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ORIGINAL ARTICLE

Diffusion weighted imaging in differentiating malignant and benign neuroblastic tumors

Halil Ibrahim Serin[1] · Sureyya Burcu Gorkem[2] · Selim Doganay[2] · Saliha Cıracı[2] ·
Ekrem Unal[3] · Mahmut Guzel[4] · Ahmet Kucuk[5] · Ali Kurtsoy[5] · Abdulhakim Coskun[2]

Abstract

Purpose Our aim was to assess diffusion weighted imaging (DWI) of neuroblastic tumors and whether apparent diffusion coefficient (ADC) value may have a role in discrimination among neuroblastoma, ganglioneuroblastoma and ganglioneuroma.

Material and methods The DWIs ($b = 0$–800 s/mm^2) of 24 children (13 girls, 11 boys) who were diagnosed neuroblastic tumors on histopathological examination (neuroblastoma = 15, ganglioneuroblastoma = 5, ganglioneuroma = 4) were evaluated retrospectively. The ADC maps were performed by drawing freehand ROI on PACS (Sectra Workstation IDS7, Linköping, Sweden).

Results We observed a significant decrease in ADC value of neuroblastomas $0.869 \pm 0.179 \times 10^{-3}$ mm^2/s compared to ganglioneuroblastomas $0.97 \pm 0.203 \times 10^{-3}$ mm^2/s and ganglioneuromas $1.147 \pm 0.299 \times 10^{-3}$ mm^2/s ($p = 0.026$). There was no significant difference in between ganglioneuroblastoma and ganglioneuroma ($p = 0.16$). In detecting neuroblastomas; the sensitivity, specificity, negative and positive predictive values of ADC were 74, 67, 78.6, 66 % respectively with a cut-off value of 0.93×10^{-3} mm^2/s.

Conclusion Our study stands out as the most comprehensive study with larger sample size on this topic. Moreover, we are able to suggest a cut-off value which can discriminate neuroblastoma from ganglioneuroblastoma and ganglioneuroma. We believe that ADC will evolve to an objective, quantitative measurement in discrimination among malignant and benign neuroblastic tumors.

✉ Halil Ibrahim Serin
raddrhiserin@gmail.com

✉ Sureyya Burcu Gorkem
drburcugorkem@gmail.com

Selim Doganay
selimdoganay@gmail.com

Saliha Cıracı
atasaliha@hotmail.com

Ekrem Unal
drekremunal@yahoo.com.tr

Mahmut Guzel
Drmahmutguzel@Hotmail.Com

Ahmet Kucuk
drahmetkucuk@hotmail.com

Ali Kurtsoy
kurtsoya@erciyes.edu.tr

Abdulhakim Coskun
coskunah@yahoo.com

[1] Department of Radiology, Bozok University School of Medicine, Yozgat, Turkey

[2] Department of Radiology, Pediatric Radiology Section, Erciyes University School of Medicine, Melikgazi, Kayseri, Turkey

[3] Department of Oncology, Erciyes University School of Medicine, Melikgazi, Kayseri, Turkey

[4] Department of Pediatric Surgery, Erciyes University School of Medicine, Melikgazi, Kayseri, Turkey

[5] Department of Neurosurgery, Erciyes University School of Medicine, Melikgazi, Kayseri, Turkey

Introduction

Neuroblastoma, ganglioneuroma, and ganglioneuroblastoma are neuroblastic tumors arising from primordial neural crest cells of sympathetic nervous system [1]. Neuroblastoma is consisted of a mixture of immature neuroblasts and neutrophils whereas ganglioneuroblastoma consisted of mature gangliocytes and immature neuroblasts [2]. Neuroblastoma is the most common extracranial solid childhood malignancy [1–3]. The presence of immature tissue in neuroblastoma and ganglioneuroblastoma indicates malignant behavior. However, ganglioneuroma, arising from mature cells, is a benign tumor. Neuroblastoma and ganglioneuroblastoma are treated by surgical removal, chemotherapy or radiotherapy. They can transform to ganglioneuroma after chemotherapy [3]. The common presentation of neuroblastoma is abdomen in 65 % of the cases [1–3]. The frequency of adrenal localization is higher in older children than infants whereas cervical and thoracic presentation is more common in younger infants [1–3].

Neuroblastic tumors have relatively low signal on T1-W, high signal intensity on T2-W and variably enhancing pattern on MRI. Considering that they have similar signal characteristics on MRI, it is difficult to discriminate subgroups; therefore histopathological examination is a must [3]. DWI can distinguish tissues with similar T1-W and T2-W signals based on their microscopic organization and metabolism [4]. It can provide data regarding cellular organization and metabolism of tissue. Recently, DWI is becoming a favorable method for pediatric oncology cases [5–9].

In this study we aim to assess ADC values of neuroblastic tumors and whether ADC value may have the role in discrimination among neuroblastoma, ganglioneuroma, and ganglioneuroblastoma.

Materials and methods

Informed consents were obtained from all patients' parents.

Study patients

The DWIs ($b = 0$–800 s/mm^2) of twenty-four children [13 girls, 11 boys; mean age = 3.41 ± 3.41 years (range 10 days–14 years)] who were diagnosed neuroblastic tumors on histopathological examination (neuroblastoma = 15, ganglioneuroblastoma = 5, ganglioneuroma = 4) were included in our study retrospectively. Histopathological examination was obtained after biopsy or surgical removal.

MRI protocol

All patients underwent a routine MRI examination at 1.5 T MR Unit (Aera, Siemens, Erlangen, Germany) with a standard body coil for the initial diagnosis before biopsy or surgical removal. MRI protocol included T1-W, T2-W, STIR and contrast-enhanced T1-W and DWI. Before contrast media injection, DWI ($b = 0$–800 s/mm^2) was obtained in three orthogonal axes (x, y, z) without breath holding in axial plane. Two phase-encoding directions were measured for each orientation (FOV = 320×320 mm, matrix = 256×256 mm, slice thickness = 4 mm, time = 1 min–24 s).

Imaging evaluation

All tumors were solitary masses which did not show any invasion to adjacent solid organ. ADC maps were performed by comparing T1-W, T2-W and contrast-enhanced T1-W images on PACS (Sectra Workstation IDS7, Linköping, Sweden). The DWIs were calculated by drawing freehand ROI (min 10 cm^2–max 200 cm^2) as large as possible without risking partial volume effects along the boundary of the tumor. Single slice calculations at the level of the largest solid area for each patient were performed and mean ADC value was taken (Fig. 1a, b). Regions of increased diffusion areas including cystic and necrotic spaces which were demonstrated hypointense on T1-W, hyperintense on T2-W and did not show any contrast enhancement on contrast-enhanced images were excluded from ROI. Two pediatric radiologists reviewed all MRI studies of each patient together. ADC values were compared within each group.

Statistical analysis

Mean ADC values were calculated, and independent sample t test was performed to compare ADC values. ROC analysis was done to depict a cut-off value for neuroblastoma by using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was significant.

Results

The mean ADC value of all neuroblastic tumors was $0.936 \pm 0.222 \times 10^{-3}$ mm^2/s; (range 0.45–1.391×10^{-3} mm^2/s). The mean ADC value of neuroblastoma, ganglioneuroblastoma and ganglioneuroma were $0.869 \pm 0.179 \times 10^{-3}$ mm^2/s (range 0.45–1.068×10^{-3} mm^2/s); $0.97 \pm 0.203 \times 10^{-3}$ mm^2/s (range 0.658–1.18×10^{-3} mm^2/s) and $1.147 \pm 0.299 \times 10^{-3}$ mm^2/s (range 0.73–1.39×10^{-3} mm^2/s) respectively. We observed a

Fig. 1 a, **b** Coronal matched T2-W (**a**) and ADC (**b**) images are shown. Freehand ROI draw on the solid mass is demonstrated (**b**)
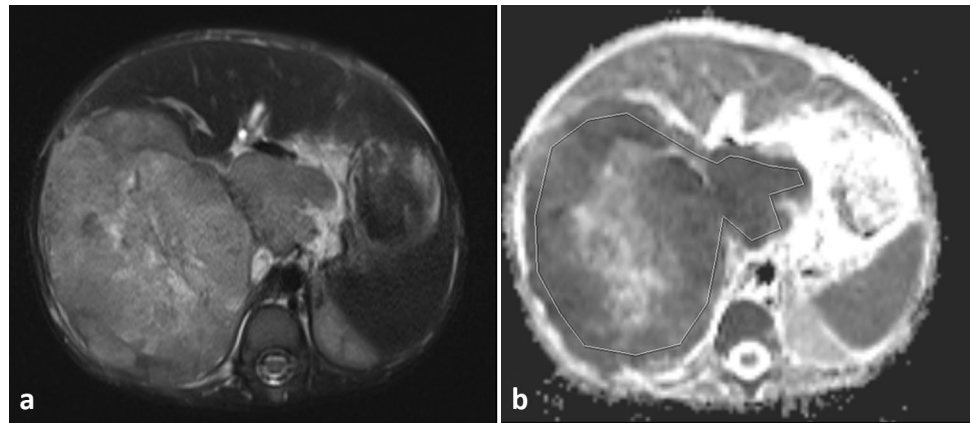
Table 1 Descriptive findings of study group

Tumor group	Patient number-sex	Age	ADC (mean $\times 10^{-3}$ mm^2)	Location
Neuroblastoma	8 g, 7 b	2.90 ± 3.75 year (range 1 week–14 year)	0.869 ± 0.179 (range 0.45–1.068)	Adrenal gland = 10, Paraaortic = 5, Paravertebral = 2
Ganglioneuroblastoma	3 g, 2 b	2.88 ± 2.03 year (range 5 month–6 year)	0.97 ± 0.203 (range 0.658–1.18)	Adrenal gland = 2, Pelvic = 1, Presacral = 1, Paraaortic = 1
Ganglioneuroma	2 g, 2 b	6 ± 2.75 year (range = 7 week–10 year)	1.147 ± 0.299 (range 0.73–1.39)	Adrenal gland = 2, Paravertebral = 2

b boy, *g* girl

significant decrease in ADC value of neuroblastomas compared to ganglioneuroblastomas and ganglioneuromas ($p = 0.026$). There was no significant difference in between ganglioneuroblastoma and ganglioneuroma ($p = 0.16$). The overall volume of all tumors was 648 ml (min 202–max 3094 ml). The age difference between neuroblastoma and ganglioneuroblastoma-ganglioneuroma was not statistically significant ($p = 0.33$). Patients' information was given in Table 1. In detecting neuroblastomas; the sensitivity, specificity, negative and positive predictive values of ADC calculation were 74, 67, 78.6, 66 % respectively with a cut-off value of 0.93×10^{-3} mm^2/s. ROC analysis of neuroblastoma versus ganglioneuroblastoma-ganglioneuroma was shown in Fig. 2. All tumors had high signal intensity on T2-W images compared to paravertebral muscle, and all of them showed intense contrast enhancement. The most common presentation was adrenal gland in 58 % ($n = 14$) of patients whereas paraaortic region was 25 % ($n = 6$), the paravertebral region was 16 % ($n = 4$), the pelvic region was 4 % ($n = 1$), and the presacral region was 4 % ($n = 1$).

Discussion

DWI reveals micro-diffusion motion of water molecules within intracellular and extracellular space [3]. Restricted diffusion within tumor appears as high signal intensity on DWI while low signal intensity in ADC maps, representing

high cellular density [4]. To the best of our knowledge, there are a limited number of studies comparing ADC values of neuroblastic tumors [5, 10–14]. To date, these tumors can only be distinguished by histolopathological examination. Mc Donald and Demir et al. showed that DWI could be used to detect the chemotherapy response in children with neuroblastoma [12, 13]. Studies dealing with pediatric abdominal tumors showed that ADC might be used to discriminate benign and malignant lesions [10, 11]. Humphries et al. reported a correlation between ADC value and tumor cellularity. In a very recent study, Gahr et al. studied fifteen neuroblastic tumors and they subgrouped them into neuroblastoma and non-neuroblastoma (ganglioneuroma and ganglioneuroblastoma) group and found that neuroblastoma had the lowest ADC values [5]. Our study is in agreement with them and additionally it is the first comprehensive study with 24 patients in the literature.

Gahr et al. found a high ADC value in a neuroblastoma infiltrating the kidney which would be possible that the ADC was not only the tumor but also part of a kidney. They also proposed that ADC calculation could not differentiate neuroblastoma and ganglioneuroma [5]. Our study group consisted of solitary tumors which did not show any infiltration to adjacent solid organ. The diagnostic accuracy of ADC in determining neuroblastoma was found significant with a cut-off value of 0.93×10^{-3} mm^2/s; furthermore, there was no significant difference in ADC values of

Fig. 2 ROC curve of ADC. Area under the ROC curve = 0.800, 95 % confidence interval = 0.623 to 0.977, significance level P area: 0.016, standard error 0.09; $p < 0.05$
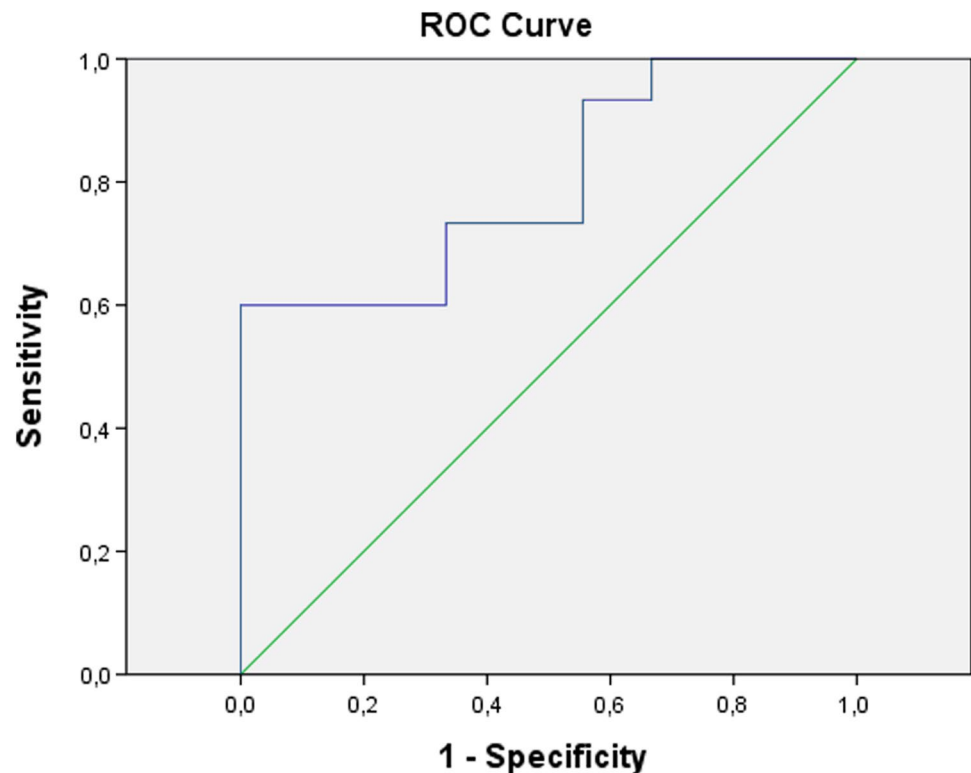
ganglioneuroblastoma and ganglioneuroma in our study. Despite the fact that we had a small sample size in nonneuroblastoma group, these findings might be helpful for radiologists to discriminate neuroblastoma from ganglioneuroblastoma and ganglioneuroma on DWI.

The major limitation of our study is the small number of study patients. We believe that the diagnostic accuracy of ADC in determining neuroblastic tumors could be found higher with more patients in future studies, so ADC calculation may be a comparable method to histopathological examination in predicting the malignancy. Radiolabeled metaiodobenzylguanidine (MIBG) with iodine-123 and laboratory tests (vanillylmandelic acid and homovanillic acid in urine) are powerful methods for staging, screening and follow up of neuroblastoma [15]. However we aim to evaluate the diagnostic accuracy of ADC calculation among neruoblastic tumors in our study. Our MRI examinations are only for the mass characterization by ADC calculation so we did not include the whole body MRI examination. MIBG scan is a whole body scan and should be compared to whole body MRI-DWI which would be an another research topic.

In conclusion, our study stands out as the most comprehensive study with larger sample size on this topic. Moreover, we are able to suggest a cut-off value which can discriminate neuroblastoma from ganglioneuroblastoma and ganglioneuroma. We believe that ADC would evolve to an objective and quantitative measurement in discrimination among malignant and benign neuroblastic tumors.

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