Neurodevelopmental Outcome of Childhood Cancer Survivors Treated at the Eric Williams Medical Sciences Complex

D Coombs[1], C Bodkyn[2], J Ramcharan[2]

ABSTRACT

Objective: *To investigate the neurodevelopmental outcome of childhood cancer survivors treated at the Eric Williams Medical Sciences Complex (EWMSC).*

Methods: *Study participants were children treated at EWMSC from January 2003 to March 31, 2012 for various childhood cancers. All had completed treatment and were in remission. The McCarthy Scales of Children's Abilities (MSCA) was administered. The study was conducted from December 2011 to March 31, 2012.*

Results: *Twenty-six children were evaluated, a response rate of 74%. There were 12 males and 14 females. Ages ranged from 3.25 to 9.00 years. Four (15.4%) children scored a general cognitive index (GCI) < 68. One child (3.8%) scored a GCI > 132. The children's mean estimated mental age was found to be significantly lower than their mean actual age (*p = *0.0086). Children treated for solid tumours had the least difference between their actual ages and estimated mental ages (*p = *0.0301). The mean GCI for the genders was 97.4 for females and 81.0 for males; this difference was statistically significant (*p = *0.0302). Age at diagnosis, type and length of treatment were not found to significantly affect development.*

Conclusion: *The paediatric cancer survivors in this survey were found to have delays in their development. This group of children should have their development closely monitored. This would ensure that any delays in development can be discovered early and appropriate interventions instituted, so that childhood cancer survivors are adequately prepared for adult life beyond cancer.*

Keywords: Childhood cancer survivors, development, neurodevelopment, Trinidad and Tobago

Resultado del Desarrollo Neurológico en Niños Sobrevivientes de Cáncer Tratados en el Complejo de Ciencias Médicas Eric Williams

D Coombs[1], C Bodkyn[2], J Ramcharan[2]

RESUMEN

Objetivo: *Investigar el resultado del desarrollo neurológico en niños sobrevivientes de cáncer tratados en el Complejo de Ciencias Médicas Eric Williams (EWMSC, siglas en inglés).*

Métodos: *Los participantes del estudio fueron niños tratados en EWMSC desde enero de 2003 al 31 de marzo de 2012, a causa de varios tipos de cáncer infantil. Todos habían terminado el tratamiento y estaban en remisión. Se les aplicó el test de Habilidades Infantiles de McCarthy (MSCA, siglas en inglés). El estudio se llevó a cabo desde diciembre de 2011 al 31 de marzo de 2012.*

Resultados: *Veintiséis niños fueron evaluados, para una tasa de respuesta del 74%. Hubo 12 varones y 14 hembras. Las edades fluctuaron de 3.25 a 9.00 años. Cuatro niños (15.4%) alcanzaron un índice cognitivo general (ICG) < 68. Un niño (3.8%) tuvo un ICG > 132. Se halló que la edad mental promedio estimada de los niños fue significativamente menor que su edad real promedio (*p = *0.0086). Los niños tratados por tumores sólidos tuvieron la diferencia menor entre sus edades reales y sus edades mentales estimadas (*p = *0.0301). El ICG promedio en cuanto a géneros fue 97.4 para las hembras y 81.0 para los varones. Esta diferencia fue estadísticamente significativa (*p = *0.0302). Se*

From: [1]Eric Williams Medical Sciences Complex and [2]Child Health Unit, Department of Clinical Medical Sciences, Faculty of Medical Sciences, The University of the West Indies, St Augustine, Trinidad and Tobago.

Correspondence: Dr C Bodkyn, Child Health Unit, Department of Clinical Medical Sciences, Faculty of Medical Sciences, The University of the West Indies, St Augustine, Trinidad and Tobago. E-mail: cbodkyn@gmail.com

DOI: 10.7727/wimj.2013.268

halló que ni la edad al momento del diagnóstico, ni el tipo y duración del tratamiento afectaban el desarrollo significativamente.

Conclusión: *Se halló que los supervivientes de cáncer pediátrico en esta encuesta tenían retrasos en su desarrollo. El desarrollo de estos niños debe ser monitoreado muy de cerca. De este modo, se garantizaría la temprana detección de cualquier retraso en el desarrollo, y la práctica de intervenciones apropiadas, para que los supervivientes de cáncer infantil estén preparados adecuadamente para la vida adulta, dejando atrás el cáncer.*

Palabras claves: Supervivientes de cáncer infantil, desarrollo, desarrollo neurológico, Trinidad y Tobago

West Indian Med J 2014; 63 (6): 583

INTRODUCTION

The overall survival of childhood cancer has increased in recent decades. In developed countries, "for every ten children diagnosed with cancer, almost eight now survive for five years or more, compared with fewer than three in the late 1960s" (1). With increasing numbers of children surviving cancer and entering adulthood, treatment protocols are frequently being revised. These revisions are needed to maximize survival and minimize long-term events such as neurocognitive dysfunction. As a result, research in long-term events and quality of life markers has become increasingly important. This helps to achieve cure at the least cost rather than cure at any cost. It also assists with the design of adequate follow-up guidelines and ensures appropriate continued support of the survivor.

The results of the existing research into the effect cancer treatment has on the development of childhood cancer survivors is quite conflicting. One study by von der Weid *et al* found that "as a group, ALL [acute lymphoblastic leukaemia] survivors showed intellectual performances within the normal range and was comparable to survivors from solid tumours outside the central nervous system [CNS]" (2). Another study by Kaleita *et al* also found that "mean scores on all cognitive and motor indices of the McCarthy scales were in the average range", concluding a generally positive neurodevelopmental outcome (3). However, other studies have shown that children who survived leukaemia typically obtained lower IQ scores than matched healthy children or children treated for solid tumours outside the CNS (4). Research from Raymond-Speden *et al* concluded that "CNS chemotherapy, and to a lesser extent, chronic illness both contribute to the poorer performance of long term survivors of ALL on measures of intellectual and academic performance" (5). The British Childhood Cancer Survivor Study 2010 reported that "childhood cancer survivors have lower educational attainment than the general population, with survivors of brain and CNS tumours and cranially irradiated leukaemia achieving the poorest educational outcomes" (6). Similar findings have been published by the North American Childhood Cancer Survivor Study 2003 (7).

Other studies demonstrated deficits in only certain areas of development. Kingma *et al* found normal cognitive functioning but "lower test scores in patients compared with controls in the test of attention, speed, sequencing, mental flexibility, and visual search" (8). Lofstad *et al* found that even though "the cognitive outcome for children with ALL treated with chemotherapy only was in the normal range, it represented a substantial decrease of as much as one standard deviation compared to matched healthy controls" (9). These decreases were noted specifically in attention, verbal function, complex visual spatial problem solving and processing speed.

This study will help to determine the neurodevelopmental outcomes of childhood cancer survivors less than nine years of age treated at the Eric Williams Medical Sciences Complex (EWMSC) in Trinidad and Tobago. It will also attempt to determine if there is any relationship between the type of cancer and treatment received and developmental delays. This will generate the information needed to develop appropriate protocols for the continued care of these children, ensuring improved long-term outcomes.

SUBJECTS AND METHODS

All children between two years, five months and nine years of age who had completed treatment for cancer before March 31, 2012 and who were treated at EWMSC were included in the study. Children with a pre-existing disease or disability that would interfere with normal development were excluded from the study. The McCarthy Scales of Children's Abilities (MSCA) was used to determine the child's neurodevelopmental level.

Procedure

Once a child met the inclusion criteria, the parents were contacted. Appointments for testing were arranged once parents gave their informed verbal consent for their child's participation in the study. At the appointment, the study was again explained to the parent(s) accompanying the child and any concerns were addressed. Informed written consent was then obtained from the parent(s) on behalf of their child. The MSCA was performed and patient demographics, type of cancer diagnosed and treatment received were abstracted from the patient records. Participating parent(s) were informed of the results of their child's performance on completion of the study. Any child who was found to have any area of concern was referred to the child development

clinic at EWMSC for further evaluation. Approval from the Ethics Committee of the Faculty of Medical Sciences of The University of the West Indies (UWI), St Augustine, Trinidad and Tobago, was obtained before the onset of any data collection or development testing.

Statistical analysis

The data generated were analysed using the Statistical Package for Social Sciences (SPSS) version 16 and Stata version 11. Frequencies and means were generated. *T*-tests were used to test for any statistically significant difference in the means between two groups. For three or more groups, analysis of variance (ANOVA) was used to test for any statistically significant differences.

RESULTS

There was a response rate of 74%. Thirty-five children who fulfilled the inclusion criteria were identified. Five of the children and their parents could not be contacted. Of the remaining 30 children, 29 were given appointments to be tested and one parent refused to have their child participate in the study. Three children and their parents failed to appear at repeated scheduled appointments. Twenty-six children were tested, 14 (53.8%) females and 12 (46.2%) males. Ages ranged from three years, three months to nine years (mean six years). The children were treated for various cancers: four cases of ALL, 15.4%, five cases of brain tumours (one infantile posterior fossa tumour, two brainstem gliomas, one pilocytic astrocytoma/medulloblastoma and one well differentiated ependymoma), 19.2% and 17 cases of solid tumours (four neuroblastomas, three hepatoblastomas, three nephroblastomas, two germ cell tumours, two retinoblastomas, one adrenocorticocarcinoma, one fibrosarcoma and one primitive neuroectodermal tumour (PNET)), 65.4% (Table 1). Twenty-one children (80.8%) were treated with a combination of chemotherapy with or without surgery. Two of the children (7.7%) were treated with radiotherapy only and three (11.5%) had surgery only. The age at diagnosis and start of treatment ranged from under one month to 78 months (mean 30.5 months). The age at completion of treatment ranged from ten to 80 months (mean 41 months). The maximum length of treatment was 42 months (mean 11 months). Treatment had been completed for a maximum of 73 months before testing (mean 31 months) [Table 1].

Test results of McCarthy Scales of Children's Abilities

The mean scores on all six scales for the children tested were below the means established by the MSCA, especially for memory and motor skills (Table 2). These mean scores were, however, within one standard deviation. Nineteen children

Table 1: General cognitive index (GCI) and demographics of study participants

No.	Gender	Type of cancer	Treatment (Tx)	Age at start of Tx	Age at end of Tx (EoT) (months)	Length of Tx (months)	Length of time since EoT (months)	Age at MSCA (months)	GCI
1	F	Fibrosarcoma	Chemotherapy ± surgery	2	13	11	26	39	100
2	M	Hepatoblastoma	Chemotherapy ± surgery	6	12	6	35	46	74
3	M	Neuroblastoma	Chemotherapy ± surgery	29	41	11	5	45	62
4	F	Nephroblastoma	Chemotherapy ± surgery	39	42	3	50	92	86
5	M	Brainstem glioma	Radiation only	25	27	2	32	59	49
6	F	Neuroblastoma	Chemotherapy ± surgery	52	–	–	–	103	77
7	F	ALL	Chemotherapy ± surgery	36	76	40	29	105	105
8	M	ALL	Chemotherapy ± surgery	30	68	38	40	109	79
9	F	Germ cell tumour	Chemotherapy ± surgery	5	10	5	40	50	84
10	F	Hepatoblastoma	Chemotherapy ± surgery	33	38	6	61	99	118
11	M	Hepatoblatoma	Chemotherapy ± surgery	20	26	6	24	50	98
12	F	PNET	Chemotherapy ± surgery	25	38	13	7	45	64
13	M	Infantile posterior fossa tumour	Chemotherapy ± surgery	1	18	17	24	42	94
14	M	Pilocytic astrocytoma	Surgery only	61	62	1	41	103	61
15	M	Neuroblastoma	Chemotherapy ± surgery	32	37	5	64	101	96
16	M	ALL	Chemotherapy ± surgery	25	68	42	16	84	88
17	M	Retinoblastoma	Chemotherapy ± surgery	52	55	3	41	96	86
18	F	Neuroblastoma	Chemotherapy ± surgery	18	28	10	73	101	90
19	F	Adrenocortico-Ca	Surgery only	15	15	0	36	51	99
20	M	ALL	Chemotherapy ± surgery	24	61	37	39	100	79
21	F	Nephroblastoma	Chemotherapy ± surgery	78	80	3	0	80	101
22	F	Brain stem glioma	Radiation only	54	55	2	2	57	142
23	F	Germ cell tumour	Chemotherapy ± surgery	34	38	3	3	40	112
24	F	Ependymoma	Surgery only	62	62	0	6	69	96
25	M	Retinoblastoma	Chemotherapy ± surgery	24	–	–	–	44	106
26	F	Nephroblastoma	Chemotherapy ± surgery	11	20	10	58	78	90

MSCA – McCarthy Scales of Children's Abilities, ALL – acute lymphoblastic leukaemia, PNET - primitive neuroectodermal tumour, Adrenocortico-Ca – adrenocorticocarcinoma

Table 2: Summary of McCarthy Scales of Children's Abilities (MSCA) scores

Scales	Mean score established by MSCA	SD established by MSCA	Mean scores of children tested	Range of scores of children tested
GCI	100	16	89.9	49–142
Memory	50	10	41.8	21–64
Motor	50	10	41.3	21–60
Perceptual performance	50	10	46.1	21–73
Quantitative	50	10	45.0	21–66
Verbal	50	10	43.5	21–73

SD – standard deviation, GCI – general cognitive index

(73.1%) scored below the MSCA mean for memory, motor and general cognitive index (GCI) [Table 1]. Twenty (76.9%) and 18 (69.2%) children scored below the MSCA mean for verbal and quantitative, respectively. Children performed best in perceptual performance with only 13 (50%) children scoring below the MSCA mean.

Based on the GCI, estimated mental ages were assigned to the children ranging from two years four months to nine years eight months (mean five years five months) [Fig. 1]. The mean estimated mental age was approximately

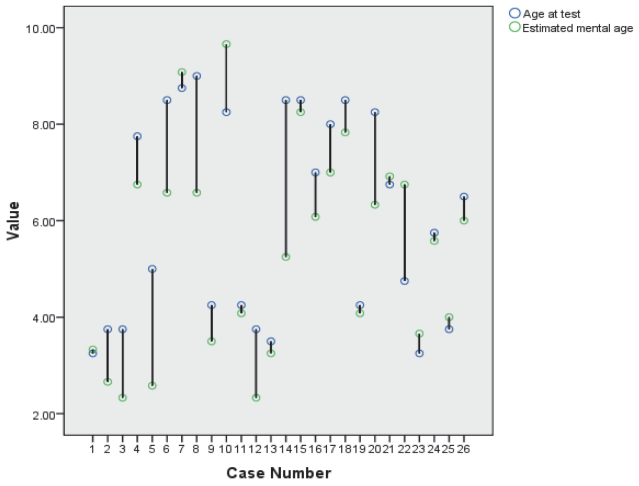

Fig. 1: Children's age at test compared to the assigned estimated mental age.

eight months below the children's mean actual age. This difference was statistically significant (p = 0.0086). Children treated for solid tumours had the least difference between their mean actual age and the mean estimated mental age. The difference was largest for the ALL subgroup. This comparison between the performances of the various subgroups was also statistically significant (p = 0.0301). A descriptive classification of abilities was also assigned based on GCI (Fig. 2). Eleven children (42.3%) were classified as average. One child (3.8%) was described as very superior (GCI > 132, + 2 SD). Four children (15.4%)

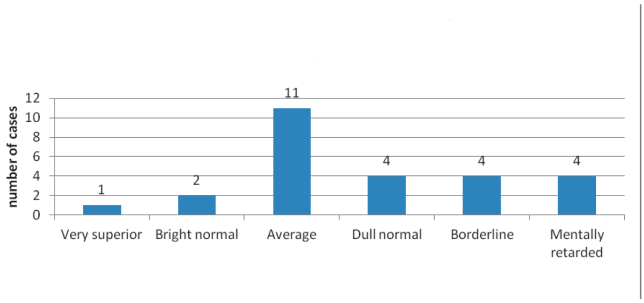

Fig. 2: Distribution of assigned descriptive classification of abilities.

were described as mentally retarded (GCI < 68, − 2 SD). Of these four children, two were cases of brain tumours (one treated with surgery only and the other with radiation only) and the other cases were solid tumours (treated with chemotherapy and surgery).

The girls sampled had a mean GCI of 97.4, whereas the boys' mean GCI was 81.0. This difference in the performance between the genders was statistically significant (p = 0.0302). Further analysis of the type of cancer treated, type and duration of treatment and length of time since treatment based on gender failed to find any statistically significant results that could account for this difference in performance. Overall, the type and length of treatment received, age at which treatment was started or completed or the length of time since the end of treatment was not found to have a statistically significant effect on the GCI.

DISCUSSION

This study demonstrated that the mean estimated mental age was found to be significantly below the mean actual age of the children tested and that there are detectable neurodevelopmental delays amongst the childhood cancer survivors. The delays were largest among the group of children treated for ALL and smallest among those treated for solid tumours, although the most profoundly delayed children were treated for brain and solid tumours.

These findings oppose those reported by von der Weid *et al* (2) and Kaleita *et al* (3) who found no evidence of cognitive delays amongst their childhood cancer survivors.

The results are more in keeping with the research from Raymond-Speden *et al* (5) and Lofstad *et al* (9) who found that childhood survivors of ALL displayed decreased intellectual performances. Also, based on the findings, children with brain tumours should have their development closely followed, as two of the five children in this group had a GCI below two standard deviations of the mean. This is similar to the findings of Walter *et al* who reported that "IQ scores significantly decreased from near normal at diagnosis to a median of 68 among survivors of infant and childhood medulloblastoma, falling in the mentally deficient range" (11).

This study also demonstrated that the girls tested performed better than the boys, opposing the findings of von der Weid *et al* in which "gender proved to be the major independent prognostic factor with girls scoring steadily poorer than boys" (2). The findings of the present study, however, are in keeping with the proven better academic performance of the girls of our population when compared with boys, demonstrated in the research by George *et al* which found that females are outperforming males at all levels of the school system (12).

A limitation of the study is the sample size. This could not have been avoided because of the age confines of the test used. Another limitation is that the MSCA was not developed specifically for our population; this may result in an unavoidable bias. However, there was another study conducted in Trinidad using the MSCA by Ali *et al* (13) with a control group of 39 healthy children. The ages at testing were 68 to 88 months (mean 73.7 months). The mean scores for the individual scales were verbal 57.33, perceptual-performance 60.63, quantitative 52.39, memory 52.33, motor 60.15 and GCI 115.36, with a mean estimated mental age of 84.6 months. The mean scores for this group of healthy children are well above the means of the cancer survivors tested in this study, confirming the findings of developmental delays. Other factors may also be responsible for the demonstrated developmental delays, including prolonged absences from school, bullying at school, fatigue and the psychological impact of having a chronic health condition. It would be difficult to eliminate all of these many factors or truly measure their impact on a child's development.

Based on the findings, all childhood cancer survivors should have their development closely monitored. This will ensure that delays in development are detected early, allowing for early intervention and rehabilitation and thus improving the child's chances for successful academic achievements. Children diagnosed with ALL and brain tumours should especially have their development closely monitored as they were found to be most at risk. There should also be repeated assessments of development at regular intervals. This will determine if developmental delays improve with increasing time from end of treatment or if they worsen. It will also help to determine if the interventions of development specialists and others improve the child's development. Screening for development at diagnosis of cancer should also be instituted so that evidence of newly developing delays after treatment can be objectively determined.

It would also be worthwhile to perform further research with a larger sample of childhood cancer survivors to determine if the statistically significant differences found in this study are maintained, especially the difference in performance between the genders. A larger sample size may also find other parameters such as length or type of treatment to significantly contribute to developing delays. The development of childhood cancer survivors should also be matched to healthy controls and compared to children with chronic illnesses that often require frequent hospitalizations such as sickle cell anaemia and poorly controlled asthma. The older childhood cancer survivors also require testing of their cognitive abilities, using other screening tests, to determine if findings will differ with age at assessment and length of time since end of treatment.

In conclusion, the findings of this study provide evidence of neurodevelopmental delays amongst childhood cancer survivors. These children should have their development closely monitored. Child development specialists and psychologists should be included as part of the team involved in the long-term care of childhood cancer survivors. This will improve the services provided and aid in the holistic medical management of these patients, ensuring that developmental delays are detected early and any necessary interventions are made. This will thus maximize their educational and vocational achievements, enhancing their quality of life in the future.

REFERENCES

1. Cancer Research UK. CancerStat: childhood cancer – Great Britain and United Kingdom. Cancer Research UK; 2010.
2. von der Weid N, Mosimann I, Hirt A, Wacker P, Nenadov Beck M, Imbach P et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age and sex related differences. Eur J Cancer 2003; **39:** 359–65.
3. Kaleita TA, Reaman GH, MacLean WE, Sather HN, Whitt JK. Neurodevelopmental outcome of infants with acute lymphoblastic leukaemia. Cancer 1999; **85:** 1859–65.
4. Anderson V, Smibert E, Ekert H, Godber T. Intellectual, educational, and behavioural sequelae after cranial irradiation and chemotherapy. Arch Dis Child 1994; **70:** 476–83.
5. Raymond-Speden E, Tripp G, Lawrence B, Holdaway D. Intellectual, neuropsychological, and academic functioning in long term survivors of leukaemia. J Pediatr Psychol 2000; **25:** 59–68.
6. Lancashire ER, Frobisher C, Reulen RC, Winter DL, Glaser A, Hawkins MM. Educational attainment among adult survivors of childhood cancer in Great Britain: a population based cohort study. J Natl Cancer Inst 2010; **102:** 254–70.
7. Mitby PA, Robison LL, Whitton JA, Zevon MA, Gibbs IC, Tersak JM et al. Utilization of special education services and educational attainment among long term survivors of childhood cancer. Cancer 2003; **97:** 1115–26.
8. Kingma A, Van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. No major cognitive impairment in young children with acute lymphoblastic leukaemia using chemotherapy only: a prospective longitudinal study. J Pediatr Hematol Oncol 2002; **24:** 106–14.

9. Lofstad GE, Reinfjell T, Hestad K, Diseth TH. Cognitive outcome in children and adolescents treated for acute lymphoblastic leukaemia with chemotherapy only. Acta Paediatr 2009; **98:** 180–6.
10. McCarthy DA. Manual for the McCarthy Scales of Children's Abilities. San Antonio, TX: The Psychological Corporation; 1972.
11. Walter AW, Mulhern RK, Gajjar A, Heideman RL, Reardon D, Sanford RA et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at the St Jude Children's Research Hospital. J Clin Oncology 1999; **17:** 3720–8.
12. George J, Quamina-Aiyejina L, Cain M, Mohammed C. Gender issues in education and intervention strategies to increase participation of boys. Trinidad and Tobago: Ministry of Education; 2009.
13. Ali Z, Ramcharan J. The neurodevelopmental abilities of very-low-birthweight children in Trinidad, West Indies. Trop Doct 2006; **36:** 210–12.