Serial Diffusion-Weighted and Conventional MR Imaging in Primary Cerebral Neuroblastoma Treated with Radiotherapy and Chemotherapy

A Case Report and Literature Review

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SUMMARY – *Primary cerebral neuroblastoma is a rare malignant tumor encountered most commonly in children. The radiological features of this entity are variable and rarely reported. The diffusion-weighted imaging (DWI) findings have not previously reported. We describe serial DWI and conventional MRI in a case of primary cerebral neuroblastoma to assess the imaging features and the role of DWI for monitoring chemoradiotherapy response.*

Introduction

Neuroblastoma is one of the most common extracranial solid malignant tumors seen in children. However, primary cerebral neuroblastoma is very uncommon and the incidence is approximately one case every decade¹. Eighty per cent of tumors occur in the first decade although there have been reports of the tumor arising in adults. Neuroblastoma is considered to be derived from the second stage of neuronal cytogenesis and a specific subset of primitive neuroectodermal tumors (PNET) (WHO grade IV) with only neuronal differentiation and the frequent exhibition of well-formed Homer-Wright rosettes. The precise diagnosis can be made only after recognition of neurosecretory granules².

The radiologic appearances of neuroblastoma are more variable. DWI can visualize the random microscopic motion of molecules and thereby provide a tissue contrast different from conventional MRI. Such sequences have been used for the differentiation of tumors with varied tissue cellularity and integrity of cell membranes, and for monitoring tumor response to therapy. There are no reports in the literature

describing diffusion-weighted imaging (DWI) findings in this lesion. Herein, we describe a boy with primary cerebral neuroblastoma and discuss the serial DWI and conventional MRI, especially the DWI for monitoring tumor response to radiotherapy and chemotherapy.

Case Report

A seven-year-old boy was hospitalized for further evaluation and treatment after ten months of intermittent dizziness and four days of nausea and vomiting. Non-enhanced computed tomography of the brain at another institution demonstrated a round mild hyperdense mass in the right thalamus (not shown). On admission, DWI and conventional MRI were performed immediately.

MRI of the brain was performed on a 3.0 T unit (GE Medical systems, Milwaukee, WI, USA). Conventional MR imaging examinations included plain and contrast-enhanced sequences obtained according to a standardized protocol for occupying lesions (i.e., axial and sagittal T2-weighted fast spin-echo imaging, axial and coronal plain and enhanced

A

B

C

Figure 1 Pretreatment T2-weighted image (A), T1-weighted image (B) and pathology image (C). A solid occupying lesion in the right thalamus is shown with isointense signal on the T2-weighted image (A), and hypointensity on the T1-weighted image (B), measuring about 41×43 mm. The tumor shows a large collection of small round cells and Homer-Wright rosette formation can be seen (C) (arrow) (Hex200).

spin-echo imaging). DWI was performed in the axial plane using a spin-echo echo-planar sequence with diffusion gradient encoding in three orthogonal directions. The parameters used to obtain diffusion-weighted images were 10000/86 (repetition time ms/echo time ms), a 240-mm field of view, a 128×128 pixel matrix, 6 mm section thickness, a 2 mm intersection gap, 1 number of excitation (NEX), and a b value of 1000 s/mm². Diffusion-weighted imaging was performed before contrast agent administration. ADC maps were calculated on a pixel-by-pixel basis by using built-in software on the MR workstation. The ADC value was

measured manually by placing five to ten 15-30 mm² regions of interest (ROI) within solid tumor components on the ADC maps, which were identified on conventional T2-weighted images and post-contrast images to avoid volume averaging with cystic or necrotic regions that might influence ADC values. Approximate same-size ROIs were also drawn in matching structures in the contralateral thalamus to obtain ADC values of normal-appearing thalamus for the purpose of normalization. Then, the mean ADC values and ADC ratio (divide ADC value in lesion by ADC value of contralateral thalamus) were calculated.

Figure 2 Serial DWI and contrast-enhanced T1-weighted images in primary cerebral neuroblastoma. The pretreatment image demonstrates a tumor in the right thalamus enhanced heterogeneously. DW image demonstrates signal hyperintensity with decreased ADC value. After the end of radiotherapy, the tumor size decreases with a decreased signal on DWI. After two cycles of chemotherapy, the tumor size decreases further, the tumor signal decreases owing to reduction of restricted diffusion. After four cycles of chemotherapy, the tumor signal decreases mildly on DWI, whereas there is no obvious size change in the tumor; 16 months later, no obvious signal and size change are seen.

Pretreatment initial MRI revealed a solid mass lesion in the right thalamus with an isointense signal on T2-weighted images (Figure 1A) and hypointense signal on T1-weighted images (Figure 1B). The mass had necrotic-cystic areas. Peritumoral edema was mild. The mass showed an intense inhomogeneous enhancement after contrast agent administration (Figure 2). The DW images demonstrated the mass of high signal intensity, which was mildly hypointense on the ADC maps (Figure 2). The radiological diagnosis was glioma or lymphoma.

After admission, following MRI histological specimens were obtained by stereotactic biopsy. Histopathologically, the tumor was quite cellular and composed of small round cells with hyperchromatic nuclei, inconspicuous nucleolus, and scant cytoplasm.

The cells formed Homer-Wright rosettes (Figure 1C). Given the fact that metastases are present in up to 70% of patients with neuroblastoma at the time of diagnosis³, computed tomography of chest, abdomen, bone scan and MRI of the whole spine were performed to verify that cerebral neuroblastoma was the exclusive lesion.

The final diagnosis was approved as primary cerebral neuroblastoma. Afterwards, the patient received radiotherapy consisting of DT 36 Gy in 1.8 Gy fractions to the whole brain and DT 18 Gy in 2 Gy fraction boosts to the tumor. After completion of radiotherapy, he received six courses of chemotherapy with a combination of nimustine and carboplatin. Serial MRI were performed two days after the end of radiotherapy, after the end of the second and fourths cycles of chemotherapy (early and later chemotherapy), and 16 months after radiotherapy (Thus, a total of five time points). The ADC values of pretreatment and post-radiotherapy were 1.03 ± 0.04 and $1.29 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{s}$. There was a conspicuous difference between the tumor size at the pretreatment, post-radiotherapy and early chemotherapy time points (size measured 41×43 , 30×29 , $20 \times 19 \text{ mm}$ respectively), meanwhile, the ADC ratio increased dramatically from 0.89, 1.08 to 1.24. There were no visual size changes at later chemotherapy and 16 months later (size measured 19×18 and $18 \times 16 \text{ mm}$). However, the ADC ratio increased from 1.24 to 1.59 and then to 1.58.

The patient was alive 16 months after radiotherapy without any evidence of tumor relapse, metastases or a deterioration of clinical symptoms.

Discussion

According to our results, primary cerebral neuroblastoma located unusually in the thalamus is a solid tumor showing intense heterogeneous enhancement with no hemorrhage and obvious calcification, which is slightly different to features in the literature⁴. Our observations suggest that neuroblastoma shows an obvious increased signal due to restricted water motion on DW images and DWI can be used to evaluate treatment response. In our search of the literature, we were unable to find any reports on DWI of primary cerebral neuroblastoma to date. The ADC of neuroblastoma was usually lower than $1.13 \times 10^{-3} \text{ mm}^2/\text{s}$ in a single study concerning differentiation of neuroblastoma and ganglioneuroblastoma/ganglioneuroma in the abdomen⁵. In another study of extracranial neuroblastoma, diffusion-weighted images showed an increased tumor signal with mean ADC of $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ ⁶. The initial pretreatment ADC value in our case was $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$ similar to that of these reports.

DWI can be used to describe information on water diffusion allowing evaluation of the rate of microscopic water diffusion within biologic tissues. ADC is measured by DWI to detect and quantify tissue water diffusion values. Although there was no significant difference in ADC between benign and malignant lesions, all highly cellular lesions had an ADC lower than $1.5 \times 10^{-3} \text{ mm}^2/\text{s}$ ⁷.

Neuroblastoma consists of densely packed, small, immature cells containing little cytoplasm, which limit intracellular motion and inhibit effective motion of extracellular water protons. Restricted proton motion leads to a reduction in the rate of apparent diffusion and to a marked increase in signal on diffusion-weighted images⁶.

Some other tumors with densely packed cells, such as malignant lymphomas, high-grade gliomas and other types of PNET show similar signal appearances on conventional and DW images. Accordingly, all these tumors must be considered in the differential diagnosis. DWI and ADC are useful for differentiation of some human brain tumors, particularly DNT, malignant lymphomas versus glioblastomas and metastatic tumors, and ependymomas versus PNETs⁸. The exact diagnosis can be made only on the basis of detailed electron microscopic studies.

ADC is deemed to be related to the ratio of intracellular water to extracellular water. Ef-

fective treatment results in tumor lysis, loss of cell membrane integrity, increased extracellular space, and, therefore, an increase in water diffusion⁹. Thus, changes in ADC are inversely correlated with changes in cellularity after treatment. In this scenario, ADC has been used to detect the response to treatment earlier than the size change even within one week of initial treatment¹⁰. According to our results, the ADC value and ADC ratio increased considerably after radiotherapy, reflecting increased water diffusivity and the fact that the neuroblastoma in this patient was sensitive to radiotherapy. The size change in the tumor was not visual between early and later chemotherapy time points, but the ADC ratio increased over time. Our results suggest that the ADC ratio may be useful for detecting response to therapy even though there is no tumor size change. Serial ADC evaluation could detect successive response to radiotherapy and chemotherapy be-

cause ADC changes can precede size changes.

One major limitation of our study was that only one case was available for analysis. Further studies in more subjects are necessary to determine the MRI features and usefulness of DWI for tumor differentiation and monitoring of therapy response. Second, the longest follow-up time is only 16 months. A much longer follow-up in the future is necessary to elucidate the role of DWI in therapy effects or tumor recurrence.

In conclusion, primary cerebral neuroblastoma shows similar MRI appearances to other brain tumors with densely packed cells. Our results suggest that DWI is appropriate as a follow-up method to monitor response to treatment. Further study on serial DWI should be performed in large numbers of neuroblastoma patients to validate its role in evaluating treatment response and in optimizing the treatment regimen.

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