Volume 22, No 4 | International Journal of Radiation Research, October 2024

Diffusion characteristics of diffusion-weighted imaging in children with hippocampus injury during complex acute febrile seizure: a prospective observational study

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► ***Original article***

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Received: March 2023
Final revised: June 2024
Accepted: July 2024

Int. J. Radiat. Res., October 2024; 22(4): 971-975

DOI: 10.61186/ijrr.22.4.971

Keywords: *Febrile seizures, hippocampus injury, diffusion characteristics, b-value, DWI, ADC map.*

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ABSTRACT

Background: To explore the diffusion characteristics of the hippocampus injury (HI) in children during the complex acute febrile seizure (CAFS) through multiple b value (1000-2000 s/mm^2) of diffusion-weighted imaging (DWI). ***Materials and Methods:*** This prospective observational study enrolled children with HI during CAFS, and nasopharyngeal and sinus disease (NSD). The multiple b value from DWI of the hippocampus were scanned. ***Results:*** A total of 41 children were included, with 21 of them had HI during CAFS, while the other 20 children were NSD. There was significant difference in apparent diffusion coefficient (ADC) values of the left and right hippocampus between children with HI during CAFS and NSD ($r < 0.05$). The corresponding ADC graphs were relatively clear at b = 1000 s/mm2 and 1200 s/mm^2. ***Conclusion:*** Hippocampal DWI scans at b = 1000 s/mm^2 and 1200 s/mm^2 might be recommended clinical b value point for diffusion characterization of HI.

INTRODUCTION

Febrile seizure (FS), a specific response to high temperature in the infants and young children, are encountered in pediatric practice with comparable frequency [1]. Prevalence of FS in China is about 3%-5% and increasing in recent years, making it one of the most common critical and severe childhood seizures [2,3]. In advanced cases seizures can occur repeatedly, with following development of complex febrile seizures (CFS) and status epilepticus (SE) [4].

These complications are most likely reflecting some underlying brain pathology, which has not been defined yet, but is widely discussed [1,5]. Hippocampus in particular was the area of interest in relation to the FS development and prognosis. Recent experimental study performed on young rats reported that hippocampal synaptic plasticity was impaired due to FS [6], while antiepileptic drugs effective in CFS were reportedly related to the BCL-2 regulated apoptosis of the hippocampus [7]. Moreover, hippocampal diffusion abnormality after febrile status epilepticus was shown to be linked with the subsequent epilepsy 8. Whether FS onset in children can cause long-term hippocampal injury is therefore a critical question.

Hippocampal signal changes can be assessed during the acute period by DWI [8,9]. The commonly used DWI parameters are denoted by b, and the selection of b value has an important influence on the ADC value of tissue [10]. When a smaller b value parameter is selected, the difference in diffusion between tissues is not easy to observe, but the signal-to-contrast ratio is higher and the image contrast is relatively clear [11,12]. On the contrary, poor signal-to-contrast ratio of the DWI image and relatively blurred image contrast is explained by the selection of large B value parameter, when the applied diffusion gradient magnetic field strength is large, the tissue scanning time is long, but the difference of diffusion between tissues is easy to reveal [13,14]. At present, data on optimal b-values for hippocampal studies in children with FS are scarce and a definite conclusion cannot be drawn. The authors' previous study 2 reported that the diffusion characteristics of the hippocampus in the acute attack of complex febrile seizure in children were different from simple FS or intact brain when b = 1000 s/mm^2. Since the variance was found at a single b-point, and the b-value was low, the exact value was not determined. Therefore, this study aimed to explore the diffusion characteristics of the HI in children during the CAFS through multiple b-value (1000-2000 s/mm^2) of DWI. The B-value

point is recommended for clinical evaluation of HI diffusion characteristics. To provide a basis for early detection of HI in children with CAFS.

At home and abroad using DWI observing children complicated acute fever convulsion can hippocampal damage research is less. Hydrogen proton nuclear magnetic resonance spectroscopy (MRS), MRI measurement of hippocampal volume and hippocampal T2 relaxation time are used to observe HI [16-18]. This prospective observational study enrolled children with HI during CAFS, to explore the diffusion characteristics of the HI in children during the CAFS through multiple b value (1000-2000 s/mm^2) of DWI.

MATERIALS AND METHODS

Study design and patients

This prospective observational study enrolled children with HI during CAFS, as well as children with NSD as controls at Hainan Women and Children's Medical Center between June 2019 and May 2020. The diagnostic criteria of HI during CAFS were based on the expert consensus on the diagnosis, treatment and management of febrile seizures [15]. The age of the first seizure was between 6 months and 6 years old and the body temperature during the seizure was lower than 38°C. Complex febrile seizures were defined as one of the follows: long duration seizures (duration ≥15 min); cluster seizures (repeated seizures equal to or greater than 2 times in 24 hours); localized or generalized seizures; paralysis symptoms appearing after seizures. All children with HI during CAFS completed the MRI examination within 72 hours. Exclusion criteria: children with a history of epilepsy, history of perinatal abnormalities, abnormal signals in the hippocampus (including congenital abnormalities, infection, mass, *etc*.), recurrent seizures or persistent SE and incomplete data. The children with NSD (due to sinusitis or nasopharyngeal adenoid hypertrophy), who were enrolled as control group, had the comparable age to those with CAFS, and no central nervous system diseases.

The inspection process was explained to children's parents and carried out after the consent of parents was obtained and parents signed the informed consent form. The approval number of the ethics committee (Hainan Women & Children's Medical Center) for this study is 2022 Lunxun No. 40.

Procedures

Scanners, sequence and parameters

The PHILIPS Ingenia 3.0T Mr Diagnostic instrument was selected as the instrument and the head coil was selected. Multiple B values of DWI imaging were adopted for the single-shot echo plane sequence of oblique axis scan (scan parameters TR 2300 ms, TE 77 m, matrix 116×89, bandwidth 14.076/30.9 (pix/HZ), FOV 230 mm, slice thickness 3.5 mm, interval 0.35 mm, excitation times 3, Phase enc. dir. A>>P). The diffusion sensitivity coefficient b values were 0, 1000, 1200, 1400, 1600, 1800, 2000 s/mm^2, respectively. Free breathing scan was used, and the scan time for all b values (1000-2000 s/mm^2) was about 12 minutes and 48 seconds. According to the MRI accreditation program clinical image quality guide of American College of Radiology (ACR), the low b value in this study referred to 0-200 s/mm^2, medium b value to 300- 1600 s/mm^2 and high b value was defined as 1700-4500 s/mm^2.

Both children with HI during CAFS and the NSD underwent bilateral hippocampal multiple b value DWI oblique axis scanning and ADC values were measured after reconstruction of the multiple b value ADC map. The scans were performed by experienced senior doctors in the MRI room and three regions of interest (ROI) of bilateral hippocampal head, body and caudal regions were drawn on the ADC reconstructed image obtained by multiple b value post-processing. The ROI of both sides were selected as symmetrical as possible, avoiding the ventriculocival region, and the range was about 20 mm^2. After the average ADC value of the hippocampus was calculated and all data were entered into a database (figure 1), the ADC graph with the relatively high image quality was finally selected. The subjective evaluation of image quality was performed by two professionals who were not involved in the scanning process, according to the MRI Accreditation Program Clinical Image Quality Guide of ACR (the evaluation included 4 indicators): pulse sequence and image contrast; essential sequence; scan range and imaging plane; spatial resolution).

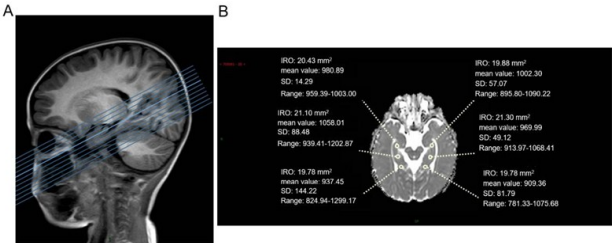

Figure 1. Oblique axial scan **(A)** and ADC image **(B)** of the hippocampus after midsagittal scan.

Statistical analysis

Statistic Package for Social Science (SPSS) software 22.0 (IBM Corp., Armonk, N.Y., USA) were used for statistical analysis. According to the characteristics of data distribution, the ADC values of the children with HI during CAFS and the NSD were compared by two independent samples t test or rank sum test, and the ADC values of different b values in the left and right hippocampus of the children with HI during CAFS were compared by paired *t test*. Receiver operating characteristic curve (ROC)

analysis was used for ADC values with different b values in diagnosing hippocampus injury, and the sensitivity (%), specificity (%), and area under the ROC (AUC) were calculated. R < 0.05 indicated that the difference was statistically significant.

RESULTS

Among included children with HI during CAFS, there were 12 males, accounting for 57.1% and 9 females; majority of children in this group were < 2 years old. The NSD group included 8 males and 12 females, ranging from 1 to 12 years old. In children with HI during CAFS, there were 11 cases of family history of seizures, accounting for about 52.4%. Among them, 11 experienced one seizure, 4 had two seizures, 3 had 3 seizures and 2 had 6 seizures; one person had 7 seizures (including this admission). The basic characteristics of the children with HI during CAFS and the NSD were compared (table 1).

Table 1. Basic characteristics of the study participants. nasopharyngeal & sinus disease (NSD). complex acute febrile seizure (CAFS).

		Children with HI during CAFS (n=21)	Children with NSD (n=20)	*r*
Gender	male	12	8	0.272
	female	9	12	
Age	≤ 2 years old	16	1	< 0.01
	> 2 years old	5	19	

There was no statistically significant difference in ADC values between the left and right hippocampus of the children with HI during CAFS under the conditions of medium and high b values (r > 0.05). However, there was a statistically significant difference in ADC values between the left and right hippocampus of the children with HI during CAFS and the NSD (r < 0.05) (tables 2 and table 3).

Table 2. Comparison of ADC values with different b values in left and right hippocampus of children with hippocampus injury (HI) during complex acute febrile seizure (CAFS) and the nasopharyngeal and sinus disease (NSD).

Site b value	Children with HI during CAFS		Children with NSD		R
	Mean ($10^{-3}mm^2/S$)	Standard deviation	Mean ($10^{-3}mm^2/S$)	Standard deviation	
1000	994.44	48.641	939.17	64.153	0.003
1200	967.62	41.098	910.83	49.060	<0.01
1400	938.73	42.420	893.67	50.874	0.004
1600	911.43	34.279	865.33	43.628	0.001
1800	890.95	36.011	840.50	47.637	<0.01
2000	874.13	37.207	827.17	38.484	<0.01
1000	1009.68	41.485	940.83	58.966	<0.01
1200	979.84	38.665	910.00	51.821	<0.01
1400	953.17	44.064	896.50	49.103	<0.01
1600	924.92	32.891	868.50	40.717	<0.01
1800	902.54	25.732	852.83	45.154	<0.01
2000	874.60	23.511	826.83	38.090	<0.01

The ROC analysis and pairwise comparison of AUC showed that the ADC value for diagnosis hippocampus injury under different b values were comparable (all P > 0.05) (figure 2 and table 4). Similarly, with the gradual increase of multi-fit b value, the ADC values of bilateral hippocampal in the HI during CAFS group showed a linear trend of gradual decline, and their mean value and standard deviation also gradually decreased, with the data volatility gradually narrowing (figure 3). With b values = 1000 s/mm2 and 1200 s/mm2, the corresponding ADC graphs were relatively clear (figure 4).

Table 3. Comparison results of ADC values with different b values in the left and right hippocampus of the children with hippocampus injury (HI) during complex acute febrile seizure (CAFS).

b value	Standard error difference, 95% confidence interval	*R*
1000	8.72, (-2.95-33.43)	0.096
1200	7.08, (-2.54-26.98)	0.100
1400	9.04, (-4.41-33.30)	0.126
1600	7.39, (- 1.92-28.90)	0.083
1800	7.98, (-5.07-28.24)	0.162
2000	8.30, (- 16.83- 17.78)	0.960

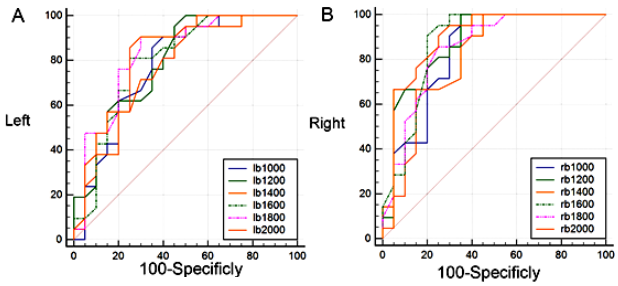

Figure 2. ROC analysis for ADC values with different b values in diagnosing hippocampus injury. Note: **A)** left side, **B)** Right side.

Table 4. Comparison of apparent diffusion coefficient (ADC) values with different b values in diagnosing hippocampus injury.

Side	b value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
L	1000	85.71	65	0.780(0.623~0.894)
	1200	95.24	55	0.798(0.643~0.907)
	1400	95.24	50	0.799(0.644~0.908)
	1600	80.95	75	0.761(0.602~0.880)
	1800	90.48	70	0.830(0.680~0.929)
	2000	85.71	75	0.826(0.676~0.926)
R	1000	90.48	70	0.835(0.686~0.932)
	1200	100	65	0.875(0.734~0.957)
	1400	100	55	0.810(0.657~0.915)
	1600	90.48	80	0.874(0.733~0.957)
	1800	85.71	75	0.849(0.702~0.941)
	2000	90.48	75	0.893(0.756~0.968)

Note: The area under the curve is compared pairwise, and the difference is not statistically significant.

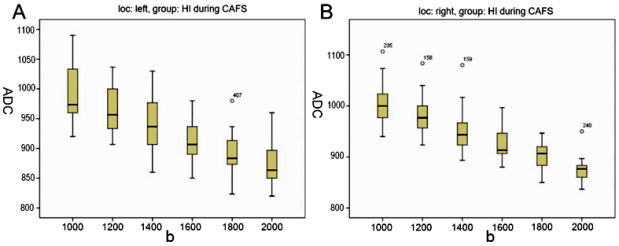

Figure 3. Box plots of ADC values at high b value in the bilateral hippocampus of the children with HI during CAFS. Note: **A)** left side, **B)** right side. The horizontal axis is the b value and the vertical axis is the ADC value.

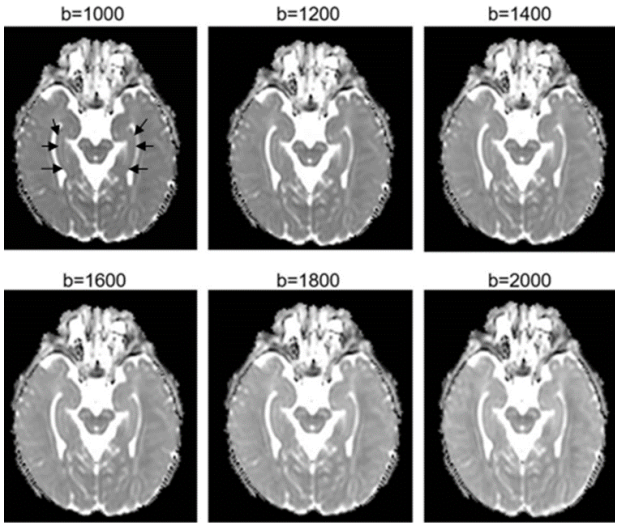

Figure 4. ADC plots at different b values. Black arrow from top to bottom, from left to right refers to the left and right sides of the hippocampal head, body and caudal regions.

This study showed that the corresponding ADC graphs were relatively clear with the medium and high b-values of b = 1000 s/mm$_2$ and 1200 s/mm^2. Another notable finding was the significant difference in ADC values of the left and right hippocampus between children with HI during CAFS and NSD. Above values might be recommended as a clinical b value point in evaluating hippocampal injury.

DISCUSSION

FS are the most common convulsive lesions in infants and young children, with a high incidence and an increasing trend in recent years. Recurrent seizures of CAFS can cause brain damage. In recent years, some scholars [16-18] have used MRS and MRI to measure hippocampal volume and hippocampal T2 relaxation time, which provide help for the diagnosis of HI in children with FS. In this study, DWI was used to evaluate the changes of hippocampal signal in the acute phase of CAFS. Feasibility of DWI in visualizing different tissues is still under discussion and b value is one of the parameters that undoubtfully influence the quality of obtained images [20]. A wide range of B values was reported to be applicable, from 600 s/mm^2 in the differentiation of the gynecological lesions [20] to 1000 s/mm^2 in rectal cancer [21] and 3000 s/mm^2 in pancreatic ductaladenocarcinoma, focal autoimmune pancreatitis [22] and gliomas [21]. Through comparative observation this study has found that although the stability of the data can be increased by increasing the b value, the signal-to-contrast ratio of the ADC image will be reduced, and the ADC images corresponding to 1000 s/mm^2 and 1200 s/mm^2 are optimal for the judgment of clinical HI. In the early stage of our study [15], by observing the box plots of ADC values of each b-value point in the left and right hippocampus of the two groups and the mean and standard deviation of ADC values with each b-value point in the two groups it was confirmed that the stability of the ADC value in the hippocampus was increased with the increase of the multiple b value data. As the multiple b value data became higher and higher, the ADC values gradually decreased in a linear manner, and their standard deviations also became lower, while their discrete trends tended to be concentrated, which also indirectly indicates that the factors affecting tissue perfusion decrease with the increase of b value [22]. The pairwise comparison of ADC values between the two groups of bilateral hippocampus also found that with the increase of the fitting b value parameter, the difference between them was more obvious, and the stability of the data was also higher. Those observations were in line with the previous study by Thoeny *et al.* [23], who reported that when a smaller b value parameter is selected, the influence of tissue microcirculation blood perfusion on the ADC value is relatively obvious, the ADC value is too large, the data is unstable and the accuracy is low. Therefore, there is a theoretical basis for gradually increasing the b-value point and when obtained value is accurate and stable, it is because a larger b value parameter is selected, and the influence of tissue microcirculation blood perfusion on the ADC value is relatively small.

However, there is a clinical applicability to be taken into account, when making a decision to use higher b values. In particular, Erbay *et al.* [24] believed that in order to reflect the true diffusion of normal tissues or pathological conditions and reduce the influence of microcirculation perfusion on the tissue, the b values > 400 s/mm^2 are effective. In this study, the b-value was gradually increased to the relative middle and high range (1000-2000 s/mm^2) and it was found that the ADC value of hippocampus still showed a linear and gradual decline and its standard deviation became lower and lower, while its discrete trend was still concentrated. The factors influencing tissue perfusion decreased with the increase of B-value, which was further confirmed [18,19].

Although sample size of this study was comparatively small, it corresponds to the real world prevalence of HI during CAFS in children [25], with males accounted for about 57.1%, and about 52.4% of the children having a family history of seizures. The study found that ADC values in the children with HI during CAFS were significantly increased rather than limited in diffusion, suggesting the presence of the loose changes in hippocampal tissues in children caused by multiple and prolonged seizures [25]. Moreover, significant difference in ADC values of the left and right hippocampus found in children with HI during CAFS and absent in children with NSD needs to be further addressed. The study has some obvious limitations. Firstly, this was a single center study with

an inherited selection bias. Moreover, children cannot fully express themselves to doctors, while the majority of parents had a low educational background and the integrity of oral information needs to be improved. Secondly, majority of the children were checked only when their condition was relatively stable, and the time between a seizure and admission was more than 24 hours. Finally, there is a difference in age between the children with HI during CAFS and the NSD, which is also a factor that should be considered. Therefore, our next study requires stricter case access, as well as increased hippocampal volume measurement and multi-mode scanning of DTI and MRS [16,17,26,27], so as to reduce the influence of these objective factors on data. However, in order to reduce the long-term impact of SAR value on children, animal experiments are the next step we need to consider.

In conclusion, the multiple b value (1000-2000 s/mm^2) DWI has a certain clinical value in evaluating hippocampal injury during the acute attack of complex febrile seizure in children and it is recommended to perform hippocampal DWI scans at b=1000 s/mm^2 and 1200 s/mm^2.

Declaration of competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: Foundation Items: Natural Science Foundation of Hainan Province (810097215013); Hainan Clinical Medical Center Construction Project (QWYH202175).

Ethical statement: The inspection process was communicated with parents, and was carried out after the consent of the children's parents, and the parents signed the informed consent. The approval number of the ethics committee of this study is: Ethics Review No. 40 2022. (810097215013).

Data declaration: All data generated or analysed during this study are included in this published article [and its supplementary information files].

Author contributions: X.H., Y.W.: Conceptualization, methodology, writing original draft preparation. S.W., F.H.: Investigation, software, statistical analysis. K.Z., D.D.: Reviewing and editing, funding acquisition, supervision. All authors read and approved the final manuscript.

REFERENCES

1. Mewasingh LD, Chin R and Scott RC (2020) Current understanding of febrile seizures and their long-term outcomes. *Developmental Medicine and Child Neurology*, ***62(11):*** *1245-1249*.
2. Chung B, Wat LC and Wong V (2006) Febrile seizures in southern Chinese children: incidence and recurrence. *Pediatric Neurology*, ***34(2):*** *121-126*.
3. Yau MM, Hon KL and Cheng CF (2019) Febrile seizures in children: A condensed update. *Hong Kong Medical Journal*, ***25(6):*** *499-500*.
4. Chung S (2014) Febrile seizures. *Korean J Pediatr*, ***57(9):*** *384-395*.
5. Christensen KJ, Dreier JW and Skotte L, *et al*. (2021) Birth characteristics and risk of febrile seizures. *Acta Neurologica Scandinavica*, ***144(1):*** *51-57*.
6. Postnikova TY, Griflyuk AV and Amakhin DV, *et al*. (2021) Early life febrile seizures impair hippocampal synaptic plasticity in young rats. *International Journal of Molecular Sciences*, ***22(15)***.
7. Li B, Wu Y, He Q, Zhou H and Cai J (2021) The effect of complicated febrile convulsion on hippocampal function and its antiepileptic treatment significance. *Translational Pediatrics*, ***10(2):*** *394-405*.
8. Yokoi S, Kidokoro H and Yamamoto H, *et al*. (2019) Hippocampal diffusion abnormality after febrile status epilepticus is related to subsequent epilepsy. *Epilepsia*, ***60(7):*** *1306-1316*.
9. Solar KG, Treit S and Beaulieu C (2021) High resolution diffusion tensor imaging of the hippocampus across the healthy lifespan. *Hippocampus*, ***31(12):*** *1271-1284*.
10. Kitazume Y, Tsuchiya J and Takenaka K, *et al*. (2020) High b-value computed diffusion-weighted imaging for differentiating bowel inflammation in Crohn's disease. *European Journal of Radiology*, ***133:*** *109362*.
11. Cha SY, Kim E and Park SY (2021) Why is a b-value range of 1500-2000 s/mm (2) optimal for evaluating prostatic index lesions on synthetic diffusion-weighted imaging? *Korean Journal of Radiology*, ***22(6):*** *922-930*.
12. Hori M, Kamiya K and Murata K (2021) Technical basics of diffusion -weighted imaging. *Magnetic Resonance Imaging Clinics of North America*, ***29(2):*** *129-136*.
13. Al-Agha M, Abushab K, Quffa K, Al-Agha S, Alajerami Y and Tabash M (2020) Efficiency of high and standard b value diffusion-weighted magnetic resonance imaging in grading of gliomas. *Journal of Oncology*, ***2020:*** *6942406*.
14. DelPriore MR, Biswas D and Hippe DS, et al. (2021) Breast cancer conspicuity on computed versus acquired high b-value diffusion-weighted MRI. *Academic Radiology*, ***28(8):*** *1108-1117*.
15. Wei Y, Deng D, Wu S, *et al.* (2022) Application of DWI with different b value in the hippocampus of children during acute attack of complex febrile seizures on 3.0T MR system*. *Chinese Journal of CT and MRI*, ***20(4):*** *7-9*.
16. Chen R, Yang L, Chen Y, *et al.* (2021) Clinical analysis of proton nuclear magnetic resonance spectroscopy in the hippocampus of children with febrile seizures. *Laboratory Medicine and Clinic*, ***18 (16):*** *2406-2408.*
17. Huang J and Wang H (2021) Recurrent hot convulsions of the dynamic variation of the hippocampal volume in children with clinical research. *Chinese Contemporary Journal Pediatrics*, ***23(4):*** *350-355.*
18. Cao Q and Wang H (2021) Clinical study on hippocampal volume changes in children with febrile seizures in acute phase. *Chinese Contemporary Pediatrics*, ***12(4):*** *259-261*.
19. Laino D, Mencaroni E and Esposito S (2018) Management of pediatric febrile seizures. *International Journal of Environmental Research and Public Health*, ***15(10):*** *2232.*
20. Koc Z, Erbay G, Ulusan S, Seydaoglu G and Aka-Bolat F (2012) Optimization of b value in diffusion-weighted MRI for characterization of benign and malignant gynecological lesions. *Journal of Magnetic Resonance Imaging*, ***35(3):*** *650-659*.
21. Chen L, Shen F and Li Z, *et al*. (2018) Diffusion-weighted imaging of rectal cancer on repeatability and cancer characterization: an effect of b-value distribution study. *Cancer Imaging*, ***18(1):*** *43*.
22. Ichikawa S, Kromrey ML, Motosugi U and Onishi H (2021) Optimal target b-value on computed diffusion-weighted magnetic resonance imaging for visualization of pancreatic ductal adenocarcinoma and focal autoimmune pancreatitis. *Abdominal Radiology*, ***46 (2):*** *636-646*.
23. Thoeny HC, De Keyzer F, Oyen RH and Peeters RR (2005) Diffusion-weighted MR imaging of kidneys in healthy volunteers and patients with parenchymal diseases: Initial experience. *Radiology*, ***235(3):*** *911-917*.
24. Erbay G, Koc Z, Karadeli E, Kuzgunbay B, Goren MR and Bal N (2012) Evaluation of malignant and benign renal lesions using diffusion-weighted MRI with multiple b values. *Acta Radiologica*, ***53(3):*** *359-365*.
25. Dreier JW, Li J, Sun Y and Christensen J (2019) Evaluation of long-term risk of epilepsy, psychiatric disorders and mortality among children with recurrent febrile seizures: A national cohort study in Denmark. *Jama Pediatrics*, ***173(12):*** *1164-1170*.
26. Zhu D, Zhang T, Jiang X, *et al.* (2014) Fusing DTI and fMRI data: A survey of methods and applications. *Neuro Image,* ***102(1):*** *184-191*.
27. Remy F, Vayssiere N, Saint-Aubert L, *et al.* (2015) White matter disruption at the prodromal stage of Alzheimer' s disease: Relationships with hippocampal atrophy and episodic memory performance. *Neuro Image Clin,* ***7:*** *482-492.*