HK J Paediatr (new series) 2021;**26**:135-140

Original Article

Attention Deficit Hyperactivity Disorder in Paediatric Patients with Malignant Haematologic Diseases or Epilepsy: Experience at a Tertiary Care Hospital in Korea

JY ***Han***, JW ***Lee***, B ***Cho***, NG ***Chung***, IG ***Lee***

Abstract ***Background***: Paediatric patients with epilepsy and malignant haematologic diseases (MHD) are at increased risk of mental health problems compared to the general population. The purpose of this study was to determine the prevalence of attention-deficit hyperactivity disorder (ADHD) among paediatric patients treated for MHD or epilepsy compared to that in healthy children in South Korea. ***Methods***: We retrospectively reviewed 184 patients diagnosed with epilepsy and 172 patients diagnosed with malignant haematologic diseases in the paediatric department of Seoul St. Mary's Hospital from May 2009 to May 2013. Normal controls were selected from the out-patient clinic among those who visited the clinic for vaccination. ***Results***: Paediatric patients with epilepsy or MHD exhibited significantly higher rate of ADHD compared to the controls (37.5% or 29.6% vs. 11.9%, *P*=0.039). Among children with both MHD and ADHD, 69.5% had the inattentive subtype and 30.5% had the combined subtype of ADHD. Among children with both epilepsy and ADHD, 70.6% had the inattentive subtype, 23.5% had the combined subtype, and 5.9% had the hyperactive type of ADHD. There were statistically significant differences between MHD patients with ADHD and MHD patients without ADHD of sex, age at onset of haematologic diseases (≤5 years), intrathecal chemotherapy, treatment duration and cranial radiation. Patients with epilepsy and concomitant ADHD showed significantly poorer response to epilepsy treatment than patients without ADHD. ***Conclusions***: Paediatric patients with MHD and epilepsy are at significant risk for ADHD. Baseline testing of all patients with MHD or epilepsy is needed to assess their neuropsychological and academic skills over time to facilitate early intervention and prevent academic failure.

Key words *Attention deficit hyperactivity disorder; Epilepsy; Malignant haematologic diseases*

Department of Pediatrics, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seocho-gu, Seoul 06591, Republic of Korea

JY **Han**（韓智潤） *MD, PhD*
JW **Lee**（李在郁） *MD, PhD*
B **Cho**（趙斌） *MD, PhD*
NG **Chung**（鄭樂均） *MD, PhD*
IG **Lee**（李寅九） *MD, PhD*

Correspondence to: Dr IG **Lee**
Email: iglee@catholic.ac.kr

Received January 23, 2019

Introduction

With the introduction of multimodal therapy in the early 1970s, 5-year survival rates for most paediatric malignant haematologic diseases have improved dramatically. Over the past four decades, improved prognosis of childhood acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) has resulted in 5-year survivor rate of around 80% in developed country.[1,2] Although medical advances have resulted in increased life expectancy of many chronically ill children, a substantial proportion of

these children experience long-term neurocognitive sequelae associated with treatment- and disease-related factors.

Children surviving cancer frequently experience deficits in attention, learning, and memory, that are secondary to the disease process itself and requisite treatment that may include surgery, chemotherapy and/or cranial radiation therapy.[3] Attention problems occur frequently among childhood cancer survivors. It has been estimated that approximately one-quarter of ALL survivors demonstrate significant dysfunction.[4]

The prevalence of epilepsy in the general population ranges from 0.5% to 1%. Attention deficit hyperactivity disorder (ADHD) occurs in 3-7% of all children.[5,6] Among children with epilepsy, the prevalence of ADHD is much higher than that among the general paediatric population, ranging widely from 8 to 77%.[7] Difficulties with attention appear to be very prevalent in patients with childhood epilepsy compared to those in healthy children. It is possible that ADHD could be attributable to seizure characteristics or effect of antiepileptic drugs (AED).

Paediatric patients with epilepsy or malignant haematologic diseases (MHD) are at increased risk of mental health problems compared to the general population. The purpose of this study was to determine the prevalence of ADHD among children treated for MHD and epilepsy in South Korea. This knowledge will be helpful for developing clinical intervention and determining relevant outcomes.

Methods

We retrospectively reviewed 184 patients diagnosed as epilepsy who were treated with AEDs in Pediatric Neurology Department of Seoul St. Mary's Hospital from May 2009 to May 2013. We also retrospectively reviewed 172 patients diagnosed as MHD who were in continuous complete remission since initial diagnosis in paediatric haematology departments of Seoul St. Mary's Hospital from May 2009 to May 2013 ALL lymphoblastic leukaemia (87 patients). Their ages ranged from 6 to 18 years old at the time of diagnosis. Children who had pre-existing neurologic conditions affecting behavioural development (cerebral palsy, developmental delay, or mental retardation) were excluded. Normal controls were selected at the out-patient clinic of Seoul St. Mary's hospital from those who visited the clinic for vaccination. Children who had significant medical illnesses or neuropsychiatric problems were excluded.

The Korean Child Behaviour Checklist (K-CBCL) and the Korean ADHD Rating Scale (K-ARS) were used as screening instruments. Diagnoses were confirmed through the Diagnostic Interview Schedule for Children Version IV (DISC-IV). We also used parent and teacher questionnaires based on the DSM-IV criteria, parent interviews and direct observation of children. These data were compared between patients with ADHD and those without ADHD. The following tests were performed for pre-treatment functioning: K-WISC-II (Korean-Wechsler Intelligence Scale for Children) and Neuropsychological test. ADHD diagnosis was established by child psychiatrist in all patient groups. Electroencephalography (EEG) abnormalities defined as epileptiform discharges according to abnormal frequency, height or shape based on ILAE classification of the Epilepsies (2017). SPSS (ver. 19.0) was used for all statistical analyses. Chi-square test, Fisher's exact test and one-way analysis of variance (ANOVA) were used to estimate significant differences. Values were considered statistically significant at $P<0.05$. This study was reviewed and approved by the Institutional Review Board of St. Mary's Hospital (approval number: KC13RASI0366).

Results

A total of 758 patients aged 6-18 years were identified, including 172 patients with a history of MHD, 184 patients who were diagnosed as epilepsy and 402 healthy controls. Baseline characteristics of the study population are shown in Table 1. Healthy controls with the same male-to-female ratio and age (11.0±5.9) were assessed. Children with MHD were younger than children with epilepsy and controls. Children with epilepsy or MHD exhibited significantly higher rate of ADHD) compared to controls (29.6% or 37.5% vs. 11.9%, $P=0.039$). Among patients who had both MHD and ADHD, 69.5% had the inattentive subtype and 30.5% had the combined subtype of ADHD. Among children with both epilepsy and ADHD, 70.6% had the inattentive subtype, 23.5% had the combined subtype and 5.9% had the hyperactive type of ADHD. The inattentive subtype of ADHD was more predominant in all groups than the combined subtype of ADHD. There was no significant group differences in sex or age.

Of 172 patients with MHD, 69 (37.5%) patients had both ADHD and MHD. When compared with patients

without ADHD, MHD patients with ADHD were more likely to be male, five or younger at the onset of haematologic diseases, and had intrathecal chemotherapy with longer treatment duration and cranial radiation ($P<0.05$). However, relapse of MHD did not show a significant difference between MHD patients with ADHD and MHD patients without ADHD ($P=0.081$).

Fifty-one (29.6%) out of 184 epileptic patients had both ADHD and epilepsy. In epileptic patients with ADHD, males outnumbered females by almost two-fold (46 males vs. 23 females, $P=0.022$). For 59.1% of patients without ADHD, their seizures remained under control with a single AED compared to 33.3% of patients with both ADHD and epilepsy ($P=0.020$). Out of 184 patients, 106 (57.6%) had partial seizures, 72 (39.1%) had generalised seizures, and 6 (3.3%) had mixed seizures. There was no statistically significant differences in age, seizure type, or EEG abnormalities between epilepsy patients with ADHD and those without ADHD ($P=0.068$, $P=0.355$, $P=0.742$, respectively).

Table 1 Comparison of characteristics in controls, patients with malignant haematologic diseases, and patients with epilepsy

Parameters	Patients with MHD	Patients with epilepsy	Controls	p-value
No. of participants	172	184	402	
Age (year, mean ± SD)	10.2±3.2	12.62±3.4	11.0±5.9	0.121
Male:Female	88:84	103:81	191:211	0.081
ADHD accompaniment	69 (37.5%)	51 (29.6%)	49 (11.9%)	0.039
Inattentive	69.5% (48/69)	70.6% (36/51)	63.2% (34/49)	0.075
Hyperactive	0% (0/69)	5.9% (3/51)	4.5% (2/49)	0.198
Combined	30.5% (21/69)	23.5% (12/51)	26.5% (13/49)	0.072

MHD: malignant haematologic diseases; ADHD: attention deficit hyperactivity disorder; SD: standard deviation.

Table 2 Comparison of malignant haematologic disorders with ADHD and without ADHD

	MHD with ADHD (N=51)	MHD without ADHD (N=121)	p-value
Mean age (year)	10.0± 4.1	10.4± 3.4	0.475
Male:Female	35:16	53:68	0.002
Age group of onset (year)			0.004
11-18	11 (21.6%)	43 (35.5%)	
6-10	11 (21.6%)	42 (34.7%)	
1-5	29 (56.8%)	36 (29.8%)	
Treatment			0.031
Intrathecal chemotherapy	46 (90.2%)	97 (80.2%)	
No intrathecal chemotherapy	5 (9.8%)	24 (19.8%)	
Response to treatment			0.081
No relapse	42 (82.3%)	105 (86.8%)	
Relapse	9 (7.7%)	16 (3.2%)	
Cranial radiation			0.049
Yes	8 (15.6%)	12 (10.0%)	
No	43 (84.4%)	109 (90.0%)	
Treatment duration (year)	3.0±1.1	1.9±0.7	0.042

MHD: malignant haematologic diseases; ADHD: attention deficit hyperactivity disorder.

Discussion

The prevalence of ADHD in Korean studies has been reported to be 3.9-13.3%.[8,9] Estimated ADHD prevalence during paediatric period has shown wide variation around the world, ranging from 0.9% to 20%.[10,11] In our study, ADHD prevalence was 11.9% in healthy controls. It is generally accepted that the combined type of ADHD is the most common type in the general population.[7] However, the inattentive type of ADHD was more common in healthy, epileptic and MHD children in our study.

ADHD is a common neuropsychiatric disorder that impairs social, academic and vocational functions in children and adolescents. By their young adulthood, ADHD youth are at high risk for a wide range of adverse psychiatric outcomes, including elevated prevalence of antisocial, addictive, behavioural and anxiety disorders.[12]

The scope of chronic health condition is broad. It can affect the neuropsychiatric system. Survivors of paediatric brain tumour and ALL are at risk for lasting cognitive impairment attributable to disease and treatments that can affect the central nervous system (e.g., cranial radiation therapy, intrathecal chemotherapy).[13,14] Patients diagnosed with ALL at younger age suffer greater cognitive deficits than patients diagnosed at older age, especially when they are treated with cranial irradiation.[15] Neurocognitive impairment is estimated to occur in 20-40% of long-term survivors of childhood ALL. Neurocognitive deficits can negatively impact learning and academic achievement of patients compromising their educational and vocational opportunities.[16] Despite these well-established findings, there have been few empirically validated interventions to remediate cognitive impairments emerging secondary to treatment for MHD.[17]

Results of our study demonstrate that the rate of symptoms of ADHD in survivors of MHD is higher than that in healthy controls, suggesting that MHD has a significant relation with ADHD in paediatric patients. In addition, in males under 5 years of age at onset, intrathecal chemotherapy and cranial radiation might be necessary to predict ADHD. Therefore, early detection and establishment of countermeasure for ADHD are needed to maintain their quality of life.

Paediatric patients with epilepsy are more likely to have difficulties with 'attention problems' than healthy controls. It is often assumed to be the consequence of recurrent seizures, medical treatment, or characteristics of epilepsy.[18] Patients with epilepsy and concomitant ADHD show significantly poorer response to epilepsy treatment compared to patients without ADHD. In our study, there

Table 3 Comparison between epilepsy patients with ADHD and those without ADHD

	Epilepsy with ADHD (N=69)	Epilepsy without ADHD (N=115)	p-value
Mean age (year)	12.5±3.5	12.3±2.9	0.068
Male:Female	46:23	57:58	0.022
Age group of onset (year)			0.126
11-18	23 (33.3%)	41 (35.7%)	
6-10	32 (46.4%)	58 (50.4%)	
1-5	14 (20.3%)	16 (13.9%)	
Duration of treatment (year)	2.2±0.8	1.8±0.7	0.036
Number of AEDs			0.020
Monotherapy	23 (33.3%)	68 (59.1%)	
Polytherapy	46 (66.7%)	47 (40.9%)	
Seizure types			0.355
Partial	46 (66.7%)	60 (52.2%)	
Generalised	18 (26.1%)	54 (46.9%)	
Mixed	5 (7.2%)	1 (0.9%)	
EEG abnormalities			0.742
Abnormal	50 (72.5%)	83 (72.2%)	
Normal	19 (27.5%)	32 (27.8%)	

ADHD: attention deficit hyperactivity disorder; AED, antiepileptic drug.

was no difference in ADHD accompaniments between partial and generalised seizure types. However, treatment duration and polytherapy could influence the diagnosis of ADHD. The presence of ADHD in patients with epilepsy could be related to therapeutic response to AEDs and could be a useful predictive factor for response in early stage. Another study has found that ADHD is related to illness and seizure frequency.[19] ADHD can increase the risk of subsequent epilepsy and vice versa.[20] Thus, it is important to manage ADHD in children with epilepsy. However, ADHD might be under treated in children with epilepsy.[21]

Stimulants remain to be the first-choice pharmacological agents for the management of ADHD. Psychosocial, behavioural and educational strategies that can enhance specific behaviours may improve educational and social functioning in children with ADHD.[22] Evidence from a one-year efficacy trial of methylphenidate (MPH) in paediatric cancer survivors experiencing cognitive late effects has recently emerged, suggesting long-term cognitive and behavioural benefits of stimulant treatment in this population.[23] There are also reports of good response to MPH in children with epilepsy.[24] Children could be selected for early intervention trials to reduce symptoms of ADHD. The goal of a comprehensive epilepsy clinic/service is to perform an assessment and provide treatment not only for seizures, but also for cognitive and behavioural difficulties experienced by children with epilepsy.[25] Children with MHD and epilepsy are at significant risk for ADHD. There is a need for more studies focusing on safe and efficacious intervention for symptoms of ADHD. Baseline testing of all patients with MHD or epilepsy is needed to assess their neuropsychological and academic skills over time to facilitate early intervention and prevent academic failure. These results highlight the need for continued monitoring of ADHD in survivors of paediatric MHD and epilepsy. Future studies shall address these issues and guide paediatrician, nurses and teachers to work together to develop individualised plans that can help children with MHD or epilepsy fulfill their educational goals. Long-term social prognosis of these children appears to be of considerable importance. Future studies are needed to confirm our results in a larger population.

Conclusions

This study shows that paediatric patients with MHD or epilepsy are at significant risk for ADHD. Children with MHD were younger than children with epilepsy and controls. Children with epilepsy or MHD exhibited 2 to 3 folds higher rate of ADHD compared to controls. When compared with patients without ADHD, MHD patients with ADHD were more likely to be male, five or younger at the onset of haematologic diseases, and had intrathecal chemotherapy with longer treatment duration and cranial radiation. Patients with epilepsy and concomitant ADHD showed significantly poorer response to epilepsy treatment than patients without ADHD. Thus, baseline testing of all MHD or epilepsy children is needed to check their neuropsychological and academic skills over time to facilitate early intervention and prevent academic failure.

Declaration of Interest

None.

Acknowledgement

We would like to acknowledge the St. Mary's Hospital and patients.

References

1. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. Cancer 2002;95:1767-72.
2. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. Hematol Oncol Clin North Am 2010;24:35-63.
3. Nicholls E, Hildenbrand AK, Aggarwal R, McCarthy L, Daly B. The use of stimulant medication to treat neurocognitive deficits in patients with pediatric cancer, traumatic brain injury, and sickle cell disease: a review. Postgrad Med 2012;124:78-90.
4. Krull KR, Brouwers P, Jain N, et al. Folate pathway genetic polymorphisms are related to attention disorders in childhood leukemia survivors. J Pediatr 2008;152:101-5.
5. Association AP. Diagnostic criteria from dsM-iV-tr: American Psychiatric Pub; 2000.
6. Sander JW. The epidemiology of epilepsy revisited. Cur Opin Neurol 2003;16:165-70.
7. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. Dev Med Child Neurol 2003;45:50-4.
8. Yang SJ, Cheong S, Hong SD. Prevalence and correlates of attention deficit hyperactivity disorder: school-based mental health services in Seoul. J Korean Neuropsychiatr Assoc 2006;45:69-76.
9. Yang YH, Kim JW, Kim YN, Cho SC, Kim BN. Screening for attention deficit/hyperactivity disorder for children in Seoul. J Korean Neuropsychiatr Assoc 2008;47:292-8.
10. Goodman R, Dos Santos DN, Nunes AR, de Miranda DP, Fleitlich-Bilyk B, Almeida Filho N. The Ilha de Maré study: a survey of child mental health problems in a predominantly African-Brazilian

rural community. Soc Psychiatry Psychiatr Epidemiol 2005;40: 11-7.
11. Cornejo JW, Osio O, Sanchez Y, et al. [Prevalence of attention deficit hyperactivity disorder in Colombian children and teenagers]. Rev Neurol. 2004;40:716-22.
12. Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med 2006;36:167-79.
13. Peterson CC, Johnson CE, Ramirez LY, et al. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;51:99-104.
14. Fossen A, Abrahamsen TG, Storm-Mathisen I. Psychological outcome in children treated for brain tumor. Pediatr Hematol Oncol 1998;15:479-88.
15. Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, Veerman AJ. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. Pediatr Blood Cancer 2005;45:281-90.
16. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 2003;97:1115-26.
17. Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol 2005;30:65-78.
18. Jones JE, Watson R, Sheth R, et al. Psychiatric comorbidity in children with new onset epilepsy. Dev Med Child Neurol 2007; 49:493-7.
19. Caplan R, Siddarth P, Stahl L, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia 2008; 49:1838-46.
20. Chou I-C, Chang Y-T, Chin Z-N, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. PLoS One. 2013;8:e57926.
21. Boyes C. Question 2 Should a child with ADHD and epilepsy be given Ritalin? Arch Dis Child 2010;95:759-61.
22. Wigal S, Swanson JM, Feifel D, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d, l-threo-methylphenidate hydrochloride in children with attention-deficit/ hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2004; 43:1406-14.
23. Conklin HM, Khan RB, Reddick WE, et al. Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double-blind, cross-over trial. J Pediatr Psychol 2007;32:1127-39.
24. Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. J Child Neurol 2009;24:727-33.
25. Dunn DW, Austin JK, Perkins SM. Prevalence of psychopathology in childhood epilepsy: categorical and dimensional measures. Dev Med Child Neurol 2009;51:364-72.