Published in final edited form as:

J Pediatr Hematol Oncol. 2017 January ; 39(1): 20–25. doi:10.1097/MPH.0000000000000707.

HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND CHRONIC HEALTH CONDITIONS IN SURVIVORS OF CHILDHOOD ACUTE MYELOID LEUKEMIA (AML) WITH DOWN SYNDROME (DS): A report from the Children's Oncology Group

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Abstract

Survival rates for children with Down syndrome (DS) and acute myeloid leukemia (AML) are high; however, little is known regarding the health-related quality of life (HR-QOL) of these survivors. Individuals who survived ≥5 years following diagnosis of childhood AML were invited to complete parent or patient-report surveys measuring HR-QOL and chronic health conditions. Twenty-six individuals with DS had a median age at diagnosis of 1.8 years (range, 0.77-10.9) and median age at interview of 15 years (range 8.3-27.6). Participants with DS and AML were compared to AML survivors without DS whose caregiver completed a HR-QOL survey (CHQ-PF50). Seventy-seven percent of survivors with DS reported ≥1 chronic health condition compared to 50% of AML survivors without DS (p=0.07). Mean physical and psychosocial QOL scores for children with DS and AML were statistically lower than the population mean, though not discrepant from AML survivors without DS. Although the overall prevalence of chronic health conditions in survivors with DS is higher than in survivors without DS, prior studies of children

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with DS have reported similarly high rates of chronic health conditions, suggesting that AML therapy may not substantially increase this risk.

Keywords

leukemia; Down syndrome; quality of life; chemotherapy

INTRODUCTION

Children with Down syndrome (DS) face elevated risks of acute leukemia including both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), usually acute megakaryocytic leukemia.[1,2] Survival for children with AML and DS is higher than for children with AML without DS which is thought to be due to increased sensitivity to chemotherapy in children with DS. Treatment regimens for AML in patients with DS have included lower intensity regimens due to concerns for increased treatment-related morbidity and mortality.[3] It is well-known that children with DS are at risk for a wide range of chronic medical conditions as well as cognitive, developmental, behavioral and psychiatric disorders, all of which have clear implications for health-related quality of life. Despite this, very little information is available regarding health-related quality of life (QOL) or chronic health conditions in survivors of childhood AML with DS. In studies evaluating QOL after cancer treatment, children with Down syndrome have been historically excluded from analyses of survivors, which has limited our understanding of the unique medical and psychosocial difficulties DS children may face after treatment.

Health-related quality of life is a multi-factorial concept that encompasses broad domains of physical functioning and health status, as well as the emotional, behavioral, and social functioning of the child and family. In the context of children with chronic medical illness, QOL is often measured through parent and patient perceptions of the impact of illness on important functional domains. During and after treatment for childhood leukemia, a variety of treatment factors could impact QOL. For example, anthracyclines used in AML therapy may lead to cardiac toxicity, with implications for physical functioning after treatment.[4,5] Infectious complications may impact functional outcomes.[6] Neurocognitive functioning, including neurocognitive late effects after cancer treatment, also have implications for QOL.[7-10]

Children with DS and leukemia face additional challenges to QOL, specifically intellectual disability and associated health problems that predate cancer diagnosis and treatment. Few studies have attempted to quantify QOL in children with DS. No DS-specific QOL measure has been developed/validated for this purpose [11] which further limits our understanding of this potentially vulnerable group. One study using a generic QOL instrument found reduced QOL in children with DS compared to healthy population controls, but did not investigate the impact of chronic health conditions or other factors that could influence QOL in DS.[12] Children with DS face health risks including increased risks for endocrine dysfunction such as hypothyroidism as well as infection and autoimmunity regardless of the presence of malignancy.[13] In general, hypothyroidism is seen in 4–18% of children with DS and in up to

half of adults with DS but may also be associated with cancer-directed therapy.[13] Infections of the respiratory and gastrointestinal systems are more common in individuals with DS than in the general population and altered immunity associated with immunosuppressive therapies also increase the likelihood of infections.[6] Likewise, cataracts and sensorineural hearing loss are seen more commonly in individuals with DS but are also seen more commonly among survivors of intensive therapies such as radiation.[14] These factors may differentially impact quality of life following completion of cancer-directed therapy.

This analysis sought to determine the prevalence of chronic health conditions and measure quality of life of survivors of childhood AML with DS compared to survivors of childhood AML without Down syndrome. It was hypothesized that survivors with DS would have a higher prevalence of chronic health conditions and lower reported quality of life than children with AML without DS.

METHODS

The individuals described in this report were surveyed as a part of a larger quality of life analysis following therapy for childhood AML. Results for the 180 participants without Down syndrome have been previously reported.[15] The focus of this paper is on 26 individuals with Down syndrome for whom proxy-reported quality of life surveys and chronic health conditions were available.

Participants

All participants were diagnosed with AML at less than 21 years of age, received treatment between 1979 and 1995 on one of 3 Children's Oncology Group legacy protocols (CCG-251, 213, 2891) and survived at least 5 years following diagnosis.[16-18] Although included in the previous analyses, individuals treated on CCG 2861 were excluded as no participants with DS received therapy on this protocol. Human subjects committees at participating institutions approved all study protocols.

In this analysis, survivors with DS were compared to survivors without DS whose proxy caregiver completed the CHQ PF50. Individuals who underwent allogenic bone marrow transplantation (BMT) were excluded from the comparison group as no study participants with DS underwent allogenic BMT. Treatment data was determined from the Children's Oncology Group database, however, incomplete data was available as to therapy modifications and inclusion of cranial radiation.

Measures

The Child Health Questionnaire (CHQ-PF50, Boston, MA[19]) is a 50-item parent-report survey commonly used for assessment of the physical and psychosocial well-being of children and has been used in the assessment of QOL in a wide range of patient populations, including individuals with cancer,[20] psychiatric disorders[21] and severe developmental disabilities.[22] While the CHQ-PF50 is normed for parents of children 5-18 years of age, caregivers of all participants with DS completed this survey, as the majority of children with DS function cognitively in the mild to moderately impaired range which may impact their ability to read and process the lengthy questionnaires independently on self-report surveys.

The CHQ-PF50 assesses 14 physical and psychosocial domains: general health perceptions, physical functioning, role/social physical functioning, bodily pain, role/social emotional functioning, role/social behavioral functioning, parent impact-time, parent impact-emotional, self-esteem, psychosocial health, behavior, family activities, family cohesion, and change in health. Scales are transformed to a 0-100 scale, where 0 = the worst possible health state and 100 = the best possible health state. The individual scale scores are aggregated to derive two summary component scores: the physical functioning and psychosocial health summary scores. These scores are converted into norm-referenced T-scores with a mean of 50 and a standard deviation of 10.

Demographic characteristics and chronic health conditions were measured using the Childhood Cancer Survivor Study Baseline (CCSS) Questionnaire (designed for those less than 18 years of age). The full questionnaire is available at www.stjude.org/ccss. Chronic health conditions were reported by proxy caregivers and coded as described by Oeffinger et al.[23,24] Using this methodology, 137 health conditions were scored as grade 1 (mild); grade 2 (moderate); grade 3 (severe); grade 4 (life threatening or disabling) or grade 5 (fatal). For this analysis, grades 3 and 4 were considered severe.

For comparison of individuals with DS and AML to AML survivors without DS, Wilcoxon rank sum test and two-sample t-test were used to compare continuous variables and Chi-square test was used to compare categorical variables. In linear regression models predicting QOL, models were adjusted for age of diagnosis, age at interview, or time since diagnosis. One-sample t-test was used to compare the mean physical/psychosocial summary score of individuals with DS to the population mean of 50.

RESULTS

Demographics and Treatment Characteristics

Of 206 eligible participants for the Quality of Life Study in AML, 26 were reported to have DS. Characteristics of the remaining participants have been described elsewhere.[15] For all 26 survivors with DS, a parent completed the CHQ-PF50 and the CCSS Questionnaire. Median age at diagnosis was 1.8 years (range 0.77-10.9). Survivors with DS were a median age of 15.0 years (range 8.3-27.6) at interview. All survivors received intensive chemotherapy including two who also underwent autologous stem cell transplant. No survivor underwent allogenic BMT. Eighty-five percent were white (n=22); half were female (Table 1).

Chronic Health Conditions

Per parental report, 77% of survivors of AML with DS had at least one chronic health condition (grades 1-4) compared to 50% of AML survivors without DS (p=0.07). Severe or life threatening chronic health conditions (grades 3 and 4) were not significantly more common in the group of survivors with DS. Twenty-three percent of survivors with DS were reported to have a severe or life-threatening chronic health condition compared with 13% of AML survivors (p=0.40). Thirty-one percent reported ≥ 3 chronic health conditions compared with 19% of survivors without DS (p=0.39).

Chronic health conditions reported by proxy caregivers are noted in Table 2. Hypothyroidism, valvular heart disease, speech difficulty (stammering/stuttering), and hearing loss, were the most common conditions reported by proxy caregivers of DS AML survivors. No secondary malignancies were reported in this group of survivors with DS who were all alive at time of interview.

Health-Related Quality of Life

Health related QOL median physical summary score was 45.8 (SD 15, range 10-58.7). Median psychosocial summary score was 45.6 (SD 8, range 28-59.1). We also compared the results in the individuals with DS to the population mean. For individuals with DS, mean physical summary score (41.2, SD=15.0) and mean psychosocial summary score (45.3, SD=8.4) were lower than the population mean of 50 (p=0.006 and 0.008 respectively). Health status was reported as excellent, very good or good for 89% of survivors with DS vs. 94% without DS (p=0.57).

Sixty-nine percent of survivors with DS were reported to have some functional impairment compared with 19% of survivors without DS (p=0.002). Nineteen percent reported an activity limitation (compared with 7%, p=0.27) and thirty-one percent were reported to need help in personal cares (compared with 6% in among survivors without DS (p=0.06). No survivors in either group had cancer-related pain.

We also compared physical summary score, psychosocial summary scores, presence of any chronic health condition, presence of 2+ chronic health condition, functional impairment and needing help via regression models adjusting for either age of diagnosis, age at interview, or time since diagnosis. The results of these regression models, shown in Table 3, are similar to the unadjusted analyses in Table 1 with few exceptions. Functional impairment remained significantly more common in individuals with DS. Prevalence of any chronic health condition was marginally higher among DS. However, there was no significant difference in the proportion needing help in personal cares in the unadjusted or adjusted models. In these regression models, age at diagnosis, age at interview, or time since diagnosis did not reach statistical significance as linear predictor for the outcome variables.

DISCUSSION

To our knowledge, this is the first analysis of chronic health conditions and functional outcomes including health-related quality of life in survivors of childhood AML with DS. We studied prevalence of chronic health conditions and quality of life via parental report. Chronic health conditions were more frequent among survivors with DS; however, rates of severe chronic health conditions were similar. Importantly, DS patients were reported to have equally good general health and not more pain or anxiety as result of their cancer than AML survivors without DS. While mean physical and psychosocial QOL scores were lower than the general population mean, the QOL of survivors with DS did not differ significantly from those without DS after adjusting for age at survey or time since treatment.

Half of participants with DS in this study were reported to have 2 or more chronic health conditions. Hypothyroidism was the most common diagnosis reported. This was not

surprising as regardless of cancer history, hypothyroidism is a common endocrine problem in children and adults with DS. Between 4–18% of children and up to half of adults with DS have thyroid disease.[13,14] Other studies have also found a high prevalence of chronic health conditions in children and adults with DS. In a population-based study of eight-year-old children with DS in the Netherlands, chronic health conditions were common with 67% of participants reporting 2 or more chronic diseases (e.g. visual impairment, chronic airway infections, congenital heart defect, hearing impairment and thyroid dysfunction).[12] General health supervision guidelines for children with Down syndrome reflect a high prevalence of hearing (75%) and vision problems (60%) and cataracts (15%).[13]

This study presents two limitations which should be considered. In this study, sample size was small due to the numbers of participating AML survivors with DS resulting in limited power. Individuals in the comparison group, comprised of AML survivors without DS, were younger than survivors with DS at the time of interview, and the presence of chronic health conditions may increase with increasing age. A more appropriate control group to gauge the impact of therapy on quality of life and prevalence of chronic health conditions would have been an age-matched sample of children with DS who had never had AML. This would have allowed better differentiation between the types of chronic health conditions that are commonly associated with DS compared to conditions which represent late effects of AML treatment. Nonetheless, this report is (to the best of our knowledge) the first to describe QOL and prevalence of chronic health conditions in children with DS after treatment for AML, who are far too often excluded from studies reporting on psychosocial and chronic health late effects of childhood cancers and provides an important first step to assist in the design of future measures and studies to assess HRQOL in individuals with DS with and without leukemia.

This analysis of a small number of survivors of AML with DS suggests the prevalence of severe health conditions is similar to survivors of AML without DS. Median health related QOL is slightly lower than for other survivors of AML, though this difference was not significant ($p = 0.16$). There was a trend towards increased prevalence of chronic health conditions in survivors of AML with DS compared to AML survivors without DS ($p = 0.07$). This is consistent with prior studies that have reported similarly elevated rates of chronic health conditions among individuals with DS without AML, suggesting that AML therapy may not substantially increase this risk.[12,25] Future studies should compare QOL and functional outcomes between participants with Down syndrome with and without a history of malignancy in prospective longitudinal design. Assessment of QOL at diagnosis of AML (i.e., prior to initiation of therapy) in children with DS will be important to determine how cancer-directed therapy impacts these critical outcomes. Additionally, as other authors have suggested, research is needed to develop quality of life instruments which are validated in individuals with DS and to collect baseline data for use in future therapeutic trials.

Acknowledgments

The authors thank Michelle Roesler, Wendy Leisenring and Pam Goodman for their kind assistance in research coordination and manuscript preparation. We thank Children's Cancer Research Fund, Children's Oncology Group, and the National Cancer Institute (U24CA55727, 5U10 CA07306 and 1R01CA78960) for their support of this

research. The authors also wish to gratefully acknowledge the patients, families and referring physicians who contributed to this work.

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Table 1

Demographic and clinical characteristics of survivors.

	DS & AML n=26	AML, No DS**: (n=21)	P value*:
Age at diagnosis			
median in years (range)	1.8 (0.77-10.9)	1.5 (0.06-4.8)	0.27
Age at interview			
median in years (range)	15.0 (8.3-27.6)	10.6 (8.1-18.3)	0.003
Time since diagnosis			
median in years (range)	12.8 (6.8-19.6)	8.7 (6.7-18.1)	0.003
QOL physical summary score median (range)	45.8 (10.0-58.7)	54.0 (6.4-57.4)	0.16
QOL physical summary score mean (SD)	41.2 (15.0)	47.7 (12.2)	0.11^
QOL psychosocial summary score median (range)	45.6 (28.0-59.1)	50.3 (15.5-62.1)	0.28
QOL psychosocial summary score mean (SD)	45.3 (8.4)	46.3 (13.6)	0.75^
Gender			0.63
Male	13 (50%)	9 (42.9%)	
Female	13 (50%)	12 (57.1%)	
Race			0.55
White (including Hispanic)	22 (84.6%)	19 (90.5%)	
Nonwhite	4 (15.4%)	2 (9.5%)	
Treatment study			0.003
CCG213/213P	8 (30.8%)	0	
CCG 251	5 (19.2%)	1 (4.8%)	
CCG2891	13 (50.0%)	20 (95.2%)	
Chronic health conditions			0.07
Yes	20 (76.9%)	8 (50.0%)	
No	6 (23.1%)	8 (50.0%)	
Any severe chronic health condition (grade III or IV)			0.40
Yes	6 (23.1%)	2 (12.5%)	
No	20 (76.9%)	14 (87.5%)	
Two or more chronic health conditions			0.23
Yes	13 (50.0%)	5 (31.3%)	
No	13 (50.0%)	11 (68.7%)	
Three or more chronic health conditions			0.39
Yes	8 (30.8%)	3 (18.8%)	
No	18 (69.2%)	13 (81.2%)	
Reports general health			0.57
Excellent, very good or good	23 (88.5%)	15 (93.7%)	
Fair or poor	3 (11.5%)	1 (6.3%)	
Has pain as a result of cancer			n/a

	DS & AML n=26	AML, No DS**: (n=21)	P value*:
Yes	0	0	
No	26 (100.0%)	16 (100%)	
Has anxiety as a result of cancer			0.95
Yes	5 (19.2%)	3 (20.0%)	
No	21 (80.8%)	12 (80.0%)	
Functional impairment			0.002
Yes	18 (69.2%)	3 (18.8%)	
No	8 (30.8%)	13 (81.2%)	
Activity limitation			0.27
Yes	5 (19.2%)	1 (6.7%)	
No	21 (80.8%)	14 (93.3%)	
Need help in personal cares			0.06
Yes	8 (30.8)	1 (6.3%)	
No	18 (69.2%)	15 (93.7%)	

*2-sided P value based on Wilcoxon rank sum test for continuous measures (^ for P values from two-sample t-test) and Chi-square test for categorical measures.

**Survivors without Down syndrome whose proxy caregiver completed the CHQ PF50. Of these 16 also completed the CCSS baseline questionnaire.

Table 2

Chronic health conditions seen in survivors of childhood AML with DS.

			DS & AML (N=26)		AML, No DS* (N=21)	
Organ System	**Category**	**Grade**	**N**	**%**	**N**	**%**
Vision and Eye	Cataracts without surgery	**1**	1	3.85	1	4.76
	Glaucoma	**1**	0	0	0	0
	Disorder of refraction	**1**	1	3.85	0	0
	Esotropia	**1**	2	7.69	0	0
	Disorder of binocular eye movements	**1**	2	7.69	0	0
	Unspecified eye disorder	**1**	1	3.85	0	0
	Cataracts requiring surgery	**2**	0	0	0	0
	Legally blind or loss of an eye	**3**	1	3.85	2	9.52
Vision and Eye			8		3	
Hearing	Hearing loss, not requiring device	**1**	1	3.85	0	0
	hearing loss, requiring device	**2**	1	3.85	0	0
	Other forms of hearing loss	**2**	3	11.54	1	4.76
	Deafness	**3**	1	3.85	0	0
Hearing			6		1	
Speech	Stammering/stuttering	**1**	5	19.23	0	0
	Abnormal taste Problems	**1**	0	0	3	14.29
	chewing/swallowing	**1**	3	11.54	1	4.76
	Developmental language problem	**2**	2	7.69	0	0
Speech			10		4	
Cardiovascular	Dysrhythmia, not on medication	**1**	3	11.54	0	0
	Hypertension, not on medication	**1**	0	0	1	4.76
	Valvular disease, unspecified	**1**	4	15.38	0	0
	Cardiomyopathy, not on medication	**2**	1	3.85	0	0
	Dysrhythmia, on medication	**2**	0	0	0	0

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			DS & AML (N=26)		AML, No DS* (N=21)	
Organ System	**Category**	**Grade**	**N**	**%**	**N**	**%**
	Hypertension, on medication	**2**	0	0	0	0
	Raynaud's syndrome	**2**	0	0	0	0
	Congestive heart failure, on medication	**3**	0	0	0	0
	Cerebrovascular accident	**4**	0	0	1	4.76
Cardiovascular			8		2	
Pulmonary	Chronic cough or shortness of breath	**1**	1	3.85	0	0
	Pulmonary fibrosis, not on O2	**1**	3	11.54	0	0
	Thromboembolic disease, leg or arm	**3**	0	0	0	0
Pulmonary			4		0	
Gastrointestinal	Hepatitis	**2**	0	0	0	0
	Cirrhosis	**3**	1	3.85	0	0
	Surgery for intestinal obstruction	**3**	0	0	1	4.76
Gastrointestinal			1		1	
Renal	Other non-specified disorders of the bladder	**1**	0	0	0	0
	Recurrent bladder/kidney infection	**2**	1	3.85	0	0
	Dialysis/kidney transplant	**4**	0	0	0	0
Renal			1		0	
Neurological	Seizure disorder, not on medication	**1**	1	3.85	1	4.76
	Problems with balance/vertigo	**1**	1	3.85	0	0
	Tremors	**1**	0	0	2	9.52
	Weakness in legs, mild limitation	**1**	0	0	1	4.76
	Other nervous system disorders	**1**	1	3.85	0	0
	Facial nerve palsy	**1**	0	0	1	4.76
	Weakness in arms, mild limitations	**1**	1	3.85	1	4.76
	Decreased sense of touch/feeling in hands, fingers	**1**	1	3.85	1	4.76
	Seizure disorder on medication	**2**	0	0	1	4.76
	Weakness in legs, moderate limitation	**2**	1	3.85	0	0

Organ System	Category	Grade	DS & AML (N=26)		AML, No DS* (N=21)	
			N	%	N	%
	Cognitive deficit, severe	**4**	3	11.54	0	0
	Hemiplegia	**4**	0	0	1	4.76
Neurological			9		9	
Endocrine	Hypothyroidism not on medication	**1**	0	0	0	0
	Hypothyroidism, on medication	**2**	5	19.23	0	0
	Diabetes, on oral medication	**2**	0	0	0	0
	Growth hormone deficiency	**2**	1	3.85	0	0
	Osteoporosis	**2**	1	3.85	1	4.76
	Ovarian failure, on replacement	**3**	0	0	0	0
Endocrine			7		1	

*Survivors without Down syndrome whose proxy caregiver completed the CHQ PF50.

Table 3

Regression models comparing selected quality of life and chronic health condition measures between DS survivors and AML survivors without DS

	Model = Age at Dx + Group		**Model = Age at Interview + Group**		**Model = Time since Dx + Group**	
	Age at Dx Coefficient (P value)	**Group Coefficient (P value)**	**Age at Interview Coefficient (P value)**	**Group Coefficient (P value)**	**Time since Dx Coefficient (P value)**	**Group Coefficient (P value)**
Physical summary *	1.48 (0.25)	7.28 (0.08)	-0.26 (0.62)	5.41 (0.26)	-0.61 (0.29)	4.14 (0.38)
Psychosocial summary *	0.093 (0.93)	1.11 (0.74)	0.052 (0.90)	1.30 (0.73)	0.044 (0.93)	1.24 (0.74)
	Age at Dx Odds Ratio (P)	Group Odds Ratio (P)	Age at Interview Odds Ratio (P)	Group Odds Ratio (P)	Time since Dx Odds Ratio (P)	Group Odds Ratio (P)
Any Chronic conditions ^	0.80 (0.26)	0.26 (0.06)	0.90 (0.26)	0.18 (0.05)	0.93 (0.49)	0.22 (0.07)
2+ chronic conditions ^	0.81 (0.38)	0.41 (0.19)	1.06 (0.47)	0.59 (0.48)	1.11 (0.23)	0.69 (0.62)
Functional impairment ^	0.73 (0.23)	0.08 (0.002)	1.00 (0.96)	0.10 (0.008)	1.06 (0.56)	0.13 (0.013)
Need help ^	0.93 (0.76)	0.15 (0.086)	0.99 (0.87)	0.14 (0.098)	1.00 (0.96)	0.15 (0.11)

Dx= diagnosis;

* Linear regression, DS group as the reference group for coefficient;

^ Logistic regression, DS group as the reference group for coefficient