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Health-Related Quality of Life, Cognitive Functioning and Behavior Problems in Children with Langerhans Cell Histiocytosis

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Abstract

Goals of work. This study was designed to evaluate generic and disease-specific health-related quality of life (HRQoL), cognitive functioning and behavior problems of children with Langerhans Cell Histiocytosis (LCH). Furthermore, we investigated which medical determinants and social demographic factors were predictive for HRQoL, cognitive functioning and behavioral problems. *Methods.* In this cross-sectional case-control study 24 children ranging from 7 to 17 years of age were administered a HRQoL questionnaire, cognitive tests and behavior ratings. In addition, a disease-specific HRQoL measure was developed and tested. Results were compared to a reference group consisting of healthy peers and to proxy-ratings by parents and teachers. *Results.* Children with LCH reported a lower physical HRQoL than the reference group ($p \leq .05$). Children older than 12 reported lower HRQoL scores. Scores on the disease-specific HRQoL questionnaire were lower than on the generic measure used. Performances on cognitive tests varied widely, short term visual memory was most affected. Twenty-five percent of the children follow special education. According to parents and teachers, children with LCH had more internalizing behavior problems (i.e. anxiety and depression), compared to the instrument norms. Children with Diabetes Insipidus, other CNS involvement and children who have had chemotherapy had more cognitive and behavior problems than the other children with LCH. *Conclusions.* HRQoL is affected in children with LCH, especially in older children. Children with LCH show more internalizing problem behavior than their peers. Teachers are important additional informants about behavior problems.

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare non-malignant disease that can manifest itself in diverse ways. It is the result of an abnormal proliferation of pathologic Langerhans cells, accompanied by other inflammatory cells in various tissues. The lesions are destructive, and healing results in scarring and fibrosis [3,23]. Symptoms can range from a single bone lesion to a life threatening multi-system disorder. The peak onset of LCH is between 1 and 4 years, although it can occur at any age [8]. Children may suffer from severe consequences of the LCH. The highest incidence (20%) of Central Nervous System (CNS) disease is the involvement of the posterior pituitary, resulting in Diabetes Insipidus (DI) [32]. Besides this endocrinopathy, other neurological CNS-related sequalae are reported as well, although at a lower incidence: ataxia, physical problems, neuropsychological problems and learning difficulties [7,11,23,24]. LCH-treatment depends on the extent of the disease. Localised disease might be treated with local therapy, including the application of corticosteroids or surgical curettage. In case of disseminated LCH, chemotherapy is often the backbone of treatment [2,12].

In a large retrospective survey, neurological sequelae were found in 11 percent of 182 children with LCH [11]. Some of these became apparent years after diagnosis, with the latest reported after 14 years. Cognitive deficits have been reported in subgroups of pediatric LCH patients [21]. The first cohort-study on cognitive outcome in children with LCH was done by Nanduri et al. [23] who reported intellectual deficits (IQ's below 85) in 11 of 38 children (39%), eight of the 11 children showed evidence of CNS involvement.

Whether health related quality of life (HRQoL) of children with LCH is affected in the long-term is still a matter of debate. HRQoL is defined as the subjective response to situations in daily life [10]. One of the few studies on HRQoL of children with LCH showed that the domain 'emotional functioning' was most often affected [24]. Lau et al. [20] found no differences with healthy peers in a large retrospective study of patients with 'only' bone lesions using generic questionnaires. However, in another study more than 50% patients with multi-system disease LCH [24] reported an adversely affected HRQoL. Most research has relied on generic HRQoL measures, but these instruments lack the sensitivity to assess areas of functioning important to children with a specific illness [22]. For LCH, no disease-specific measures have been developed. Behavior problems in children with LCH have been reported as well: a wide range of behavioral and/ or psychological problems were reported in 27.5 % of long-term survivors of pediatric LCH, namely: varying combinations of depression, anti-social behavior and difficulties with inter-personal relationships [24].

Most sequelae were found in children in whom multiple organ systems were involved [11,24] and children with CNS involvement [23,24,32]. So far it is unclear whether impairments in cognitive functioning are caused by LCH or by its treatment. Chemotherapy

is a common treatment for children with LCH and a recent meta-analysis by Campbell et al. in this journal [4] has shown that contemporary treatment for acute lymphocytic leukemia causes neurocognitive deficits. Of course, dosage varies between the illnesses and there are other contributing factors that need to be taken into account.

Considering the neurological and psychological consequences as well as the physical complaints described, the present study aimed to answer the following questions: (1) Does HRQoL of children with LCH differ from a norm group of healthy children? (2) What disease-specific consequences do children and parents report about LHC? (3) What are the cognitive deficits and behavior problems?

Methods

Patients

All eligible members of the Dutch LCH family association who have a child (8-18 years) with LCH were approached by letter about the study. Twenty-four families agreed to participate and were contacted by phone and visited by one of the authors (VMK). During this visit, informed consent forms were signed, patient characteristics were registered and questionnaires and tests were administered to the children. Parents completed their questionnaires in a separate room. Teachers of the children received the questionnaire by mail. In total 24 children were included, 16 boys and 8 girls. Teachers of twenty-two children participated in the study (two could not be contacted). The percentage of children visiting special education schools is 25 % (High for the Netherlands, normally 3-5 %). They visit schools for children with learning problems, schools for speech and hearing problems and schools linked to a rehabilitation center. These six children all had CNS-involvement. For a detailed description of the study group, see Table 1.

Table 1. Description of LCH Study Group

No.	Sex /Age (years)	System involved	Age at diagnosis (years)	Duration treatment (years)	Years since end treatment	CNS Involve-ment	DI	Chemo therapy	Permanent consequences
1	M /10	Skin, Pituitary, GI, Liver *	2	3	5	+	+	+	Growth hormone deficiency, vision problems
2	F / 16	Pituitary	15	1	0	-	+	-	Fluid balance problems
3	M / 9	Bone	4	3	2	-	-	-	Muscle pains
4	M /11	Bone, Skin	2	9	0	-	-	+	Hearing problems
5	M / 9	Bone, Liver *	.9	1	0	-	-	+	Back pain
6	F / 12	Bone	3	8	1	-	-	+	Headache, fatigue
7	M / 17	Bone, Pituitary, Skin	1	1	15	+	+	+	-
8	M / 11	Skin	.6	10	1	-	-	-	-
9	F / 10	Bone	1	2	7	-	-	+	Obesity
10	M /10	Bone	9	0.5	1	-	-	-	-
11	M / 10	Bone, Lymph nodes, GI	4	0.5	6	-	-	-	-
12	M / 13	Skin	1	0.3	12	-	-	-	Lung-, bladder- and ear infections
13	F / 10	Bone, Skin	.3	0.5	9	-	-	+	-
14	F / 10	Bone, Skin	3	7	1	-	+	+	Wheezing, does not go outside
15	M / 16	Bone, Sinuses, Mouth	2	2	13	+	-	+	Behavior problems
16	M / 9	Bone	6	0.5	3	-	+	+	Skin problems
17	F / 7	Bone, Skin, GI	.9	1	7	-	+	+	Vaginal discharge, fatigue
18	M / 14	Bone, Brain *	2	1	12	+	+	+	Infections of ear, bronchia & teeth. Headaches
19	M / 13	Bone, Skin, Mouth, Liver, Kidney *	.1	7	6	-	-	+	Headaches
20	M / 8	Bone	1	0.5	7	-	-	+	-
21	F / 16	Bone	16	1	0	-	-	+	Fatigue, obstipation, infections
22	M / 9	Bone, Skin	1	1	8	-	-	-	Bumps on the skull
23	M / 11	Bone, Lymph nodes	8	1	3	-	-	-	-
24	M / 10	Bone, Skin, GI, Brain *	.4	3	7	+	+	+	Growth hormone deficiency, obesity
	M 11.9 SD 2.9		M 3.4 SD 4.5	M 2.7 SD 3.0	M 3.4 SD 3.2	+ 5 (20.8%)	+ 8 (33.3%)	+ 16 (66.7%)	

CNS, Central Nervous System; DI, Diabetes Insipidus; GI, gastro-intestinal; * Risk organs

Measures

Dutch Children's AZL/TNO Quality of Life Questionnaire (DUX 25) [16]. This questionnaire was used to asses how children evaluate HRQoL in their day-to-day functioning. There are four domains: family, physical, emotional and social functioning plus a total HRQoL score. Item are formulated as: "I often feel...." Answers can be given on a 5 point Likert-scale, visualized as smiley's ranging from very happy to very sad. Items scores are converted to a 1-100 scale, with higher scores representing a higher quality of life. The DUX 25 consists of a child form (CF) and a parent form (PF). Both forms were found to be sufficiently internally consistent (i.e., reliable) in this sample (CF: α = .74-.90, PF: α = .79-.88. Values between .7 and. 8 are considered good). Scores were compared with a norm group of 935 healthy peers stratified by age [15].

*LCH-specific Quality of life Questionnaire (LCH DUX)***.** This disease-specific questionnaire was developed to look for the effects of the disorder on the daily lives of the patients and their families. Item lists were developed from clinical experience (RME), literature search and parent interviews (IvdL). A team of researchers (HMK, VK, AMK) collaborated on item development. Items were reviewed and discussed by the other team members to ensure appropriateness. Questions were adjusted accordingly. The disease-specific LCH DUX contains 22 items (see appendix). The instrument has a similar lay-out as the DUX 25, also with a child (CF) and parent (PF) form. Items are scored identically on a 1-5 scale and converted to a 1-100 scale, with higher scores representing better HRQoL.

We found good reliability for the child and parent forms (Cronbach's α = .73 and α = .85 respectively).

Wechsler Intelligence Scale for Children- Third Edition (WISC-III nl) [18,31]. Four subtests of the WISC-III were administered to estimate cognitive functioning: Arithmetic, Coding, Information and Digit span. Results were compared to Dutch norm groups [18]. Raw cognition scores were standardized into reference scores with a mean of 103. A child was considered to score "below average" on a subtest when the score was one standard deviation or more below the mean.

Child Behavior Check List 6-18 (CBCL), Youth Self Report (YSR), Teacher Report Form (TRF) [1]. Three parallel questionnaires (standardized Dutch versions [28-30]) were used to assess the presence of behavior problems. Parents completed the CBCL, children (13 years and older, 14 in total) filled in the YSR and the teachers were sent the TRF. Informants had to rate 112 items on how true each item for the child is: 0 = not true; 1= somewhat or sometimes true; 2 = very or often true. The items on all three questionnaires can be transformed in 3 domains: internalizing problems, externalizing problems and a total score. Results were compared to Dutch norm groups. Problem scores are classified as normal (≤ 85th percentile), borderline clinical (85th-93rd percentile) and clinical (≥ 93rd percentile), for boys and girls separately.

Demographic and disease characteristics. Age, onset of LCH, schooling and sex of the child plus marital status and level of education of the parents were obtained, as well as disease-related characteristics of the children. We recorded time since diagnosis, duration of treatment, time since the end of treatment, location of LCH, whether there was DI, other CNS involvement (defined by us as non-pituitary related issues like ataxia, neuropsychological or learning problems) and whether the children had received chemotherapy. Lastly, we recorded permanent consequences for all patients (Table I).

Statistical Analysis

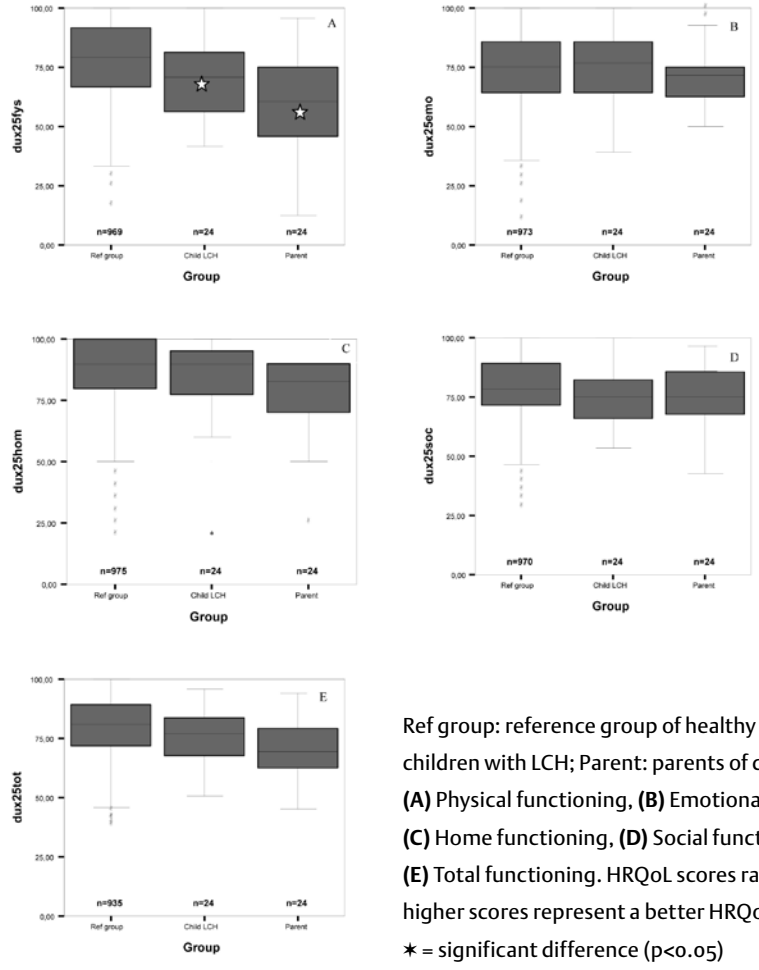
The reliability of the DUX and LCH DUX scales were analyzed with Cronbach's alpha coefficients. Multivariate analysis of variance (MANOVA) was used to compare mean HRQoL scores between children with LCH, a reference group of healthy children and parent ratings. Cognition and behavior scores were compared to norm scores using one sample T-tests. For all analyses an α-value less than 0.05 was required for significance.

Results

Health-related quality of life

Children with LCH reported a significantly lower score ($p < .05$) on the physical domain of the generic HRQoL questionnaire than the reference group, indicating a lower HRQoL concerning their own health and physical appearance. Parents even reported a significantly lower score ($p < .03$) on the physical domain than their children (Figure 1). Scores on the other domains were not statistically different from to the reference group. No differences were found between ratings of parents of children who ended their treatment more or less than 5 years ago, no gender differences and no relations between generic HRQoL and disease characteristics. Children older than 12 showed significantly lower scores on the scales physical functioning (p = 0.001), home functioning (p = 0.019) and total generic HRQoL (p =0.003).

Figure 1. Health-related quality of life (HRQoL)



Ref group: reference group of healthy children; Child LCH: children with LCH; Parent: parents of children with LCH.
(A) Physical functioning, **(B)** Emotional functioning,
(C) Home functioning, **(D)** Social functioning,
(E) Total functioning. HRQoL scores range from 0-100, higher scores represent a better HRQoL .
∗ = significant difference ($p<0.05$)

Compared to generic HRQoL the disease-specific HRQoL scores were low. On the LCH DUX scale parents showed a mean total score of 57 and children scored 59 on average (on the generic DUX 25 scale the mean scores were 71 and 76 respectively). Four items showed scores that were one standard deviation (SD) or more below the total mean score: *Having to take medications I find…*; *Not being able to play with other children makes me feel…; Not being able to go to school because of my LCH is…* and *Compared to other children, I feel…* See the Appendix for the full LCH DUX questionnaire.

Cognitive functioning

Participants showed wide-ranging WISC subtest scores (from 3 SD below (1) to 3 SD above (19) the mean norm score (10). In total 54 % of the children scored one SD or more below average on one or more subtests and 25% on two or more subtests (See Table 2). The subtest *Coding* (visual short-term memory and quick responding) was the most difficult for children with LCH; 38 % of the children scored one SD below the mean on this subtest. The children scored highest on the subtest *Digit Span* (auditory short term memory): 33 % of the children scored one SD above the mean on this subtest.

Table 2. IQ-subtest scores

WISC III-NL Subtest	**Norm score* Mean (SD)**	**-1 SD N (%)**
Information (general factual knowledge & long-term memory)	9.8 (3.7)	6 (25)
Coding (visual motor coordination, speed & concentration)	8.3 (3.2)	9 (38)
Arithmetic (attention, concentration & numerical reasoning	9.7 (3.1)	6 (25)
Digit Span (short-term auditory memory & concentration)	12.1 (4.4)	4 (17)
Number of subtests ≤ 1 SD	**N (%)**	
0 subtest	11 (46)	
1 subtest	7 (29)	
2 subtests	2 (8)	
3 subtests	4 (17)	

WISC III-NL, Wechsler Intelligence Scale for Children, Dutch version;
* Norm scores range from 0-20, the average score lies between 7 and 13.

Behavior problems

Teachers reported three times and parents reported twice as many problems as the children. Compared to the norm groups of healthy peers, the rates of internalizing behavior problems (i.e. anxious and depressive behavior) in children with LCH were significantly higher, according to both parents and teachers. Total problems reported by the parents in the LCH group were significantly higher than the control group. Children self-reported behavior problems were not statistically different from the control group. However, the percentage of children with LCH scoring above the 93rd percentile (clinical range) compared to the norm groups was larger in various scales, e.g., self-reported externalizing behavior (See Table 3).

Table 3. Problem behavior reported by children, parents and teachers

	Parents (N=24) (CBCL)		**Teachers (N=22) (TRF)**		**Children (N=14) (YSR)**	
	Mean (SD)	Clinical N (%)	Mean (SD)	Clinical N (%)	Mean (SD)	Clinical N (%)
Internalising behavior						
Sample	10.17 (8.2) *	9 **(30)**	9.8 (9.7) *	7 **(32)**	10.4 (5.1)	1 (7)
Norm group	4.5 (4.3)	7	5.0 (5.6)	7	8.4 (5.5)	7
Externalising behavior						
Sample	6.6 (5.3)	1 (4)	7.3 (10.2)	4 **(17)**	11.0 (7.1)	2 **(14)**
Norm group	8,2 (6.3)	7	6.7 (8.4)	7	11.2 (6.4)	7
Total problems						
Sample	31.5 (20.4) *	4 **(14)**	32.4 (29.1)	5 **(23)**	30.4 (13.8)	0 (0)
Norm group	21.3 (14)	7	21.9 (21.4)	7	32.8 (16.3)	7

CBCL, Child Behavior Checklist; TRF, Teachers Report Form; YSR, Youth Self Report; * Significant difference with the norm group ($p \leq .05$); Clinical, scores above the 93rd percentile; Significant differences with the norm group ($p \leq .05$) are printed in bold.

Discussion

This study evaluated both generic and specific HRQoL in children with LCH as well as cognitive functioning, (teacher and parent rated) behavior problems and disease characteristics. Considering the severity of LCH, generic HRQoL scores evaluating emotional, social and home functioning were comparable to reference groups of healthy peers. Children with LCH did report a significantly lower HRQoL regarding their physical functioning, compared to the norm group. This is in line with HRQoL research in pediatric oncology: children with bone tumors and their parents report more problems in physical

functioning than a healthy control group [17]. As previous research in other illness groups has shown [9,15], older children with LCH report a lower HRQoL, possibly due to a growing consciousness about their disease.

The LCH DUX disease-specific questionnaire showed lower scores than the generic measure. It seems that children with a chronic illness, when asked in general how they think they are doing, tend to 'leave out' their illness and report relatively high HRQoL scores. It is unclear if this generic 'not including the illness process' happens unconsciously or results from repressive adaptation, as described in children with cancer [25] or if 'response shift' takes place: as a result of health state changes, an individual may undergo changes in internal standards, values or the conceptualisation of HRQoL [26,27] and as a consequence, may report a higher HRQoL than expected. When children are approached directly about their illness experiences in a disease-specific questionnaire, they are forced to focus on difficulties they might come across because of their illness.

Teachers reported by far the most behavior problems compared to parents or children with LCH. According to the answers of teachers and parents, children with LCH showed more internalizing behavior problems (anxiety, depression) than norm groups. Discrepancies between self-report and parent proxy-report have been documented in other illness groups before: parents tend to underestimate their child's HRQoL [5,9]. Many researchers have noted that parents and teachers frequently disagree on their assessment of behavioral/emotional problems in children [14,19]. Such differences do not mean that either reporter is inaccurate, because parents and teachers see the child in different situations and their ratings may be affected by many different factors [13].

While interpreting the results of this study, limitations should be kept in mind. To shorten the total assessment time per child, only four subtests of the intelligence test were used to assess cognition, which only generates a general indication of cognitive functioning. Furthermore, the heterogeneity of the study group with respect to age, time since diagnosis and disease characteristics, combined with the relatively small sample size, limited the choice of statistical analyses. All children being members of the Dutch LCH Family Association, also may have introduced a bias. Lastly, due to the small sample size we were unable to evaluate all psychometric qualities of the new HRQoL instrument. This is one of our future aims.

It is recommended that future studies in this area are longitudinal in design and aim to enhance sample size, preferably through international studies including the involvement of the Histiocyte Society. Effort should be made to enable children with LCH to participate and to live 'normal lives' as much as possible, with the aid of parents, teachers and multidisciplinary hospital staff. Additionally, a 'buddy' or peer might be helpful as a model figure.

Involving teachers as informants of child behavior offers another frame of

reference and enables the gathering of more objective information. The newly developed LCH-specific questionnaire might be a first start to come to a common language to study HRQoL in this group of patients, analogue to the tool for assessing disease activity, developed by Donadieu et al.[6]. Lastly, considering the behavioral and cognitive problems experienced by a large percentage of children with LCH, more thorough and longer psychosocial follow-up assessment and care is needed.

Acknowledgements

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Items and scores of the LHC DUX

	Item	Mean score *
1.	Having to take medications, I find…	35**
2.	Not being able to play with other children makes me feel…	15**
3.	Giving a class presentation about ICD is…	56
4.	How the doctors speak with me, I find…	58
5.	How my parents deal with my LCH, I think is…	70
6.	Doing what the doctor says I find…	52
7.	About my LCH I often feel…	45
8.	Not being able to go to school because of my LCH is…	21**
9.	Compared to other children, I feel…	29**
10.	Talking about LCH with other children I find…	41
11.	Taking medication in front of others I find…	46
12.	Later, when I'll be older, my LCH will be…	67
13.	Going to the hospital is…	44
14.	When I am visiting someone I feel…	85
15.	At this moment I think about my LCH as…	48
16.	What I know about LCH is…	56
17.	Explaining LCH to others is…	41
18.	At school my LCH is…	72
19.	At home my LCH is…	74
20.	Doing sports for me is…	72
21.	Taking a rest in the daytime is…	46
22.	Having to do everything on time is…	56
	Total score LCH DUX child form	**59 (SD 14)**

* Scores range from 0-100, a higher score means a higher quality of life; **
1 SD or more below the total mean score

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