and the scores related to each VABS subscale.

The possible socio-demographic differences between the two samples (clinical and control) were investigated by adopting paired sample t-tests to estimate the comparability of the samples. Inferential comparisons between cancer patients and control samples, matched by gender and age, were run by adopting paired sample t-tests. The effect size was controlled for each domain, sub-domain and for the descriptive items belonging to each sub-domain.

The evaluated statistical significance attested at the nominal P = 0.05 level; multiple comparison adjustments were adopted after controlling for the normal distribution of the test scores and the homogeneity of variances. All data were analysed using SPSS Version 20 (SPSS Inc., Chicago, IL).

3. Results

3.1 Developmental domains in children with leukaemia compared with healthy peers

Parents of children with leukaemia reported significantly lower developmental scores in their children compared to healthy peers, both in composite (t 47= - 9.37; p = 0.001) and in three out of the four adaptive domains: Communication (t 47= - 9.37; P = 0.001), Socialization (t 47= - 5.52; P = 0.001) and Motor Abilities (t 47 = - 3.72; P = 0.001) (Figure 1a). For Communication, significant differences were identified in the following sub-domains: Receptive (t 47 = - 5.40; P = 0.001) and Expression (t 47 = - 5.42; P = 0.001). Socialization sub-domains were all significantly lower in children with leukaemia: Interpersonal relationships (t 47 = - 3.73; P = 0.001), Play and Leisure (t 47 = - 3.42; P = 0.001) and Coping skills (t 47 = - 2.62; P = 0.01). The two Motor Abilities subscales both obtained lower scores: Gross (t 47 = - 2.38; P = 0.002) and Fine (t 47 = - 1.93; P = 0.05) (Table 2 and Figure 1b).

We also have to take into consideration that the mother's education was different when comparing the clinical and control groups, this variable could be associated with the children's developmental tasks. We therefore ran a series of Pearson's correlations in the clinical and control groups between mothers' schooling years and VABS domain scores. None of these statistical analyses obtained significance (p>0.05), and so this variable did not have a significant association with children's developmental tasks.

Table 2. Adaptive functioning in children with leukaemia and healthy controls.

Scales	Leukaemia Children		Controls		Statistical Analyses		
	Mean	*SD*	*Mean*	*SD*	*t*	*P*	*d*

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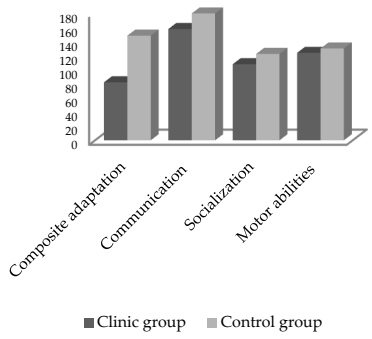
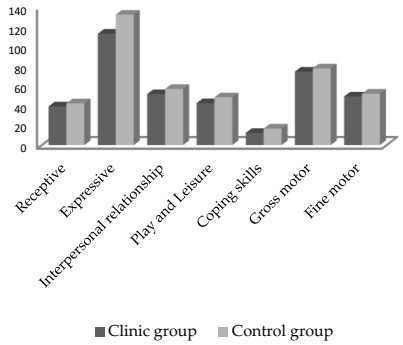
Adaptive functioning composite	82.07	51.22	148.19	25.51	-9.37	0.0001	10.54
Communication	157.58	40.72	179.66	28.19	-5.52	0.0001	0.58
Receptive	39.18	4.27	42.35	2.25	-5.40	0.001	0.89
Expressive	112.93	34.74	132.22	23.46	-5.42	0.001	0.61
Socialization	107.70	30.41	122.31	96.98	-3.72	0.001	0.51
Interpersonal Relationship	51.79	11.70	57	9.19	-3.73	0.001	0.49
Play and Leisure	42.54	12.35	48.50	13.35	-3.42	0.001	0.46
Coping Skills	12.43	8.14	16.81	9.24	-2.62	0.01	0.50
Motor Abilities	123.87	23.06	130	13.75	-2.36	0.02	0.30
Gross	74.54	11.89	77.81	6.10	-2.38	0.02	0.60
Fine	49.33	12.25	52.18	8.18	-1.94	0.05	0.26



(**a**)



(**b**)

Figure 1. VABS Adaptive functioning domain scores comparing: (**a**) children with leukaemia one year post-diagnosis and controls; (**b**) VABS Adaptive functioning sub-domain scores comparing children with leukaemia one year post-diagnosis and controls.

3.2 Differences in developmental skill performance in age groups (23-36 months, 37-48 months, 49-71 months)

We divided the children into three age groups: 23-36 months (N = 5), 37-48 months (N = 12) and 49-71 months (N = 31) to better investigate developmental skills by age. We ran the paired sample t-test

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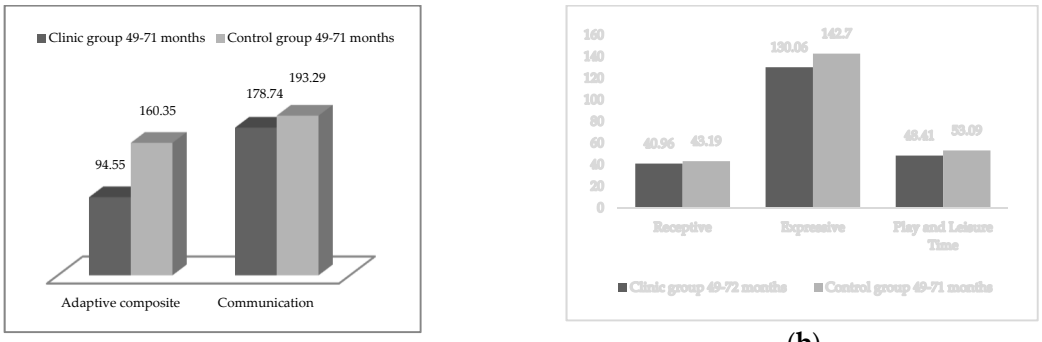
in each age band. A significant difference between the clinical and control groups was obtained for the VABS composite score of children aged 37-48 months (t 11 = - 5.57; P = 0.001; d = 2.02) and of those aged 49-71 months (t 30 = - 7.40; P = 0.001; d = 1.64), with the clinical group showing lower scores than the control one.

Reduced communication abilities were recognized in the clinical group of children aged 37-48 months (t 11 = - 3.82; P = 0.003; d = 1.51), in particular in the Receptive (t 11 = - 3.14; P = 0.009; d = 1.47) and Expressive (t 11 = - 3.57; P = 0.004; d = 1.45) subscales. The same result was obtained in those aged 49-71 months (t 30 = - 4.61; P = 0.001; d = 1.03), specifically in the Receptive (t 30 = - 4.42; P = 0.0001; d = 1.01) and Expressive (t 30 = - 5; P = 0.0001; d = 1.27) subscales.

Parents of children aged 37-48 months reported significantly lower Socialization scores (t 11 = - 5.89; P = 0.001; d = 1.85) in all the threes subscales, Interpersonal relationships (t 11 = - 4.72; P = 0.001; d = 1.54), Play and Leisure time (t 11 = - 3.49; P = 0.005; d = 1.59) and Coping skills (t 11 = - 2.22; P = 0.048; d = 0.95).

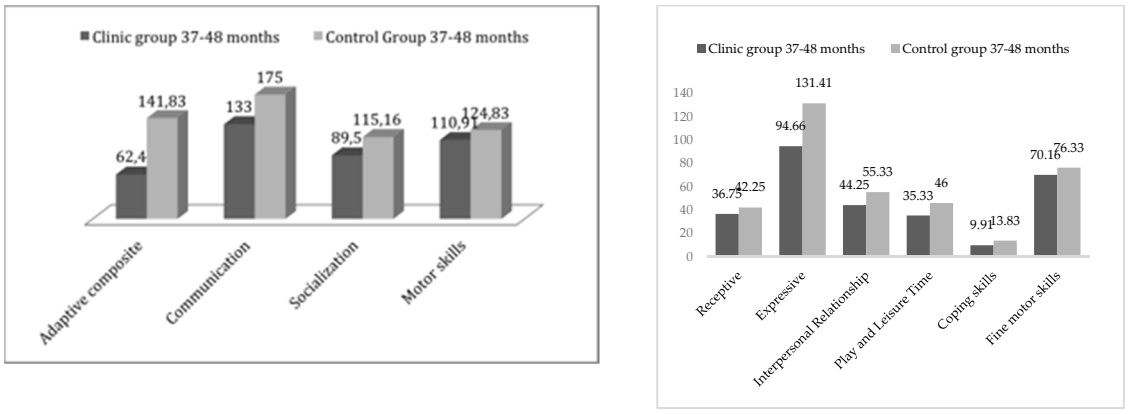
Parents of children aged 23-36 months belonging to the clinical group reported significantly lower scores in Coping skills (t 4 = - 3.14; P = 0.035; d = 2.06). Moreover, the group of children aged 49-71 months showed lower scores in the Play and Leisure time subscale (t 11 = - 2.20; P = 0.003; d = 0.44).

Following parental reports, children aged 37-48 months showed lower scores in Motor Abilities (t 11 = - 2.26; P = 0.004; d = 1.05), in particular in Gross motor skills (t 11 = - 2.29; P = 0.042; d = 1.03). Figure 2 (a and b) and 3 (a and b) demonstrate these results.



(**a**) (**b**)

Figure 2. VABS Adaptive functioning domain scores comparing: (**a**) children with leukaemia aged 49-71 months one year post-treatment and matched controls; (**b**) VABS Adaptive functioning sub-domain scores comparing children with leukaemia aged 49-71 months one year post-treatment and matched controls.



(**a**) (**b**)

Figure 3. VABS Adaptive functioning domains' scores comparing: (**a**) children with leukaemia aged 37-48 months one year post-treatment, and matched controls; (**b**) VABS Adaptive functioning sub-domains' scores comparing children with leukaemia aged 49-72 months one year post-treatment and matched controls.

3.3 In which domain cluster (Communication, Daily living skills, Socialization, Motor abilities) did children show more difficulties?

Children with leukaemia showed significantly lower levels of development, according to parental perceptions, with respect to some items grouped into specific clusters. We ran the paired t-tests to evaluate the statistical differences between the clinical and control groups in each domain, sub-domain and in the associated clusters. Table 3 documents the results.

Table 3. Clinic and control group comparisons along VABS items, grouped by cluster.

		Patients		**Control**		**Statistical Analyses**		
Sub-domain, Cluster	Item	M	SD	M	SD	t	df	p
Receptive, Attention	E1	1.33	0.85	1.91	0.34	-4.54	47	0.001
	E2	1.16	0.95	1.52	0.68	-2.15	47	0.003
	E3	0.83	0.91	1.66	0.55	-6.20	47	0.0001
	E4	0.72	0.86	1.58	0.60	-5.85	47	0.0001
	E5	0.14	0.5	0.04	0.28	1.22	47	0.23 ns
Expressive, Vocabulary	E1	1.79	0.61	2	0	-2.34	47	0.02
	E2	1.70	0.71	2	0	-2.83	47	0.007
	E3	1.70	0.71	1.91	0.34	-2.40	47	0.017
Expressive, Language in sentences	F1	1.81	0.57	2	0	-2.27	47	0.027
	F2	1.75	0.66	1.89	0.42	-2	47	0.05
	F3	1.71	0.71	1.97	0.14	-2.77	47	0.008
	F4	1.71	0.71	1.87	0.49	-2.06	47	0.04
Expressive, Use of proper names	G1	1.83	0.55	2	0	-2.06	47	0.044
	G2	1.83	0.55	2	0	-2.06	47	0.044
	G3	1.70	0.71	2	0	-2.83	47	0.007
	G4	1.70	0.71	1.95	0.20	-2.72	47	0.009
Expressive, Questions formulation	H1	1.70	0.71	1.95	0.29	-2.59	47	0.013
	H2	1.70	0.71	1.89	0.42	-2.02	47	0.048
	H3	1.75	0.66	1.91	0.40	-2.06	47	0.044
	H4	1.74	0.67	1.89	0.42	-1.73	47	0.090 ns
	H5	1.75	0.66	1.91	0.40	-2.06	47	0.044
	H6	1.70	0.71	1.85	0.05	-1.73	47	0.090 ns

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Expressive, Abstract concepts use	I1	1.70	0.71	1.87	0.49	-2.06	47	0.044
	I2	1.79	0.61	1.91	0.40	-1.77	47	0.083 ns
	I3	1.77	0.62	1.91	0.40	-2	47	0.05
	I4	1.66	0.72	1.89	0.42	-2.68	47	0.010
Expressive, Tell their own experiences	J1	1.70	0.68	1.91	0.40	-2.48	47	0.017
	J2	1.62	0.76	1.75	0.63	-1.23	47	0.22 ns
	J3	1.62	0.78	1.83	0.55	-1.94	47	0.05
	J4	1.62	0.78	1.77	0.62	-1.31	47	0.19 ns
	J5	1.66	0.75	1.79	0.61	-1.13	47	0.26 ns
Expressive, Use of connectors	L1	1.75	0.66	1.91	0.40	-2.06	47	0.044
	L2	1.64	0.75	1.68	0.71	-0.33	47	0.74
	L3	1.52	0.82	1.85	0.5	-3.06	47	0.004
	L4	1.58	0.79	1.79	0.61	-1.75	47	0.08
	L5	1.54	0.82	1.81	0.57	-2.45	47	0.018
Expressive, Articulation	M1	1.41	0.84	1.79	0.61	-3.18	47	0.003
	M2	1.41	0.84	1.77	0.62	-2.93	47	0.005
	M3	1.27	0.91	1.77	0.93	-3.85	47	0.0001
	M4	1.16	0.93	1.45	0.89	-2.14	47	0.038
Expressive, Recitation	N1	1.54	0.85	1.75	0.66	-1.69	47	0.096 ns
	N2	1.43	0.89	1.77	0.62	-2.61	47	0.012
	N3	0.68	0.92	1.72	0.67	-6.61	47	0.0001
	N4	1	0.98	1.58	0.76	-3.65	47	0.001
Expressive, Use of plurals and verbs times	O1	1.10	0.97	1.77	0.62	-5.09	47	0.0001
	O2	1.06	0.97	1.70	0.71	-4.47	47	0.0001
	O3	0.89	0.97	1.64	0.69	-5.19	47	0.0001
	O4	0.79	0.96	1.62	0.78	-5.92	47	0.0001
	O5	0.25	0.60	1	0.79	-6.20	47	0.0001
	O6	0.33	0.69	1.35	0.83	-7.39	47	0.0001
Expressive, Provide information about yourself	P1	1.33	0.95	1.79	0.61	-3.74	47	0.001
	P2	1.33	0.95	1.71	0.68	-3.18	47	0.003
	P3	1.20	0.98	1.77	0.62	-4.34	47	0.0001
	P4	0.85	1.31	0.98	0.94	-3.02	47	0.004
	P5	0.39	0.79	0.66	0.85	-1.64	47	0.11 ns
	P6	0.12	0.49	0.16	0.55	-0.44	47	0.66 ns
	P7	0.33	0.75	1.12	0.89	-5.21	47	0.0001

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Expressive, Expressive complex ideas	Q1	0.22	0.62	0.91	0.98	-4.07	47	0.0001
	Q2	0.22	0.62	0.43	0.82	-1.43	47	0.16 ns
	Q3	0.04	0.28	0.22	0.62	-1.84	47	0.07 ns
Interpersonal relationships, Recognition of emotions	E1	1.79	0.61	1.79	0.58	0	47	1 ns
	E2	1.91	0.40	2	0	-1.43	47	0.16 ns
	E3	0.06	0.32	1.87	0.44	-23.59	47	0.0001
Interpersonal relationships,	F1	1.54	0.84	1.87	0.49	-3.066	47	0.004
People identification	F2	1.5	0.87	1.87	0.48	-3.29	47	0.002
	F3	1.31	0.92	1.75	0.66	-3.38	47	0.001
	F4	1.20	0.96	1.77	0.62	-4.23	47	0.0001
Interpersonal relationships,	G1	1.12	0.95	1.56	0.79	-3.57	47	0.001
First forms of social communication	G2	1.16	0.99	1.52	0.85	-2.27	47	0.028
	G3	0.75	0.95	0.75	0.95	0	47	1 ns
Interpersonal relationships,	H1	0.95	1	1.37	0.93	-2.48	47	0.017
Friendships	H2	0.91	1	1.14	0.98	-1.29	47	0.20 ns
	H3	0.66	0.98	1.33	0.95	-3.87	47	0.0001
	H4	0.06	0.32	0.21	0.61	-1.14	47	0.16 ns
	H5	0.54	0.89	0.79	0.98	-1.52	47	0.13 ns
Interpersonal relationships, Give presents	I1	0.31	0.71	0.52	0.87	-1.20	47	0.23 ns
	I2	0.29	0.71	0.41	0.82	-0.83	47	0.41 ns
	I3	0.12	0.48	1.91	0.4	-20.10	47	0.0001
	I4	0.08	0.40	0.06	0.32	0.33	47	0.74 ns
Play and Leisure, Sharing and cooperation	E1	1.47	0.77	1.70	0.65	-1.97	47	0.05
	E2	1.43	0.84	1.52	0.74	-0.57	47	0.57 ns
	E3	1.14	0.94	1.43	0.79	-1.85	47	0.07 ns
	E4	1.08	0.94	1.54	0.82	-2.46	47	0.017
Play and Leisure, Watching TV	F1	1.08	1	1.70	0.68	-3.99	47	0.0001
	F2	1.25	0.97	1.5	0.82	-1.69	47	0.096 ns
	F3	0.75	0.97	0.70	0.89	0.28	47	0.78 ns
Play and Leisure, Following play rules	G1	0.91	0.98	1.43	0.87	- 2.91	47	0.005
	G2	0.83	0.99	1.31	0.92	-3.43	47	0.001
	G3	0.68	0.94	0.97	0.95	-2.09	47	0.042
	G4	0.64	0.93	1.04	0.94	-2.52	47	0.015
Play and Leisure, Games participation	H1	0.39	0.79	0.89	0.99	-3.50	47	0.001
	H2	0.37	0.78	0.79	0.98	-3.14	47	0.003
	H3	0.16	0.55	0.39	0.79	-2.11	47	0.04

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	H4	0.12	0.48	0.45	0.84	-2.69	47	0.010
Play and Leisure, Go out with friends	I1	0	0	0.25	0.66	-2.59	47	0.013
	I2	0	0	0.02	0.14	-1	47	0.32 ns
	I3	0	0	0.16	0.55	-2.06	47	0.044
Coping skills, Respect for the rules	A1	1.58	0.61	1.85	1.29	-2.65	47	0.011
	A2	1.29	0.71	1.89	0.37	-5.92	47	0.0001
	A3	1.60	0.67	1.70	0.61	-0.72	47	0.47 ns
	A4	1.37	0.81	1.91	0.27	-4.42	47	0.0001
Coping skills, Good education in conversation	C1	0.22	0.59	0.72	0.91	-3.75	47	0.0001
	C2	0.12	0.39	0.47	0.74	-3.12	47	0.003
	C3	0.14	0.50	0.45	0.84	-2.33	47	0.024
Coping skills, Responsible time management	D1	0	0	0.37	0.78	-3.29	47	0.002
	D2	0	0	0.22	0.62	-2.53	47	0.015
Gross motor, To gamble	H1	1.66	0.72	1.91	0.40	-2.28	47	0.027
	H2	1.04	0.96	1.56	0.76	-3.49	47	0.001
	H3	1.04	0.96	1.37	0.93	-2.06	47	0.044
Gross motor, To catch and throw a ball	I1	1.87	0.48	2	0	-1.77	47	0.083 ns
	I2	1.87	0.48	2	0	-1.77	47	0.083 ns
	I3	1.56	0.79	1.87	0.44	-2.23	47	0.031
	I4	1.58	0.79	1.87	0.44	-2.31	47	0.025
	I5	0.87	0.98	0.54	0.77	1.88	47	0.066 ns
Gross motor, To ride tricycles and bicycles	J1	1.77	0.62	1.91	0.40	-1.55	47	0.128 ns
	J2	1.68	0.71	1.85	0.50	-1.59	47	0.118 ns
	J3	1.43	0.89	1.70	0.71	-1.90	47	0.06
	J4	0.39	0.73	0.64	0.93	-1.66	47	0.10 ns
Fine motor, To gather objects and make models	B1	1.95	0.28	2	0	-1	47	0.32 ns
	B2	1.93	0.32	1.93	0.32	0	47	1 ns
	B3	1.89	0.42	1.95	0.28	-1.35	47	0.18 ns
	B4	1.77	0.62	1.95	0.28	-2.27	47	0.027
Fine motor, To draw	D1	1.72	0.67	2	0	-2.77	47	0.008
	D2	1.62	0.78	1.75	0.63	-0.88	47	0.38 ns
	D3	0.93	0.95	1.20	0.94	-1.64	47	0.11 ns
	D4	1.12	1	1.37	0.89	-1.63	47	0.11 ns
	D5	1.47	0.87	1.62	0.78	-1.04	47	0.30 ns
	D6	1.22	0.92	1.27	0.89	-0.23	47	0.81 ns
	D7	1.45	0.84	1.27	0.91	1.19	47	0.23 ns

 doi:10.20944/preprints201905.0086.v1

Fine motor, To open drawers and doors	E1	1.77	0.62	1.95	0.28	-1.84	47	0.07 ns
	E2	1.79	0.61	2	0	-2.33	47	0.024
	E3	1.79	0.61	1.77	0.62	0.15	47	0.87 ns
	E4	127	0.93	1.35	0.93	-0.53	47	0.6 ns

From Table 3, we can see how preschool patients, when compared with healthy peers, showed difficulties exclusively in the attentive functions involved in the Receptive sub-domain. When dealing with expressive skills, we found several significant difficulties: vocabulary, language in sentences, use of proper names, question formulation, abstract concept use, use of connectors, articulation and recitation and use of plurals and verbs in different tenses. Children's capacity to tell their own experiences, to provide information about himself/herself and to express complex ideas appears to be unaffected.

Regarding the Socialization domain, we analyzed the possible differences in the Interpersonal relationships cluster. Recognition of emotion seemed to be unaffected, even if the paediatric patient failed to recognize or verbally classify his/her own joy, sadness, fear or anger. The identification of people and the first forms of social communication seemed to be problematic, while giving presents and maintaining friendships is largely unaffected, except for the giving of little presents to family members, the preference for some friends and the presence of a favourite friend.

The Play and Leisure subscale showed lower clusters in the clinical sample, especially when following/respecting the rules of play, participating in games and going out with friends. Sharing/cooperation and watching TV were relatively unaffected, except sharing toys or other personal items with or without being reminded to do so and the recognition of the name of at least one favourite TV program and the day and channel on which it is broadcasted. Furthermore, the Coping skills subscale presented lower levels, specifically about respect for the rules, conversational rules and responsible time management.

Gross motor abilities such as to gamble was lower in children with leukaemia, in addition to activities such as grabbing a large ball thrown from a distance of two meters and throwing a ball in a certain direction. The scoring of other activities such as riding a tricycle or bicycle were comparable in the two groups.

Fine motor skills such as gathering objects and making models or drawings were comparable between the clinical and control groups, except for drawing a square model or trapezoids with a pencil and constructing three-dimensional structures of at least five cubes. Opening drawers and doors is not a compromised activity in the clinical group, with the exception of opening locks with a key, in which they obtained lower mean scores.

4. Discussion

Early childhood is a crucial time of life, where basic adaptive skills experience rapid and dynamic growth, significantly impacting learning. The child has to overcome different daily tasks, such as "feeding oneself, maintaining hygiene (by washing hands, brushing teeth, and bathing), changing a variety of clothes, and controlling bowel and bladder" [(30)]. The child also has to develop gross motor abilities, including to gamble, catching/throwing the ball and riding a tricycle or bicycle. Furthermore, important fine motor skills should be developed, such as gathering objects, making models, drawing and opening drawers or doors. Language activities during preschool years include attention tasks, vocabulary level, use of language in sentences, use of proper names/plurals and verb tenses, question formulation, the use of abstract concepts and the type of articulation. Children at this stage learn to recount their own experiences and provide information about themselves, but also to take turns and negotiate social interactions. However, these conceptual, social and practical skills could be negatively influenced by cancer experiences and treatments, so much so that delays in their psycho-social and motor competencies may occur.

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Negative treatment sequelae in children with leukaemia can be attributable to different drugs [(31)]: i.e. mucositis is due to daunoblastina, where possible neuropathy could be caused by VCR. Steroids could lead to humour and behavioural difficulties, psychosis, bone fragility, myopathies, eye problems and neuropathies, while Peg-asparaginase could cause trembling fingers and gastrointestinal disorders. Nausea and vomit could be attributable to ifosfamide, while working memory and attention difficulties could be caused by intrathecal methotrexate. These negative treatment effects could contribute to increased developmental delays, together with other aforementioned hospitalization stressors.

Research on the development of children with cancer has focused less on the overcoming process of developmental tasks in early childhood during cancer treatments and instead remains in the maintenance phase of the therapy.

In this study, preschool children receiving therapy for leukaemia showed important developmental difficulties and delays that could contribute to maladaptive personal growth. The major limitations of these children, compared with matched healthy peers, were found in communication, socialization and motor skills, especially in children aged 37-48 months. In the 49-71 months age range, the main limitations were identified in the communication skills and adaptive skills composite scores.

At this purpose, it becomes fundamental to identify children more at risk for adaptive skills delays. Precedent studies [(32);(24)] identified important delays in children in their gross and fine motor performance just during the maintenance therapy phase and also after completion of therapies, with the frequency of days of hospitalization and HSCT experience that could drastically dampen all the children's adaptive skills.

This study also facilitates a focus on the main difficulties of children, as reported by parents, adopting a qualitative approach, allowing detailed information to be collected on the specific clusters of each domain and sub-domain.

Attention functions in receptive domains were reduced, like, for example, the capacity of listening to the teacher/a story/lesson for a certain period of time, ranging from five to 30 minutes. This problem could be associated with chemotherapy and CNS treatment, which reduces executive functions [(17)], with possible consequent difficulties in academic achievement when children start school [(33)].

Confirming the literature on childhood cancer survivors on reduced verbal competence and processing speed and attention in ALL [(13)], parents reported significantly reduced expressive functions. Children's vocabulary was limited, their language in sentences was poor and complex phrases were not formulated. Other limitations were reported in the use of proper names such as the name and surname of family members and the formulation of questions starting with "what", "where", "who", "why" and "when". Abstract concept abilities could also be delayed, including: making simple generalizations; understanding simple adjectives that indicate quality; and evaluating measurements of magnitude. Language form is also less developed: i.e. the use of connectors was limited, the use of plural and verb tenses could be incorrect and the articulation of words could be inaccurate, with letters or sounds being confounded.

In the medical setting, children very often became silent both with the paediatric staff and even with parents; they either could not speak due to trauma or because they feared to ask questions about their illness. The adults could also not correct their children's language mistakes because their parenting attitude was more comprehensive for children's difficult health conditions. Children with leukaemia were very often isolated from their peers (e.g. kindergarten activities and park visits), and in the hospital it was difficult to play with other patients as children in other settings would. The medical setting and hospitalization could potentially involve such language delays.

On the other hand, the capacity to recount their own experiences and provide information about themselves, such as talking about their experiences using a detailed narrative form, was intact, together with the ability to express complex ideas. Their receptive and expressive abilities seemed to be unaffected, while correct formulation and articulation did not always escape unharmed.

Studies involving social behaviour and peer relationships generally concluded that children with leukaemia were more sensitive and isolated than peers, thus developing social competence limitations [(26)]. In this study, children with leukaemia confirmed socialization difficulties compared with healthy

peers. Specifically, they had limitations in their interpersonal relationships: even if their recognition of emotions was maintained, they didn't recognize or verbally classify their own, had difficulties identifying people and expressing initial social communications. The capacity of making/giving presents and friendship bonds were maintained, even if they failed to show a preference for some friends or for a favourite friend.

Other limitations dealt with the activities of following play rules, participating in games and going out with friends, likely due to their medical condition(s). Sharing/cooperation was relatively maintained, except for sharing toys or other personal items with or without being reminded to do so. Coping skills attested at lower levels, specifically respecting the rules, conversational turns and responsible time management.

Impairments in motor adaptive skills were identified in children with leukaemia during the therapy [(24)]. This study confirmed difficulties in gross motor abilities such as to gamble, grabbing a large ball thrown from a distance of two meters and throwing a ball in a certain direction. The scoring of other activities such as riding a tricycle or bicycle was comparable in the two groups, as was rolling the ball while sitting and throwing the ball. Other compromised fine motor skills were making copies of a square model or trapezoids with a pencil, constructing three-dimensional structures of at least five cubes and opening a lock with a key. Other fine motor skills didn't show any significant difference. Generally, there is some impact of therapies on motor abilities, but it is principally on gross motor skills. In the clinic during hospitalization, there is the possibility of playing with the volunteers (wood buildings, work with play dough or clay and decoupage) and parents are helped by psychologists to stimulate their children at home (i.e. to cook, hang out the laundry, draw or perform daily living activities). However, being persistently bedridden and its associated fatigue could impair gross motor achievements, subsequently impairing muscle strength and balance, both during the therapies [(20)] and after HSCT [(33)]. Fine motor skills may display a long-term delay, for example after therapy or HSCT, as documented in Taverna et al. [(32)].

One limit of this study is that children are not very numerous, and so it is difficult to generalize these results. AML patients are fairly infrequent, however we decided to include them anyway to have explorative data as these patients experience common stressors, such as isolation, gastrointestinal problems, chemotherapy sequelae and steroids sequelae.

We have not any baseline measure of children's adaptive skills before or close to the cancer diagnosis. However, it would have been impossible to assess the adaptive behaviour prior to the illness, and, similarly, it would have been very difficult to have the parents' collaboration and their valid reports immediately after the diagnosis, when the therapies begin, as it is a very critical time. Since the children were evaluated only one year post-diagnosis, it would also have been of great interest to compare changes in the areas tested from baseline in both the patients with leukaemia and the controls, instead of this limited cross-sectional approach. Future studies explore this with a longer follow-up of pre-school children.

One strength of this study is the in-depth interviews with parents of preschool patients during the maintenance phase of therapy, when the children can partially re-enter their normal daily routines, meeting peers after isolation and beginning primary school. This is the first study that focused specifically on adaptive skills in childhood leukaemia patients of preschool age during therapies. Its other strengths are the use of a comparative control group of healthy peers, allowing the identification of the degree of delays, and the innovative use of qualitative information derived from the VABS-II clusters, which facilitate the understanding of specific developmental difficulties to create psycho-educative interventions.

5. Conclusions

Based on these results, the following clinical suggestions are proposed.

Firstly, we have to take into consideration children's age for the possible psychological interventions, because we have seen, after reviewing the literature and partially in our study, how age influenced both the child's ability to cope and adaptability and, consequently, their quality of life. The 37-48 month old children seemed to be more at risk for developmental delays.

Secondly, our empirical results can help to set up specialized interventions focused on parents and children to meet the developmental difficulties associated with leukaemia. In particular, receptive attention problems, vocabulary poorness, reduced language in sentences and in questions together with interpersonal relationship difficulties, social and play rules and fine and gross motor problems were the main compromised developmental domains. Consequently, specific language and psycho-motor programs can be implemented during hospitalization. Socialization and educational programs can be proposed, both during the acute phase of treatment and day-hospital follow-ups. Social plays and educative guidelines can be taught to parents to stimulate their child at home, facilitating their children's re-entry into their normal routines as soon as possible (school, sport and hobbies).

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