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Clinical Significance of Segmental Chromosomal Aberrations in Patients with Neuroblastoma: First Report in Korean Population

Hana Lim, Meong Hi Son, Ju Kyung Hyun, Hee Won Cho, Hee Young Ju, Ji Won Lee, Keon Hee Yoo, Ki Woong Sung, and Hong Hoe Koo

Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Address for Correspondence:
Meong Hi Son, MD
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: meonghi.son@samsung.com

ORCID iDs
Hana Lim
https://orcid.org/0000-0001-7393-0311
Meong Hi Son
https://orcid.org/0000-0002-3505-5576
Ju Kyung Hyun
https://orcid.org/0000-0001-9371-3808
Hee Won Cho
https://orcid.org/0000-0002-0440-645X
Hee Young Ju
https://orcid.org/0000-0001-6744-0412
Ji Won Lee
https://orcid.org/0000-0003-0084-1304
Keon Hee Yoo
https://orcid.org/0000-0002-5980-7912
Ki Woong Sung
https://orcid.org/0000-0001-5989-4772

ABSTRACT

Background: This study aimed to investigate the incidence and clinical significance of segmental chromosomal aberrations (SCAs) in Korean patients with neuroblastoma.
Methods: Patients diagnosed with neuroblastoma from 2012 to 2018 were included for retrospective review. Fluorescence in situ hybridization (FISH) was used to analyze four SCAs (*MYCN* amplification, 1p deletion, 11q deletion, and 17q gain). Clinical characteristics at diagnosis, early tumor response (reduction in primary tumor volume and neuron-specific enolase level after the first three cycles of chemotherapy), and survival rates were compared according to SCAs.
Results: Among 173 patients with FISH results, 92 (53.2%) had at least one of the four SCAs, while 25 (14.5%) had two co-aberrations, and eight (4.6%) had three co-aberrations. SCAs detected in our study were *MYCN* amplification (n = 17, 9.8%), 1p deletion (n = 26, 15.2%), 11q deletion (n = 44, 25.6%), and 17q gain (n = 46, 27.1%). Patients with *MYCN* amplification showed a better early response but a worse survival than those without (5-year overall survival: 46.2% ± 13.1% vs. 88.6% ± 3.4%). Furthermore, 1p deletion was associated with a better early response but a worse survival; however, it was not an independent factor for survival. We could not find any prognostic significance associated with 11q deletion or 17q gain.
Conclusion: This is the first study investigating SCAs in Korean neuroblastoma patients. Prognostic significance of SCAs other than *MYCN* amplification was different from those reported in western countries. Further study with a larger cohort and longer follow-up is needed to confirm our findings.

Keywords: Neuroblastoma; Segmental Chromosomal Aberration; Korean

INTRODUCTION

Neuroblastoma is known for its complex behavior from a very benign tumor to a highly aggressive metastatic tumor with poor prognosis. Traditionally, patients with neuroblastoma have been stratified into different risk groups according to age, stage, pathology, and segmental chromosomal aberrations (SCAs).[1] Since it was first reported in 1983, *MYCN* has

Hong Hoe Koo
https://orcid.org/0000-0001-8082-1412

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Lee JW, Yoo KH, Sung KW, Koo HH. Data curation: Hyun JK, Cho HW, Ju HY. Formal analysis: Sung KW. Methodology: Lim H, Son MH. Writing - original draft: Lim H, Son MH. Writing - review & editing: Hyun JK, Cho HW, Ju HY, Lee JW, Yoo KH, Sung KW, Koo HH.

become the most well studied SCA.[2] *MYCN* amplification has been confirmed as a poor risk factor in many previous studies including ours.[3-6] In addition to *MYCN* amplification, the clinical significance of other SCAs, including 1p deletion, 11q deletion, and 17q gain, has also been studied.[7-14] From previous reports, 1p deletion, 11q deletion, and 17q gain are generally known for adverse prognostic factors, but there are still some controversies.[9,10,12] With this background, *MYCN* amplification and 11q deletion are included as risk factors in the International Neuroblastoma Risk Group (INRG) stratification.[15] While many Western studies have reported the incidence and clinical significance of SCAs in neuroblastoma, there is no study in Korean neuroblastoma patients. For this reason, we analyzed the incidence and clinical significance of four SCAs (*MYCN* amplification, 1p deletion, 11q deletion, and 17q gain) in Korean patients diagnosed with neuroblastoma.

METHODS

Patients

Patients diagnosed with neuroblastoma from 2012 to 2018 at Samsung Medical Center were included for retrospective medical review.

Patients transferred from other hospitals with inappropriate tumor specimens for fluorescence in situ hybridization (FISH) were excluded from the analysis. Patients were staged according to the International Neuroblastoma Staging System.[16] Pathologic results were classified as ganglioneuroblastoma/differentiating neuroblastoma or poorly differentiated/undifferentiated neuroblastoma. Serum lactic dehydrogenase (LDH), ferritin, neuron-specific enolase (NSE), and urine vanillylmandelic acid (VMA) were routinely measured at diagnosis. Patients were stratified into low-risk, intermediate-risk, and high-risk groups based on age at diagnosis, stage, and *MYCN* status. In brief, stage 1, 2, and 4S tumors without *MYCN* amplification were stratified as low-risk tumors, whereas stage 4 tumors in patients older than 18 months or any tumors with amplified *MYCN* were stratified as high-risk tumors. All other tumors were stratified as intermediate-risk.[17]

FISH

MYCN amplification, 1p deletion, 11q deletion, and 17q gain were determined using FISH from paraffin-embedded tissue obtained by biopsy or surgery at initial diagnosis. For each FISH study, 50 non-overlapping nuclei were counted and the following probes were used: Vysis LSI N-MYC (2p24) SpectrumGreen/CEP2 SpectrumOrange, Vysis LSI ATM (11q22) SpectrumOrange/CEP11 SpectrumGreen, Vysis TOP2A (17q21)/CEP17 FISH (Abbott Molecular), and ZytoLight SPEC 1p36/1q25 Dual Color probe by Zytovision. The guidelines by the INRG biology committee were used to define SCAs. A four or more-fold increase in the *MYCN* signal number compared to the reference probe located on chromosome 2q was interpreted as an *MYCN* amplification. An unbalanced ratio of signal numbers between regions of interest versus reference was interpreted as a deletion while a four or more-fold excess of the region of interest was read as a gain.[18]

Treatment

An excisional biopsy of the primary tumor was performed at diagnosis if the tumor was resectable. Otherwise, an incisional biopsy was performed, and definitive surgery was deferred until after six or more cycles of chemotherapy. Chemotherapy consisted of two alternating regimens, CEDC (cisplatin, etoposide, doxorubicin, and cyclophosphamide)

and ICE (ifosfamide, carboplatin, and etoposide) as described in a previous study.[19] In low-risk patients, the primary treatment was surgery with (stage 2) or without (stage 1) six cycles of chemotherapy. Intermediate-risk patients received nine cycles of chemotherapy and 13-*cis*-retinoic acid differentiating treatment with or without adjuvant local radiotherapy, depending on whether viable residual tumor existed at the end of chemotherapy. In high-risk patients, tandem high-dose chemotherapy with autologous stem cell transplantation was routinely given as consolidation therapy following induction treatment which included nine cycles of chemotherapy and surgery.[20] All high-risk patients received local radiotherapy and differentiating therapy.

Measurement of early response

Early response to chemotherapy was determined by the reduction in primary tumor volume and NSE level after three cycles of chemotherapy. The volume of the primary tumor was measured at diagnosis and after three cycles of induction chemotherapy as previously reported.[21] In brief, tumor areas were defined by manual drawing on each slice of stacked computed tomography and magnetic resonance imaging. The tumor volume was calculated by summing the areas of the slice multiplied by the slice thickness using computer software (Advantage Workstation, Volume Share version 2.0; GE Healthcare, Little Chalfont, UK). Absolute tumor volume and the percentage of tumor volume after three cycles of chemotherapy compared with the tumor volume at diagnosis were calculated. Percent NSE levels after three cycles of chemotherapy compared with the NSE level at diagnosis were also calculated.

Statistics

A χ^2 test was used for analyzing the difference in categorical variables, and the Mann-Whitney U test was used for comparing the difference in continuous variables. Progression-free survival (PFS) and overall survival (OS) along with standard error were estimated by the Kaplan-Meier method. PFS was calculated from the date of diagnosis until the occurrence of relapse/progression or last contact if the patient remained progression-free. OS was calculated from the date of diagnosis until death from any cause. The log-rank test was used to compare survival rates. All the covariates with $P < 0.1$ from univariate analysis were used for multivariate analysis. Multivariate analysis for survival was performed with the Cox proportional hazards model. *P* value < 0.05 was accepted as statistically significant and SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center and the requirement for informed consent was waived (IRB 2019-07-153).

RESULTS

Incidence of SCAs

Among 212 patients diagnosed with neuroblastoma between January 2012 and December 2018, FISH results were available in 173 patients. Ninety-two (53.2%) patients had at least one of four SCAs. The numbers of patients with 17q gain, 11q deletion, 1p deletion, and *MYCN* amplification were 46 (27.1%), 44 (25.6%), 26 (15.2%), and 17 (9.8%), respectively. Twenty-five (14.5%) patients had two co-aberrations and eight (4.6%) had three co-aberrations. **Table 1** shows the pattern of co-aberrations. Among 17 patients with *MYCN* amplification, 11 (64.7%) had co-aberrations, which were 1p deletion (n = 10, 58.8%), 11q deletion (n = 2,

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Table 1. Pattern of co-aberrations

Variables	*MYCN* amplification	1p deletion	11q deletion	17q gain	No co-aberration
MYCN amplification (n = 17)	-	10 (58.8)	2 (11.8)	3 (17.7)	6 (35.5)
1p deletion (n = 26)	10 (38.5)	-	7 (26.9)	10 (38.5)	7 (26.9)
11q deletion (n = 44)	2 (4.6)	7 (15.9)	-	17 (38.6)	24 (54.6)
17q gain (n = 46)	3 (6.5)	10 (21.7)	17 (37.0)	-	22 (47.8)

Data are presented as number (%).

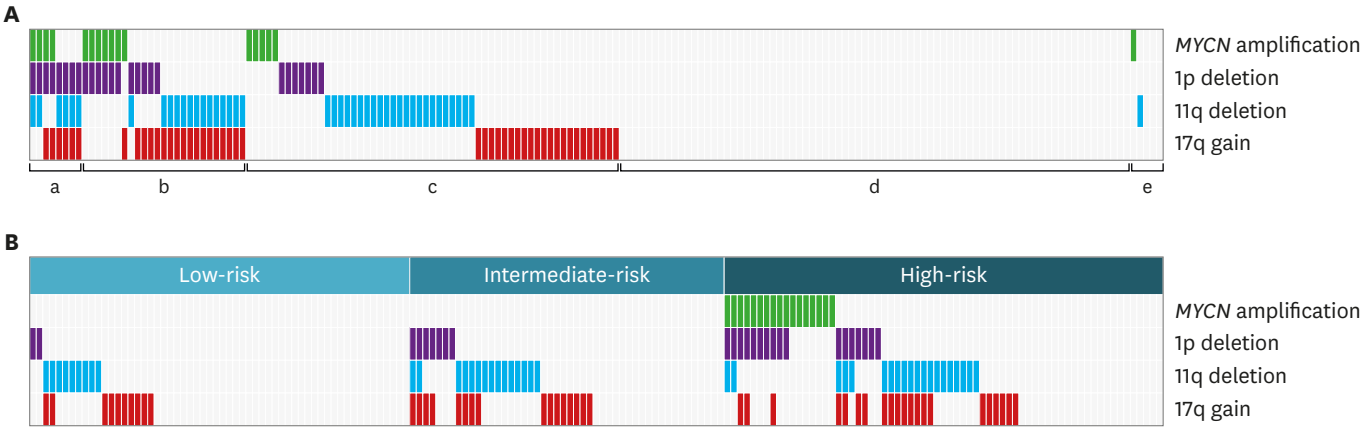

Fig. 1. Incidence of SCAs. (**A**) Proportion of co-aberration. (a) Three aberrations (n = 8, 4.6%), (b) two aberrations (n = 25, 14.5%), (c) one aberration (n = 7, 32.9%), (d) no aberration (n = 78, 45.1%), and (e) incomplete analysis (n = 5, 2.9%). (**B**) Incidence of SCAs according to risk group.
SCA = segmental chromosomal aberration.

11.8%), and 17q gain (n = 3, 17.7%) (**Fig. 1A**). Forty-five (67.2%) patients in the high-risk group had at least one of four SCAs, while intermediate-risk group and low-risk group had 28 (58.3%) and 19 (32.8%) patients, respectively (**Fig. 1B**).

Clinical characteristics according to SCAs

Table 2 shows clinical characteristics according to the presence/absence of each SCA. *MYCN* amplified tumors were associated with higher frequencies of abdomen tumor (94.1% vs. 69.9%, $P = 0.043$), poorly differentiated/undifferentiated pathology (94.1% vs. 45.8%, $P < 0.001$), and metastatic tumor (82.4% vs. 48.1%, $P = 0.007$), bigger tumor size (460 mL vs. 60 mL, $P < 0.001$), higher LDH level (5,193 IU/L vs. 698 IU/L, $P < 0.001$), higher ferritin level (323 ng/mL vs. 116 ng/mL, $P = 0.006$), higher NSE level (424.5 ng/mL vs. 30.8 ng/mL, $P < 0.001$), and lower 24-hour urine VMA level (1.7 mg/day vs. 8.7 mg/day, $P = 0.009$) compared to *MYCN* non-amplified tumors. Patients with 1p deletion had similar clinical features as those with *MYCN* amplification except urine VMA level. The 11q deletion was more often detected in male patients (72.7% vs. 42.2%, $P < 0.001$) and was associated with higher LDH level, higher NSE level, and higher 24-hour urine VMA level. A 17q gain was associated with a higher frequency of metastatic diseases and higher 24-hour urine VMA level.

Early response to chemotherapy

As a surrogate marker of early tumor response, residual primary tumor volume and reduction in serum NSE levels after three cycles of chemotherapy were compared according to the presence/absence of each SCA (**Fig. 2**). The percent residual tumor volume (12.9% vs. 42.1%, $P = 0.003$) and NSE level (4.8% vs. 38.9%, $P < 0.001$) were lower in patients with *MYCN* amplification than those without (**Fig. 2A and B**). The 1p deletion was associated with a lower

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Table 2. Patient characteristics at diagnosis according to cytogenetics

Parameters	*MYCN* amplification			1p deletion			11q deletion			17q gain		
	Absent (n = 156)	Present (n = 17)	*P* value	Absent (n = 145)	Present (n = 26)	*P* value	Absent (n = 128)	Present (n = 44)	*P* value	Absent (n = 124)	Present (n = 46)	*P* value
Sex, male	81 (51.9)	6 (35.3)	0.193	72 (49.7)	14 (53.8)	0.694	54 (42.2)	32 (72.7)	0.001	57 (46.0)	28 (60.9)	0.084
Age, yr	2.4 (0.0–19.2)	2.6 (1.2–11.2)	0.740	2.1 (0.0–19.2)	3.3 (0.4–11.4)	0.097	2.5 (0.0–19.2)	2.0 (0.0–11.4)	0.483	2.5 (0.0–19.2)	2.2 (0.0–15.0)	0.764
Age > 1.5	95 (60.9)	13 (76.5)	0.293	88 (60.7)	18 (69.2)	0.409	83 (64.8)	25 (56.8)	0.342	78 (62.9)	29 (63.0)	0.987
Primary site			0.043			0.010			0.913			0.252
Abdomen	109 (69.9)	16 (94.1)		99 (68.3)	24 (92.3)		92 (71.9)	32 (72.7)		86 (69.4)	36 (78.3)	
Others	47 (30.1)	1 (5.9)		46 (31.7)	2 (7.7)		36 (28.1)	12 (27.3)		38 (30.6)	10 (21.7)	
Stage			0.007			0.004			0.117			0.020
1, 2, 3, 4S	81 (51.9)	3 (17.6)		78 (53.8)	6 (23.1)		67 (52.3)	17 (38.6)		68 (54.8)	16 (34.8)	
4	75 (48.1)	14 (82.4)		67 (46.2)	20 (76.9)		61 (47.7)	27 (61.4)		56 (45.2)	30 (65.2)	
Pathology			< 0.001			0.003			0.088			0.765
GNB/D	84 (54.2)	1 (5.9)		79 (54.9)	6 (23.1)		68 (53.5)	17 (38.6)		62 (50.4)	22 (47.8)	
PD/UD	71 (45.8)	16 (94.1)		65 (45.1)	20 (76.9)		59 (46.5)	27 (61.4)		61 (49.6)	24 (52.2)	
Risk-group			< 0.001			0.002			0.095			0.116
Low	58 (37.2)	0		56 (38.6)	2 (7.7)		49 (38.3)	9 (20.5)		48 (38.7)	10 (21.7)	
Intermediate	48 (30.8)	0		41 (28.3)	7 (26.9)		32 (25.0)	15 (34.1)		32 (25.8)	15 (32.6)	
High	50 (32.1)	17 (100)		48 (33.1)	17 (65.4)		47 (36.7)	20 (45.5)		44 (35.5)	21 (45.7)	
Tumor volume, mL	60 (1–1,601)	460 (189–850)	< 0.001	56 (1–1,601)	255 (25–1,021)	< 0.001	71 (1–1,124)	69 (5–1,601)	0.606	69 (2–1,601)	73 (1–1,124)	0.719
LDH, IU/L	698 (287–18,245)	5,193 (2,273–9,583)	< 0.001	689 (287–8,170)	1,655 (434–18,245)	< 0.001	689 (287–18,245)	921 (410–9,583)	0.012	689 (287–9,583)	824 (343–18,245)	0.123
Ferritin, ng/mL	116 (8–2,881)	323 (100–1,491)	0.006	128 (8–1,255)	271 (32–2.881)	0.027	110 (8–2,881)	213 (19–1,491)	0.069	113 (8–1,588)	193 (19–2,881)	0.198
NSE, ng/mL	30.8 (6.6–724.0)	424.5 (6.5 –967.5)	< 0.001	29.0 (6.6–967.5)	156.4 (12.6–930.0)	< 0.001	28.0 (6.6–967.5)	74.1 (7.7–930.0)	0.024	27.4 (7.3–967.5)	41.3 (6.6–724.0)	0.134
24HU VMA, mg/day	8.7 (0.5–106.0)	1.7 (0.4–14.5)	0.009	7.2 (0.5–106.0)	8.9 (0.4–96.5)	0.746	4.8 (0.4–96.5)	19.8 (0.8–106.0)	< 0.001	5.5 (0.4–96.5)	10.9 (1.2–106.0)	0.013

Values are presented as median (range) or number (%).
GNB/D = ganglioneuroblastoma/differentiating neuroblastoma, PD/UD = poorly differentiated/undifferentiated neuroblastoma, LDH = lactic dehydrogenase, NSE = neuron-specific enolase, 24HU VMA = 24-hour urine vanillylmandelic acid.

NSE level (10.4% vs. 38.9%, $P = 0.006$); however, there was no difference in residual tumor volume (**Fig. 2E and F**). There was no difference in early response according to 11q deletion and 17q gain (**Fig. 2I, J, M, and N**).

Survival

Patients with *MYCN* amplification had poor survival outcome (5-year PFS: 45.2% ± 13.3% vs. 82.8% ± 3.6%, $P < 0.001$; 5-year OS: 46.2% ± 13.1% vs. 88.6% ± 3.4%, $P < 0.001$) (**Fig. 2C and D**). Patients with 1p deletion also had poor survival outcome (5-year PFS: 61.2% ± 10.4% vs. 82.1% ± 3.9%, $P = 0.004$, 5-year OS: 62.7% ± 11.0% vs. 88.1 ± 3.6%, $P < 0.001$) (**Fig. 2G and H**). However, there was no difference in survival rates according to 11q deletion or 17q gain (**Fig. 2K, L, O, and P**). In multivariate analysis for PFS and OS, age over 18 months (PFS: hazard ratio [HR], 4.20, $P = 0.009$; OS: HR, 3.84, $P = 0.037$), stage 4 (PFS: HR, 2.94, $P = 0.035$; OS: HR, 6.01, $P = 0.024$), and *MYCN* amplification (PFS: HR, 3.10, $P = 0.020$; OS: HR, 5.25, $P = 0.003$) were independent worse prognostic factors (**Table 3**).

Analysis of patients with *MYCN* non-amplified tumors

Among the four SCAs, *MYCN* amplification had dominant prognostic significance as shown above. However, over 90% of patients did not have *MYCN* amplification; thus, we evaluated the prognostic significance of the remaining three SCAs in patients with *MYCN* non-amplified tumors. There was no difference in the early tumor response according to the three SCAs (**Fig. 3**) except for a greater reduction in NSE level in patients with 17q deletion. Patients with 1p deletion showed worse survival (5-year PFS: 66.7% ± 12.4% vs. 84.4% ± 3.8%, $P = 0.037$; 5-year OS: 74.6% ± 13.2% vs. 90.1% ± 3.6%, $P = 0.080$) than those without although it was not

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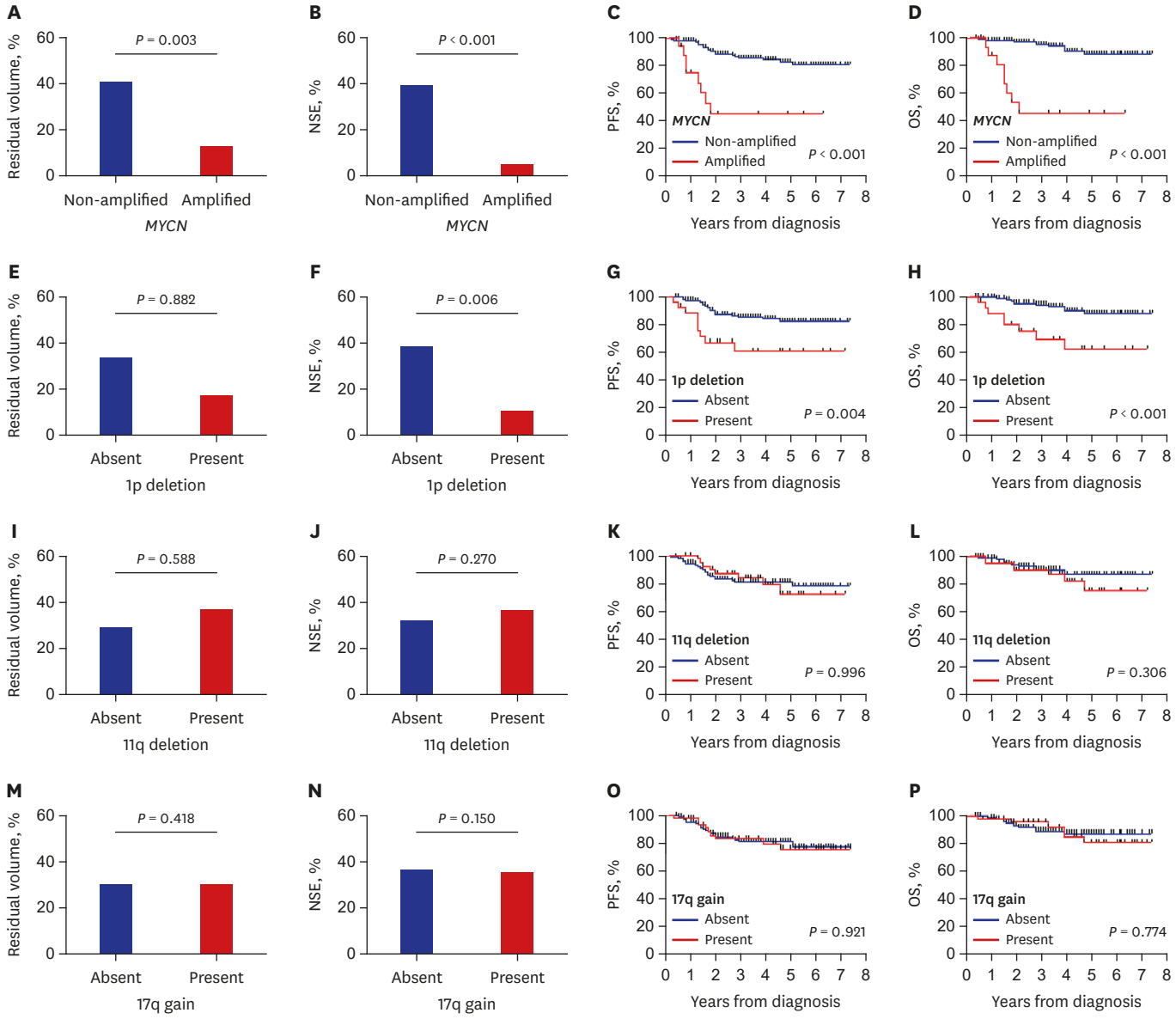

Fig. 2. Early response and final outcome in all patients. (**A**, **B**, **E**, **F**, **I**, **J**, **M**, and **N**) Reduction in tumor volume and serum NSE level after three cycles of chemotherapy compared with those at diagnosis. (**C**, **D**, **G**, **H**, **K**, **L**, **O**, and **P**) PFS and OS according to each SCA.
NSE = neuron-specific enolase, SCA = segmental chromosomal aberration, PFS = progression-free survival, OS = overall survival.

significant in multivariate analysis (**Table 4**). Otherwise, there was no difference in survival according to SCAs in patients with *MYCN* non-amplified tumors.

DISCUSSION

This is the first study reporting the incidence and clinical significance of SCAs in Korean children with neuroblastoma. This is also the first study evaluating the early response to chemotherapy according to SCAs. Unlike previous reports where patients were treated with various protocols at multiple centers, patients in this study were treated with a similar treatment scheme at a single center.

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Table 3. Multivariate analysis for PFS and OS in all patients

Characteristics	No. (%)	PFS					OS				
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
		5-yr PFS (%)	*P* value	HR	95% CI	*P* value	5-yr OS (%)	*P* value	HR	95% CI	*P* value
Age at diagnosis, mon			0.002	4.20	1.42–12.40	0.009		0.025	3.84	1.08–13.63	0.037
≤ 18	65 (37.6)	93.3 ± 3.3					95.1 ± 2.8				
> 18	108 (62.4)	70.1 ± 5.4					76.6 ± 5.6				
Stage			< 0.001	2.94	1.08–7.99	0.035		< 0.001	6.01	1.27–28.46	0.024
1, 2, 3, 4S	84 (48.6)	92.1 ± 3.1					96.3 ± 2.7				
4	89 (51.4)	66.6 ± 6.1					73.1 ± 6.1				
Pathology			0.054	1.26	0.48–3.33	0.644		0.011	1.44	0.38–5.47	0.590
GNB/D	85 (49.4)	83.1 ± 5.4					92.2 ± 4.3				
PD/UD	87 (50.6)	74.8 ± 5.1					76.9 ± 5.5				
MYCN amplification			< 0.001	3.10	1.19–8.05	0.020		< 0.001	5.25	1.78–15.52	0.003
Absent	156 (90.2)	82.8 ± 3.6					88.6 ± 3.4				
Present	17 (9.8)	45.2 ± 13.3					46.2 ± 13.1				
1p deletion			0.004	1.41	0.58–3.43	0.447		< 0.001	1.80	0.65–5.00	0.261
Absent	145 (84.8)	82.1 ± 3.9					88.1 ± 3.6				
Present	26 (15.2)	61.2 ± 10.4					62.7 ± 11.0				
11q deletion			0.996					0.306			
Absent	128 (74.4)	81.1 ± 3.8					87.3 ± 3.6				
Present	44 (25.6)	72.7 ± 9.2					75.6 ± 9.1				
17q gain			0.921					0.774			
Absent	124 (72.1)	81.1 ± 3.9					87.5 ± 3.6				
Present	46 (27.9)	76.0 ± 7.2					81.4 ± 7.0				

GNB/D = ganglioneuroblastoma/differentiating neuroblastoma, PD/UD = poorly differentiated/undifferentiated neuroblastoma, PFS = progression-free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval.

The *MYCN* amplification has been the most studied SCA in neuroblastoma since it was first reported by Schwab in 1983.[2] *MYCN* amplification is strongly associated with advanced stages, and its adverse prognostic significance was first reported in 1984.[3] In our previous study, we reported a better early response but a worse survival outcome in patients with the *MYCN* amplification than in those without.[6] Since *MYCN* is an oncogene, the tumor has aggressive features if it is amplified.[4] *MYCN* amplification is critical in the maintenance of the pluripotent state, which is associated with activated proliferation and apoptosis. Therefore, it is known to contribute to metastasis from the primary site and also explains why *MYCN* amplified tumors have a better early response to chemotherapy than non-amplified tumors. However, if *MYCN* amplified tumors progress or relapse, mutations in p53 or the p53 pathway may be present, resulting in therapy resistance. Eventually, *MYCN* amplified tumor have a worse outcome.[22]

The incidence of each SCA in previous studies varied by a wide range and various analyzing methods were used to detect SCAs. The techniques recommended by INRG to detect SCAs are FISH, polymerase chain reaction, array-based methods, and multiplex ligation-dependent probe amplification.[18] FISH was commonly used but other techniques were also used in previous reports from different study groups.[7,9-14,23] We used the FISH method and followed the INRG recommendation in the interpretation of SCAs. The incidence of *MYCN* amplification in this study seems to be lower than in previous reports by different groups using various detection methods (**Table 5**). Gehring et al.[9] considered the methods used to detect the SCAs as one of the reasons for this difference. Another possible reason for this difference might be ethnicity. While previous reports included various ethnic groups, our study only included Korean patients. Further research is needed to elucidate the reason for the difference in the incidence of *MYCN* amplification according to study groups.

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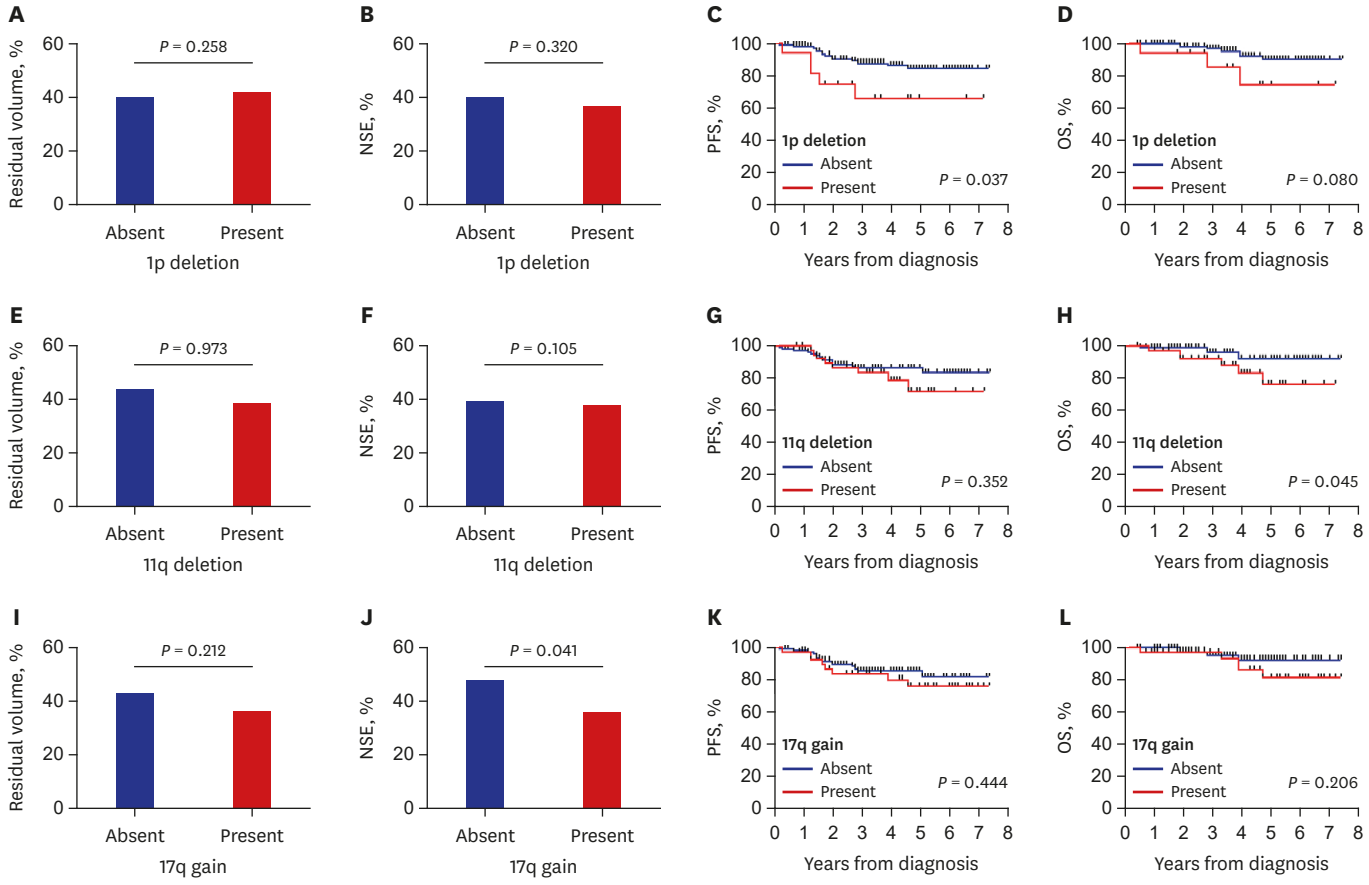

Fig. 3. Early response and final outcome in patients with non-amplified *MYCN*. (**A**, **B**, **E**, **F**, **I**, and **J**) Reduction in tumor volume and serum NSE level after three cycles of chemotherapy compared with those at diagnosis. (**C**, **D**, **G**, **H**, **K**, and **L**) PFS and OS according to each SCA.
NSE = neuron-specific enolase, PFS = progression-free survival, OS = overall survival, SCA = segmental chromosomal aberration.

Table 4. Multivariate analysis for PFS and OS in *MYCN* non-amplified patients

Characteristics	No. (%)	PFS					OS				
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
		5-yr PFS (%)	*P* value	HR	95% CI	*P* value	5-yr OS (%)	*P* value	HR	95% CI	*P* value
Age at diagnosis, mon			0.006	3.97	1.16–13.56	0.028		0.022	5.99	0.76–47.41	0.090
≤ 18	61 (39.1)	94.7 ± 3.0					98.4 ± 1.6				
> 18	95 (60.9)	74.5 ± 5.6					81.2 ± 5.7				
Stage			0.003	3.43	1.24–9.46	0.017		0.002	9.69	1.22–77.06	0.032
1, 2, 3, 4S	81 (51.9)	93.1 ± 3.0					97.5 ± 2.5				
4	75 (48.1)	71.1 ± 6.5					78.8 ± 6.4				
Pathology			0.421					0.279			
GNB/D	84 (54.2)	83.0 ± 5.4					92.2 ± 4.3				
PD/UD	71 (45.8)	81.6 ± 5.1					84.4 ± 5.6				
1p deletion			0.037	1.92	0.70–5.30	0.208		0.080	1.65	0.42–6.52	0.476
Absent	138 (89.6)	84.4 ± 3.8					90.1 ± 3.6				
Present	16 (10.4)	66.7 ± 12.4					74.6 ± 13.2				
11q deletion			0.352					0.045	2.32	0.68–7.90	0.178
Absent	113 (72.9)	86.5 ± 3.5					92.8 ± 3.3				
Present	42 (27.1)	72.4 ± 9.2					77.2 ± 9.2				
17q gain			0.444					0.206			
Absent	111 (72.1)	86.0 ± 3.6					93.2 ± 3.1				
Present	43 (27.9)	76.6 ± 7.5					82.3 ± 7.4				

GNB/D = ganglioneuroblastoma/differentiating neuroblastoma, PD/UD = poorly differentiated/undifferentiated neuroblastoma, PFS = progression-free survival, OS = overall survival, HR = hazard ratio, CI = confidence interval.

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Table 5. Incidence of segmental chromosome aberrations

Studies	No. of patients	Analysis method	Nation	*MYCN* amplification	1p deletion	11q deletion	17q deletion
Gehring et al.[9]	51	RFLP, microsatellite	Germany	10/51 (19.6)[a,b]	17/51 (32)	Not studied	Not studied
Caron et al.[10]	89	Southern blot	Netherland, Belgium	17/89 (19)[a,b]	29/89 (32.6)[a,b]	12/58 (20.7)	31/74 (41.9)
Bown et al.[11]	313	FISH, Southern blot	EU	91/313 (30.2)[a]	124/313 (46.8)[a]	Not studied	168/313 (53.7)[a]
Spitz et al.[12]	193	FISH	Germany	40/192 (20.8)[a,b]	59/188 (31.4)[b]	52/168 (31)[a,b]	118/193 (61)
Attiyeh et al.[13]	915	Various	US, EU, Canada	145/915 (16)[a]	209/915 (23)[a]	307/915 (34)[a]	Not studied
Janoueix-Lerosey et al.[7], 1st	213	Array CGH	France	43/213 (20)[b]	59/213 (28.3)[b]	46/213 (21.7)[b]	186/213 (89.4)[b]
Janoueix-Lerosey et al.[7], 2nd	260	Array CGH	France, Belgium, Germany	25/260 (9.6)[b]	41/260 (15.9)[b]	46/260 (17.9)[b]	248/260 (96.5)[b]
Carén et al.[14]	165	Array CGH	Sweden	38/165 (23)[a,b]	Not studied	22/165 (13.3)[a,b]	14/165 (8.48)[a,b]
Schleiermacher et al.[23]	8,800	Various	US, EU, Canada, Japan	1,155/7,102 (16.3)[a]	493/2,152 (22.9)	220/1,064 (20.7)[a]	175/362 (48.4)
Our study	173	FISH	Korea	17/173 (9.8)[a]	26/171 (15.2)	44/172 (25.6)	46/170 (27.1)

Corresponding patients number/studied patients number (%).
RFLP = restriction fragment length polymorphism, FISH = fluorescence in situ hybridization, CGH = comparative genomic hybridization.
[a]Adverse effect; [b]Percentage was calculated from reported patient numb.

After MYCN amplification has been reported as a significant poor prognostic marker in neuroblastoma, other SCAs have been studied for clinical significance. There have been controversies associated with the prognostic significance of SCAs other than the *MYCN* amplification. Some studies have reported the 1p deletion, 11q deletion, and 17q gain as worse prognostic factors[10,13,24] whereas in other studies they were not reliable prognostic markers.[9,12] At present, the reason for this difference is unclear.

In the present study, 1p deletion was associated with unfavorable clinical characteristics and worse outcome in the univariate analysis. However, more than half of the patients with 1p deletion also had *MYCN* amplification, and 1p deletion was not an independent worse prognostic factor in multivariate analysis. Even when the analysis was confined only to patients with *MYCN* non-amplified tumors, the 1p deletion was not an independent prognostic factor in multivariate analysis.

Neither 11q deletion nor 17q gain was a significant risk factor for survival in this study. In the INRG risk stratification, the 17q gain was excluded from analysis because data were only available for less than 5% of the patients and the 1p deletion was not a significant factor for OS. Therefore, only the 11q deletion was additionally included in the INRG risk stratification.[15] However, we could not find any prognostic significance associated with the 11q deletion and this is consistent with previously reported study with limited number of patients.[10] Patients with SCAs other than MYCN amplification was not included in high risk group, but if the patients were not high-risk, the chemotherapy for such patients were varied upon the studies. These are likely to cause a difference in survival outcomes. Here again, further studies with larger cohorts of patients are needed.

In conclusion, this is the first study reporting the incidence and clinical significance of SCAs in Korean children who were treated with essentially the same treatment protocol at a single center. Although both the *MYCN* amplification and 1p deletion were associated with aggressive clinical features at diagnosis and faster early response but worse survival, *MYCN* amplification was the only SCA with independent prognostic significance. A further study in a larger cohort of patients with longer follow-up is needed to evaluate whether there are differences in the incidence and clinical significance of SCAs according to ethnic group.

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