Original Article

The Adverse Effect of Intellectual Outcome in Childhood Cancer Survivors

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Background: Childhood cancer is a public health problem in Thailand. Improving clinical knowledge and increasing treatment intensity that may lead to complications could improve outcomes. Recently, the five-year survival rates have been increasing worldwide. However, the knowledge of long-term consequences still lacks.

Objective: To assess the intelligence quotient (IQ) of childhood cancer survivors compared with their siblings and exploring the risk factors of impaired cognitive outcomes of the survivors.

Materials and Methods: Cancer survivors, treated at Ramathibodi Hospital and in remission for more than three years were enrolled. The subjects with neurodevelopmental disorder or cranial irradiation were excluded. Their siblings were enrolled as controls. The Children's IQ were measured using the Wechsler Intelligence Scale for Children Third Edition (WISC-III).

Results: One hundred and three cancer survivors and thirty-seven healthy siblings were enrolled. The mean age of all participants was 11 years old. The cancer survivors had significant lower IQ score than the control. The low socioeconomic status (SES) and the parents' education below grade 9 were significant factors causing the childhood cancer survivor group to have significantly lower IQ score than the controls.

Conclusion: Children treated with chemotherapy had decreased neurocognitive outcomes. In addition, lower SES and lower parental education were significant factors resulting in impaired intelligence.

Keywords: Childhood cancer survivors, Intelligence quotient, Socioeconomic status, Parental education

J Med Assoc Thai 2019;102(8):841-7
Website: http://www.jmatonline.com
Received 15 Mar 2018 | Revised 22 Apr 2019 | Accepted 23 Apr 2019

Pediatric cancer is a public health problem in Thailand. New cases of childhood cancer were 74.9 cases per one million Thai children per year. Leukemia is the most common childhood cancer, followed by lymphoma and central nervous system (CNS) tumors, respectively[1,2]. Over the past four decades, due to the modern medical science and more effective chemotherapy (CMT), some types of cancer can be cured. The overall survival (OS) rate of childhood cancers was increased from 63% to 83% in the United States[2]. Whereas, the OS rate of pediatric malignancies in Thailand was 54.9%[1]. For the most common childhood cancer, acute lymphoblastic leukemia (ALL), the 5-year OS rate in the U.S., Thailand, and at Ramathibodi Hospital were 90%, 64.9%, and 88%, respectively[1-3].

Improving outcomes of cancer patients result from improving clinical knowledge and increasing intensity of treatment. However, increasing intensity of treatment leads to some complications, both physically and mentally. Pediatric oncologists aim to keep a balance between effective therapy and minimal morbidity. Cranial irradiation therapy (CRT) is well-

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How to cite this article: Ketsuwan S, Surayuthpreecha K, Chuthapisith J, Anurathapan U, Pakakasama S, Numthavaj P, et al. The Adverse Effect of Intellectual Outcome in Childhood Cancer Survivors. J Med Assoc Thai 2019;102:841-7.

known to produce significantly long-term intellectual disability, especially in ALL[4]. Furthermore, female gender and younger age at diagnosis of ALL were associated with an increased risk of worse cognitive outcome[5]. This led to the replacement of CRT by intrathecal (CNS-directed) and high-dose CMT[6,7]. Several studies showed that the patients who survived at least three years after the CMT and CRT treatment often had problems in health and intelligence. Numerous studies addressed the issue of cognitive functions after the treatment of cancers[8-10]. A previous study demonstrated that the survivors had a significantly lower intellectual score than matched healthy controls. Additionally, socioeconomic status (SES) and parents' education affect the intelligence of schoolchildren[11,12]. However, there was no such study regarding cognitive functions of pediatric cancer survivors in Thailand. The only study of the late effects in childhood ALL survivors at Thai Pediatric Oncology Group (ThaiPOG) found that overweight or obesity was the most common late effect[13].

Recently, clinical researches mainly focused on therapeutic strategies and outcomes of cancer. On the other hand, the studies on the long-term consequences have been inadequate. Many studies were limited by small sample size and lack of a control group. Therefore, the aims of the present study were to explore the long-term intelligence outcomes and to identify risk factors that affected the long-term intelligence outcomes of childhood cancer survivors after the completion of CMT.

Materials and Methods

The present study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University. Childhood cancer survivors, aged of 6 to 16 years, who followed up at the Oncology Clinic, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, were enrolled. The subjects were all in the complete remission for at least three years and returned to normal educational system. The patients who had CNS tumors, received craniospinal irradiation, post bilateral enucleation, and had known neurodevelopmental disorder were excluded.

The sample size was calculated by the Power and Sample size Calculation Program version 3.1.2 using type I error of 0.05 and power of 0.8 and the average intelligent quotient (IQ) score of 98.6 point (SD of 16.4; 95% confidence interval of 98.5 to 98.7) from the study of IQ of Thai student in 2011 by Department of Mental Health, Ministry of Public Health, Thailand (published in Thai language). The authors estimated patients would have siblings in a ratio of 1:0.6. Approximately 40 childhood cancer survivors were needed, whereas 24 patients were needed in a control group.

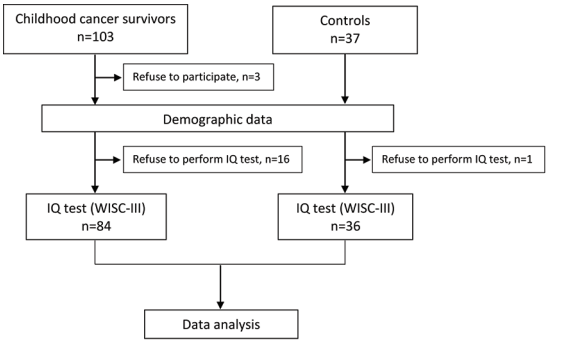

Figure 1. The protocol flow chart reveals number of subjects and the procedures performed in each group.

IQ=intelligent quotient, WISC-III=the Wechsler Intelligence Scale for Children-Third Edition

Siblings of the subjects were enrolled as controls (a control group). Their parents answered the demographic data, such as parents' age, education, and income. All subjects and controls were measured for their intellectual functions by an experienced child psychologist using the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) Thai version. Eleven subsets were tested. The following data were included, information, similarities, arithmetic, comprehension, digit span, picture completion, coding, picture arrangement, block design, object assembly and symbol search. Age-adjusted scores for specific subsets were summarized and transformed into three intelligence scales: full-scale IQ, verbal IQ, and performance IQ.

Statistical analysis

The demographic data were analyzed by comparing demographical variables with independent sample t-tests or Mann-Whitney U test. Intellectual outcomes were compared to the control group by using independent sample t-test. Univariate analysis was performed to study the impact of age at diagnosis, gender, parents' education, and income on the IQ scores. The data were analyzed using SPSS software version 22.

Results

One hundred and three cancer survivors were

Table 1. The demographic and clinical characteristics of the subjects

Characteristics	Childhood cancer survivors (n=100) n (%)	Controls (n=37) n (%)	p-value
Sex: male	59 (59.0)	25 (67.6)	0.361
The age at the time of diagnosis (years), mean±SD	4.4±3.2	N/A	-
Time since the last treatment (years), mean±SD	5.5±2.4	N/A	-
The age at the time of study (years), mean±SD	11.1±2.8	10.9±3.3	0.803
The age of parents (years), mean±SD			
Father	44.3±8.0	47.2±8.6	0.098
Mother	41.1±6.8	41.0±5.3	0.098
The education of parents			
Father			0.284
• Elementary school	17 (17.0)	2 (5.4)	
• Secondary school	24 (24.0)	9 (24.3)	
• Vocational certificate	17 (17.0)	6 (16.2)	
• Bachelor degree or higher	40 (40.0)	20 (54.1)	
Mother			0.134
• Elementary school	15 (15.0)	1 (2.7)	
• Secondary school	29 (29.0)	9 (24.3)	
• Vocational certificate	9 (9.0)	3 (8.1)	
• Bachelor degree or higher	47 (47.0)	24 (64.9)	
Community			0.400
Urban	38 (38.0)	17 (46.0)	
Rural	62 (62.0)	20 (54.0)	
Annual household income (baht per month)			0.052
<5,000 to 9,999	15 (15.0)	1 (2.7)	
10,000 to 29,999	27 (27.0)	8 (21.6)	
30,000 to 49,999	25 (25.0)	13 (35.2)	
50,000 to 100,000	23 (23.0)	6 (16.2)	
>100,000	10 (10.0)	9 (24.3)	

SD=standard deviation; N/A=not available

enrolled. Thirty-seven healthy siblings were enrolled as controls. The number of participants who refused to enroll in each step are shown in Figure 1. The common diagnoses were ALL (39%), extracranial germ cell tumor (19%), soft tissue sarcoma (15%), and neuroblastoma (12.5%). The mean age at the time of diagnosis of the childhood cancer survivors was 4.4 years. At the time of the present study, the patients were at the mean age of 11.1 years and at the mean of 5.5 years after the completion of treatment. The mean age of the controls were 10.9 years. The demographic data, including the education of parents and the annual household income, revealed no statistically significant differences between the childhood cancer survivors and the controls (Table 1).

Intellectual outcome (patients as a group versus controls)

All the childhood cancer survivors had within-normal-range full-scale IQ, verbal IQ, and performance IQ scores. The mean scores of the full-scale IQ, the verbal IQ, and the performance IQ were 99.4, 96.9, and 102.5, respectively. For the WISC-III IQ score, all three intelligence scales of the childhood cancer

Table 2. The WISC-III scores of the childhood cancer survivors and the controls

WISC-III	Childhood cancer survivors (n=84) Mean±SD	Controls (n=36) Mean±SD	p-value
IQ score			
Full scale IQ	99.4±14.3	106.7±14.0	0.012
Verbal IQ	96.9±14.9	104.1±14.8	0.017
Performance IQ	102.5±14.2	109.4±14.9	0.018
Index score			
Verbal comprehension	97.9±16.2	103.8±16.0	0.065
Perceptual organization	101.7±15.1	108.7±13.3	0.016
Freedom from distractibility	103.4±14.3	108.9±19.5	0.136
Verbal part			
Information	10.1±3.1	11.6±3.4	0.021
Similarities	9.8±3.2	11.4±3.2	0.014
Arithmetic	9.9±3.2	11.1±4.2	0.084
Comprehension	8.2±3.2	9.2±2.9	0.093
Digit span	11.0±2.9	11.6±3.7	0.300
Performance part			
Picture completion	10.4±2.6	11.5±3.7	0.063
Coding	11.0±3.2	11.6±3.9	0.350
Picture arrangement	10.4±3.1	10.9±3.1	0.387
Block design	10.5±3.5	12.3±2.6	0.006
Object assembly	9.4±3.4	10.8±2.4	0.030
Symbol search	8.2±3.2	10.3±3.2	0.057

SD=standard deviation; IQ=intelligent quotient; WISC-III=the Wechsler Intelligence Scale for Children-Third Edition

survivors had significantly lower than that of the controls. The mean differences of each intelligence scales were 7.3 points of the full-scale IQ (p=0.012), 7.2 points of the verbal IQ (p=0.017), and 6.9 points of the performance IQ (p=0.018) (Table 2). The childhood cancer survivors had the mean perceptual organization index score 7 points lower than the control group (p=0.016). Comparing the subsets of the WISC-III IQ score, the sibling group had significantly higher score than the cancer survivor group in the information, the similarities, the block design, and the object assembly subsets. Moreover, the univariate analysis showed that the annual household income of less than 20,000 baht per month and the parents' education below grade 9 (the compulsory education in Thailand) were significant factors causing significant lower IQ in childhood cancer survivors (Table 3). However, subgroup analyses among the cancer survivors diagnosed at age of less than 4 years with those diagnosed at age of more than 4 years as well as those, whom diagnosed as leukemia, received systemic CMT and CNS directed therapy versus those diagnosed with solid tumors that received only systemic CMT showed no statistically significant differences of IQ.

Discussion

Long-term survivors from any childhood cancers at the authors' institute participating in the present study had significant lower IQ scores than their healthy siblings. In the authors' study, all subjects tested for IQ levels were at the mean age of approximately 11 years and had no significant differences of parental aspects: e.g., age, education, and annual household income. Moreover, the authors enrolled cancer survivors with not only hematologic malignancies but also solid tumors. This finding corresponds to the report from a study in Norway[10]. They studied the IQ scores using

Table 3. The factors that affect the IQ scores in the childhood cancer survivors

Factor	n	Full scale IQ Mean±SD	p-value	Performance IQ Mean±SD	p-value	Verbal IQ Mean±SD	p-valve
Sex			0.817		0.541		0.836
Male	50	99.7±14.9		103.3±14.7		96.7±15.4	
Female	34	99.0±13.5		101.4±13.4		97.4±14.3	
Age at the time of diagnosis			0.161		0.452		0.093
≤4 years (pre-school age)	47	101.4±14.7		103.6±14.6		99.4±14.8	
>4 years (school age)	37	97.0±13.6		101.2±13.7		93.9±14.6	
Father's education			0.011		0.013		0.037
≤ grade 9	25	93.4±13.7		96.7±15.1		91.8±12.8	
> grade 9	59	102.0±13.9		105.0±13.1		99.1±15.3	
Mother's education			0.004		0.007		0.016
≤ grade 9	19	91.4±13.0		94.9±15.7		89.8±10.9	
> grade 9	65	101.8±13.9		104.8±13.0		99.0±15.3	
Annual household income			0.001		0.004		0.001
≤20,000 baht/month	21	90.3±13.7		94.9±14.6		87.8±13.6	
>20,000 baht/month	63	102.5±13.2		105.1±13.2		100.0±14.1	

SD=standard deviation; IQ=intelligent quotient

the WISC-III of 35 ALL survivors comparing with 35 healthy controls at the mean age of 11 years. They demonstrated that ALL survivors had significant lower IQ scores from full-scale, verbal and performance, than the healthy controls and normative standard for the WISC-III. However, a study in Switzerland reported no statistically significant differences of all measures of IQ scores, using the Wechsler Intelligence Scale for Children-Revised (WISC-R) test, among cancer survivors[6]. Moreover, another group in the Netherlands reported no major cognitive impairment in children with ALL[9]. They enrolled two consecutive groups of ALL patient treated with different protocols at their institute. The used the WISC-R test as a tool to assess the patients' IQ scores. They showed the mean full-scale IQ of ALL patients at the median age of 10 years at the time of evaluation were not statistically different from that of the matched controls. Additionally, a study in France showed normal range of the full-scale IQ scores in cancer survivors with extracranial solid tumors. They evaluated 76 extracranial-solid-tumor cancer survivors after high-dose systemic CMT with autologous stem cell rescue by the French adaptation of WISC-III child. They also performed memory and visuospatial constructional skill along with academic achievement at least five years after the end of the treatment. They found the professional and academic outcomes of those cancer survivors were satisfactory[14].

Recently, a meta-analysis evaluated the neuro-cognitive function of ALL survivors been reported[15]. They included eight non-experimental studies, 432 patients and 465 controls using different version of the Wechsler Intelligence Scale depended on age of patient. They reported that the ALL survivors had significant lower all measures of IQ scores than the control group. Nevertheless, another meta-analysis examined the neuropsychological effects of CMT in childhood cancer survivors received systemic and CNS-directed CMT from 12 published studies[16]. They demonstrated the childhood cancer survivors had significant deficits in attentional capacity especially those within five years of treatment. Therefore, these discordant results may originate from not only the different social and cultural contexts but also the different tests used to assess IQ levels of subjects and the duration after treatment at the time of study. From these findings, the authors may be able to conclude that childhood cancer survivors exposed to CMT had impacts on their neurocognitive functions. However, the authors could not define whether systemic CMT alone or systemic and CNS-directed CMT had the direct effect of intellectual performance of cancer survivors.

In our study, the childhood cancer survivors whose parental education were only completion of Thai compulsory education or whose parents' annual income were less than 20,000 baht/month had significant lower IQ scores than those with higher parental education or higher parental annual income. These findings concur with previous reports from India, Singapore, and Malaysia[12,17,18], although, they did use other tools for determination of subjects' IQ levels. They enrolled 300 to 1,000 of school-aged children to monitor IQ score from either all areas across India, Singapore or rural Malaysia. They reported that children with higher parental education or higher parental annual income/SES were more likely to have high IQ scores. In contrast, a Norwegian group used the WISC-III to assess IQ level of school-aged children and reported that only parental education was the significant predictor for intellectual function[19]. Annual household income was a minor predictor for IQ levels of children. This conflict may be from not only different educational systems among Asian countries and European countries but also the different social and cultural contexts. From these findings, the authors may summarize that the childhood cancer survivors also had similar effects from parental SES and parental education as healthy school-aged children.

The first limitation in the present study was a small number of the control group because most of the childhood cancer survivors had no siblings. Secondly, there was no documented baseline IQ scores of participants prior to treatment.

Conclusion

The present study findings indicated that children treated with CMT with or without CNS-directed CMT were associated with lower neurocognitive outcome. Furthermore, the authors found that the lower SES and lower parental education were significant factors resulting in impaired intelligence.

What is already known on this topic?

Several studies reported controversial results of intellectual levels in childhood cancer survivors compared to controls. Furthermore, some reported factors affected IQ score of children after completion of standard treatment for cancers. Recently, Thai pediatric oncologic survivors have been using novel therapeutic strategies, however there is no such study of cognitive function in long-term cancer survivors.

What this study adds?

This study showed that childhood cancer survivors had lower IQ scores than healthy controls. Moreover, lower parent education or lower socioeconomic status were the significant risk factors for lower IQ levels in pediatric oncologic survivors.

Acknowledgement

The present study was supported by a grant from the Ramathibodi Research Fund, Faculty of Medicine Ramathibodi Hospital. The authors would like to thank all participants and other health personnel, and the support from the section of Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital.

Conflicts of interest

The authors declare no conflict of interest.

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