

The Evaluation of Conventional MRI, Diffusion Tensor Imaging, and Arterial Spin Labeling Imaging for Early Brain Damage Caused by Neonatal Hyperbilirubinemia

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Abstract

Purpose: To evaluate the early bilirubin-induced neurologic dysfunction (BIND) by T1 weighted imaging (T1WI), diffusion tensor imaging (DTI), and arterial spin labeling (ASL).

Methods: Forty newborns: hyperbilirubinemia with BIND (BIND group, n=13), hyperbilirubinemia without BIND (non-BIND group, n=17), and healthy newborns (HC group, n=10). The MRI parameters of globus pallidus were measured, including the T1WI signal values from conventional MRI, apparent diffusion coefficient (ADC), the fractional anisotropy (FA), relative anisotropy (RA) and volume ratio (VR) value from DTI, and the relative cerebral blood flow (rCBF) value from ASL. The group differences were analyzed by ANOVA with Bonferroni correction. The diagnosis efficiencies were assessed by the receiver operating characteristic curve (ROC). The correlation between those parameters and serum bilirubin level was evaluated by Pearson's correlation coefficient.

Results: 1) The mean signal values of globus pallidus on T1WI and DTI parameters were significantly different among the groups ($p < 0.05$). The difference in T1WI between the non-BIND group and the BIND group was not significant ($p > 0.05$). The rCBF of globus pallidus was not significantly different among the three groups ($p > 0.05$). 2) The T1WI, FA, and RA values were positively while the VR value was negatively correlated with serum bilirubin level ($r = 0.763, 0.585, 0.586, -0.544$ respectively, $p < 0.05$). The ADC value and rCBF were not correlated with serum bilirubin ($r = -0.050, -0.275$ respectively, $p > 0.05$). 3) The area under curve (AUC) of T1WI, FA, RA, VR was 0.953, 0.897, 0.897, 0.860 respectively. And the AUC of the diagnosis method, combined T1WI, FA, RA and VR, was 0.987.

Conclusion: The index, combined T1WI and DTI parameters, was important for diagnosing early hyperbilirubinemia brain injury. ASL might not have function on diagnosing early hyperbilirubinemia brain injure.

Introduction

Due to the metabolic characteristics of neonatal bilirubin, more than 60% of newborns with hyperbilirubinemia will present with jaundice, and about 8–11% of which will progress to severe hyperbilirubinemia. When serum bilirubin exceeds a certain level, it will damage the central nervous system (CNS)^{1–5}. Bilirubin is transported to brain cells through the damaged blood-brain barrier, and when the serum bilirubin continues to increase, the toxic effect of bilirubin will be further increased. Hyperbilirubinemia often leads to necrosis of basal ganglia, hippocampus, hypothalamic nucleus, and cerebellar neurons, which is called bilirubin encephalopathy (Kernicterus)^{6,7}. The distribution of lesions is symmetrical and highly selective in bilirubin encephalopathy, mainly involving globus pallidus, hypothalamus, hippocampus, substantia nigra and various cranial nerve nucleus, among which globus pallidus is the most susceptible⁸. It is widely accepted that the early acute bilirubin encephalopathy is characterized by symmetrical high signal of bilateral globus pallidus in T1 weighted imaging (T1WI) phase, and no obvious change in T2 weighted imaging (T2WI) phase. With the continuous toxic effect of bilirubin, the signal of globus pallidus in T2WI phase will be gradually increased, indicating that bilirubin encephalopathy has been progressed from acute phase to chronic phase, and the toxic effect of bilirubin on CNS has turned to be irreversible^{9–11}.

Bilirubin-induced neurologic dysfunction (BIND) refers to the clinical signs associated with bilirubin toxicity and is typically divided into acute and chronic phases. Generally speaking, the CNS damage caused by hyperbilirubinemia within weeks after birth is during acute phase, and in this phase, the damage is reversible, while in the chronic phase it becomes irreversible. Therefore, early diagnosis and intervention are very important to prevent the disease progression¹². Currently, the hyperbilirubinemia encephalopathy was diagnosed by clinical manifestation and

serum bilirubin. The BIND scoring algorithm was developed, assigning 1, 2 or 3 points for each category of an infant's mental status, muscle tone, or cry, to indicate mild, moderate, or severe abnormalities, yielding a total cumulative BIND score ranging from 0 to 9. It has been widely used in acute bilirubin encephalopathy to evaluate the severity of the disease¹³.

In the early stage of hyperbilirubinemia, the diagnostic efficiency of acute bilirubin encephalopathy becomes lower since the slight effect of primitively increased bilirubin on the CNS and the early atypical symptoms. Therefore, some objective methods with sensitive and quantitative indices need to be applied in addition to the clinical evidence. T1WI of conventional MRI played an important role, which commonly presented with symmetrical high signal of bilateral globus pallidus in acute bilirubin encephalopathy¹¹. However, in addition to hyperbilirubinemia, hepatocerebral degeneration, myelination of special nuclei in the normal development process and other diseases can also cause the increase of globus pallidus signal¹⁴⁻¹⁶, so it may be not enough to evaluate the brain injury of hyperbilirubinemia by clinical evidence and T1WI.

As we known, diffusion tensor imaging (DTI) is a high-level form of diffusion-weighted imaging(DWI), which can provide a lot of information to help understand the brain microstructural alterations resulted from bilirubin toxicity^{15, 17}. And arterial spin labeling (ASL) is a powerful and noninvasive method to quantitatively evaluate the brain perfusion, which is more widely used and more suitable than dynamic magnetic sensitivity contrast-enhanced technology in the diagnosis of neonatal encephalopathy^{18, 19}. ASL may speculate the toxic effect of bilirubin on brain cells by monitoring the change of cerebral blood flow. However, there were only a few studies on bilirubin encephalopathy with DTI and we didn't find reports about bilirubin encephalopathy with ASL so far. Moreover, most previous studies focused on newborns with moderate and severe bilirubin encephalopathy and the discussion on the early stage of bilirubin encephalopathy was scarce. In present study, the early brain impairment caused by neonatal hyperbilirubinemia was studied by combining T1WI, DTI and ASL with comprehensive information of microstructure and cerebral blood flow, and the diagnostic efficiency was evaluated.

Methods

Participants

The study was approved by the Medical Ethics Review Committee of our institute and the relevant informed consent was obtained in accordance with the Helsinki Declaration. 30 newborns with hyperbilirubinemia were enrolled as the hyperbilirubinemia group and 10 normal newborns as the control group from February 2019 to February 2020. They were assessed by the bilirubin-induced neurological dysfunction (BIND) score, brainstem auditory evoked potential (BAEP) and amplitude integrated electroencephalogram (aEEG) tests. The total serum bilirubin (TSB), gender, gestational age, and the days from birth to MRI examination were also recorded.

30 newborns of the hyperbilirubinemia group were enrolled according to the following criteria: 1) full-term newborns whose gestational ages range from 37 to 42 weeks; 2) TSB > 221 μmol/L; 3) with jaundice as the chief complaint. The exclusion criteria included: 1) severe genetic/metabolic diseases, neonatal asphyxia, severe infection, acidosis, hypoglycemia, congenital abnormality or organic pathological changes of CNS; 2) liver function abnormality, biliary atresia or drug-induced bilirubin increase; 3) gestational age < 37 weeks.

The hyperbilirubinemia group was divided into two subgroups by BIND score: 1) non-BIND group (BIND score = 0, without neurologic dysfunction): 17 cases, include 8 females and 9 males; 2) BIND group, (BIND score ≥1, with

neurologic dysfunction) 13 cases, including 6 females and 7 males.

10 healthy newborns of control group were selected, including 5 males and 5 females, according to the following criteria included: 1) with no jaundice; 2) full-term newborns whose gestational ages range from 37 to 42 weeks; 3) BIND score was 0. The exclusion criteria included: 1) there were neurological symptoms or signs, a history of dystocia, ischemic hypoxic encephalopathy, intracranial infection, hypoglycemia, chromosomal disease, and congenital nervous system disease; 2) there were abnormalities found in brain MRI; 3) gestational age < 37 weeks.

MRI examination

All newborns underwent MRI examinations. A 3 T MR scanner (MAGNETOM Verio, SIEMENS Healthcare, Erlangen, Germany) with an 8-channel head-neck combined coil was used in the present study. All the newborns were sedated by enema with 5% chloral hydrate and the dose was adjusted by body weight (0.5ml / kg). MRI was performed within 30 minutes after sedation.

Conventional MRI sequences, DTI and ASL were performed with following parameters. 1) Axial T1WI: TR 350ms, TE 8.4ms, slice number 19, slice thickness 4.5 mm, intersection gap 1.35 mm, field of view (FOV) 220 mm × 220 mm, voxel size 0.9 mm × 0.9 mm×4.5 mm, scanning time 2min 39s; 2)Axial T2WI: TR 4950ms, TE 101ms, slice number 19, slice thickness 4.5 mm, intersection gap 1.35 mm, field of view (FOV) 230 mm × 230 mm, voxel size 1.0 mm × 0.7 mm×4.5 mm, scanning time 1min 14s; 3)Axial T2-flair: TR 8500ms, TE 94ms, scanning number 19, slice thickness 4.5 mm, intersection gap 1.35 mm, field of view (FOV) 230 mm × 230 mm, voxel size 1.3 mm × 0.9 mm×4.5 mm, scanning time 2min 39s; 4)DTI: TR 8900ms, TE 84ms, slice number 35, slice thickness 3 mm without intersection gap, FOV 220 mm × 220 mm, number of excitations (NEX) 2, matrix 128×128, b value 1000s /mm², with 20 gradient directions, voxel size 1.7 mm × 1.7 mm×3.0 mm, scanning time 6min 42s; 5)ASL: TR 4500ms, TE 12ms, slice thickness 2 mm, intersection gap 0.5 mm, slice number 4, flip angle 90 °, voxel size 3.1 mm × 3.1 mm×2.0 mm scanning time 7min 50s. The ASL was acquired to cover globus pallidus.

Data measurement of MRI

Two experienced attending radiologists, blinded to the clinical information, separately reviewed and measured the data of MR images on workstation processing. The regions of interest (ROIs) were manually defined on the layer with the largest area of globus pallidus in axial T1WI, DTI and ASL images, and three symmetrical ROIs were located on both sides of the globus pallidus respectively from anteromedial to posterolateral, as showed in Figure 1. The area of the ROI was between 20mm²-30mm². The signal values of each ROI on T1WI, DTI and ASL image, were recorded. The mean values of these parameters from six ROIs were calculated, and the final mean value was calculated by the mean value from the two radiologists.

Statistical analysis

The statistical analysis was performed by Statistical Product and Service Software (SPSS ver. 26.0). The data of T1WI, DTI parameters and rCBF were measured by two radiologists and averaged. The normality of data was tested by Shapiro-Wilk. The gender, gestational age, and days from birth to MRI examination differences among groups were analyzed by chi-square test and analysis of variance (ANOVA) respectively. The parameters values of globus pallidus among groups were analyzed by ANOVA. A p-value less than 0.05 was considered statistically significant and each p-value was adjusted using Bonferroni correction. The correlation between the parameters (FA, RA, VR,

ADC, rCBF) and serum bilirubin was evaluated by the Pearson correlation coefficient. To evaluate the diagnostic accuracy of T1WI and DTI, the receiver operating characteristic (ROC) analysis was performed and the area under the curve (AUC) was calculated by MedCalc (MedCalc statistical software, ver.19.7).

Results

Clinical data

As showed in Table 1, there were no significant differences for gender, gestational age and the days from birth to MRI examination among three groups ($p>0.05$). There were significant differences for total serum bilirubin (TSB) between non-BIND and BIND groups ($p<0.05$). And there were significant differences for BIND scores and BAEP test among groups ($p<0.05$). The difference for BAEP tests between non-BIND and BIND groups was not significant ($p>0.05$). The aEEG tests of all the newborns were negative.

MRI finding

Fifteen, 12, and 10 patients in groups BIND, no-BIND, and HC were successfully examined using DTI. Ten patients in groups BIND, non-BIND, and HC respectively were successfully examined using ASL. All the newborns were successfully examined using conventional MRI.

As showed in Table 2, the mean signal value of globus pallidus on T1WI was significantly different among the groups ($p < 0.05$). But, the difference between the HC group and the non-BIND group was not significant. There were significant differences for FA, RA, VR among groups ($p<0.05$). The ADC value of the HC group was significantly different from the non-BIND and the BIND groups ($p<0.05$). But there were no significant differences between non-BIND group and BIND group. The differences for the rCBF among the three groups were not significant ($p>0.05$).

Correlation between serum bilirubin and MRI parameters

As showed in Figure 2, there was a positive correlation between T1WI signal value of globus pallidus and serum bilirubin ($r = 0.763, p < 0.05$). FA and RA values were positively correlated with serum bilirubin ($r = 0.585, 0.586$ respectively, $p < 0.05$). VR value was negatively correlated with serum bilirubin level ($r = -0.544, p < 0.05$). There was no correlation between ADC value and serum bilirubin ($r = -0.050, p > 0.05$). There was no significant correlation between rCBF and serum bilirubin either ($r = -0.275, p > 0.05$).

ROC analysis

As showed in Figure 3, the ROC of parameters that were correlated with serum bilirubin were calculated. And the AUC of T1WI was 0.953 and that of FA, RA, VR was 0.897, 0.897, 0.860 respectively. The ROC of RA was the same as FA. And the AUC of T1WI-DTI which combined T1WI, FA, RA and VR was 0.987(supplementary Table 3).

Discussions

Neonatal hyperbilirubinemia a common clinical disorder among early newborns worldwide, also called neonatal jaundice. Newborns with hyperbilirubinemia may not only suffer yellowish skin, but also result in organ damage, especially the damage to nervous system. In severe cases, the nervous system may suffer irreversible damage, eventually leading to adverse prognosis such as sequelae and even death²⁰. The incidence of neonatal hyperbilirubinemia is increasing, but on the contrary, the progress rate of severe sequelae is declining due to the

publicity and education of health knowledge, timely clinical diagnosis and treatment²¹. The most common cases are in a relatively early stage of disease development. Bilirubin encephalopathy is diagnosed based on clinical manifestations and serum bilirubin indexes. In the present study, the clinical manifestations of bilirubin encephalopathy were quantified by using the BIND score.

BAEP, a sensitive indicator of brainstem and auditory center injury, has wide applications in clinical diagnosis and treatment. BAEP will be altered when brain stem and auditory pathway are slightly injured, even if there are no clinical manifestations and signs²²⁻²⁴. In this study, it was found that the average bilirubin level in the BIND group was higher than that in the non-BIND group. 15 newborns (8 in non-BIND group and 7 in BIND group) were positive for BAEP test. The positive results of BAEP test in non-BIND might indicated that the hyperbilirubinemia may cause the mild brain damage in newborns, even if there was no clinical manifestation. The aEEG is a non-invasive technique for continuous monitoring of brain activity with excellent precision²⁵. The mainly brain activity are processed in the cerebral cortex, while the hyperbilirubinemia is deposited in the globus pallidus at the early stage. The damage is manifested by changes in neurons and glial cells, and thus the changes in the cerebral cortex are relatively slight. Since the aEEG results of all the newborns in our study was negative, it was considered that there were no or slight degree cortical injury.

The high signal value of globus pallidus on T1WI is a typical for bilirubin encephalopathy¹¹. The high T1WI value may be attributed to the deposition of bilirubin. However, there are still some challenges in clinical practice. Currently, the T1WI signal of bilateral globus pallidus has been demonstrated to increase in normal neonates¹⁶. Moreover, considerable studies revealed that the myelin sheath is rich in lipids during the development process, and the lipids often show high signal on T1WI. The aforementioned evidence may be the main reason for the high signal on T1WI phase⁹. In this study, there were also some newborns in HC group whose globus pallidus signal was higher than that in the hyperbilirubinemia group. Ruifang Yan et al. divided the children with bilirubin encephalopathy into three groups according to the level of serum bilirubin: mild, moderate and severe, and then made a compare with the normal control group. The result showed that there was no significant difference in T1WI between the slightly increased bilirubin group and the normal control group¹⁷. In our study, there was no significant difference in T1WI signal value between HC group and non-BIND group, which was consistent with the previous studies. Some newborns with positive BAEP test results in the non-BIND group may have mild brain injure, but their T1WI signal value didn't increase significantly. There were significant differences in T1WI between the non-BIND group and the BIND group. When the TIW1 value in BIND group increased, the newborns had already appeared clinical symptoms (the BIND score ≥ 1), which indicated that the brain injury had reached a certain extent. In the study of Abdulhakim Coskun, high signal of bilateral globus pallidus on the T1WI was thought as a typical manifestation of hyperbilirubinemia encephalopathy, but how long the globus pallidus would show high signal under the toxic effect of bilirubin remained controversial¹¹. In our study, T1WI signal value of globus pallidus was positively correlated with serum bilirubin. In short, T1WI signal value of globus pallidus could increase in the development process of normal newborns. T1WI was not sensitive for mild brain injure conversely, was closely related with bilirubin concentration and toxic effect time. Therefore, evaluating early hyperbilirubinemia brain injury with high T1WI signal values alone is insufficient, other MRI examination methods should be considered in combination.

DTI is a method to study the diffusion movement of water molecules along a certain direction in three-dimensional space and it can observe and track the white matter fibers in the brain noninvasively, which has been widely used in studying the brain's white microstructure^{26,27}. Among the parameters of DTI, the FA value is the most common one

used in clinical practice. In the FA diagram, the white matter fibrous tracts are directional and show a high signal, while the gray matter and cerebrospinal show a low signal. The reduced FA values may indicate the damaged fibrous integrity²⁸. In our study, the newborns in the hyperbilirubinemia group were admitted to the hospital in time and the toxic effect was slight. The FA values of BIND and non-BIND groups were significantly higher than HC groups, and it was positively correlated with bilirubin level. Our study was consistent with the results of Ruifang Yan et al.¹⁷, which might imply that the early bilirubin toxic effect cannot damage the nerve fibrous integrity. The increase in FA value may be attributed to cytotoxic edema. And cytotoxic edema may result in nerve cell swelling and narrowing of myelin fiber bundle space. The above results further restrict the diffusion motion of water molecules. FA, RA, and VR also showed significant differences between the HC group and non-BIND group, while T1WI showed no significant differences between these two groups. We therefore speculated that the sensitivity of FA, RA, and VR to reflect mild brain injury may be higher than that of T1WI.

Not much of the application of ADC in hyperbilirubinemia and the outcome is also not universally identical. Cece, H et al. found that the ADC value of globus pallidus in the nuclear jaundice group was significantly higher than that in the normal control group and the ADC value was positively correlated with the bilirubin level²⁹. Wang X et al. found that the ADC value of globus pallidus in the nuclear jaundice group was higher than that in the control group, but it was not statistically significant³⁰. In our study, the ADC values of the BIND group and non-BIND group were significantly lower than that of the HC group, but there was no correlation between the ADC value and the bilirubin level. The decrease in ADC value may be also result from cytotoxic edema.

Arterial spin labeling (ASL) is an MRI perfusion technique that uses magnetically labeled arterial water protons as an endogenous tracer. Also, it's an advanced non-invasive perfusion imaging technique for quantifying absolute cerebral blood flow (CBF). Among these, the relative cerebral blood flow (rCBF) is a parameter of ASL^{19,31}. Bilirubin may be transported to brain through a damaged blood barrier. Consequently, we may observe the toxic effect of bilirubin by monitoring the changes of CBF. However, in our study, the rCBF of globus pallidus was not significantly different among the three groups and there was no correlation between rCBF and serum bilirubin.

To evaluate the diagnostic efficacy of T1WI, FA, RA and VR values for bilirubinemia brain injury, we compared the AUC of those parameters. The AUC of T1WI value was the largest among the single indicator. The AUC of T1WI-DTI was larger than that of any single indicator, with higher sensitivity and specificity. The combined indicator was significant for hyperbilirubinemia brain injure and it could provide a reliable basis for early clinical diagnosis.

There are some limitations in our study. First, the sample size was relatively small, which need to be enlarged in future study. Second, since no brain masks suitable for newborns and newborns have been found, and methods such as TBSS and VBA cannot be used for whole-brain data analysis, the artificial ROI method is still used for data measurement in this paper. Although the data were measured by two radiologists respectively and averaged, the measure bias was still inevitable. Third, although all neonates underwent sedation by enema before examination, slight motion artifact was still inevitable during the examination.

Conclusion

In conclusion, the T1WI high signal value of globus pallidus was typical for bilirubin encephalopathy. However, it might be not sensitive for early mild hyperbilirubinemia brain injure without neurologic dysfunction. When the T1WI value increased, the brain injury might have reached a certain extent. The DTI parameters were sensitive for mild microstructure injure, but the specificity was not higher than the T1WI. The combination of T1WI values and DTI

parameters was significant for diagnosing early hyperbilirubinemia brain injury. The ASL might not have function on diagnosis of hyperbilirubinemia brain injure.

Declarations

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Conflicts of interest

None of the authors have a conflict of interest to declare.

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Ethics approval

The study was approved by the Medical Ethics Review Committee of Taizhou People's Hospital, Fifth Affiliated Hospital to Nantong University.

Consent to participate

The relevant informed consent was obtained in accordance with the Helsinki Declaration.

Consent for publication

Not applicable. There are no patient photographs in this study.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contributions

Author contributions included conception and study design (Hui Dai and Yi Zhang and Weizhong Tian), data collection, acquisition and clinical support (Yi Zhang, Yuanqing Liu and Mengyang Ma), statistical analysis (Zhiwei Wu), interpretation of results (Zhiwei Wu, Yue Chang and Ziyang Song), drafting the manuscript work (Zhiwei Wu and Yue Chang) or revising it critically for important intellectual content (Hui Dai and Yi Zhang) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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Tables

Table 1: The clinical data of each group and inter-group differences

	A	B	C	p value			
				A verse B	A verse C	B verse C	3 groups
Gender ♀female/male♂	5/5	8/9	6/7	0.883	0.855	0.961	0.982
Gestational age (days)	270.60±11.54	270.76±8.20	265.77±6.20	1.000	0.567	0.368	0.247
*Age (days)	13.60±6.87	11.18±6.86	11.92±6.68	1.000	1.000	1.000	0.672
TSB (μmol/L)	/	316.39±45.15	441.05±62.87	/	/	0.000	/
BIND scores	0	0	1.31±0.48	1.000	0.000	0.000	0.000
BAEP (positive/negative)	0/10	8/9	7/6	0.010	0.005	0.713	0.017

A, healthy control group. B, non-BIND group. C, BIND group; TSB, total serum bilirubin. BIND, bilirubin induced neurological dysfunction. BAEP, brainstem auditory evoked potential. aEEG, amplitude integrated electroencephalogram. *Age, the days from birth to MR examination. "/" means omitted data.

Table 2: MRI parameters of each group and inter-group differences

	A	B	C	p value			
				A verse B	A verse C	B verse C	3 groups
T1WI	204.20±22.06	232.06±34.90	303.23±40.67	0.148	0.000	0.000	0.000
FA	0.171±0.017	0.195±0.012	0.215±0.017	0.001	0.000	0.003	0.000
ADC ($\times 10^{-12}$)	1126.61±39.80	1075.86±37.97	1070.65±36.89	0.008	0.005	1.000	0.003
RA	0.141±0.0145	0.161±0.010	0.179±0.015	0.002	0.000	0.003	0.000
VR ($\times 10^{-3}$)	967.11±7.91	958.17±5.60	949.24±10.16	0.028	0.000	0.019	0.000
rCBF(ml/10g/min)	586.47±74.19	546.48±56.43	540.50±61.67	0.531	0.368	1.000	0.241

A: normal control group. B: non-BIND group. C: BIND group. T1WI: T1 weighted imaging. FA: fractional anisotropy. ADC: apparent diffusion coefficient. RA: relative anisotropy. VR: volume ratio.

Figures

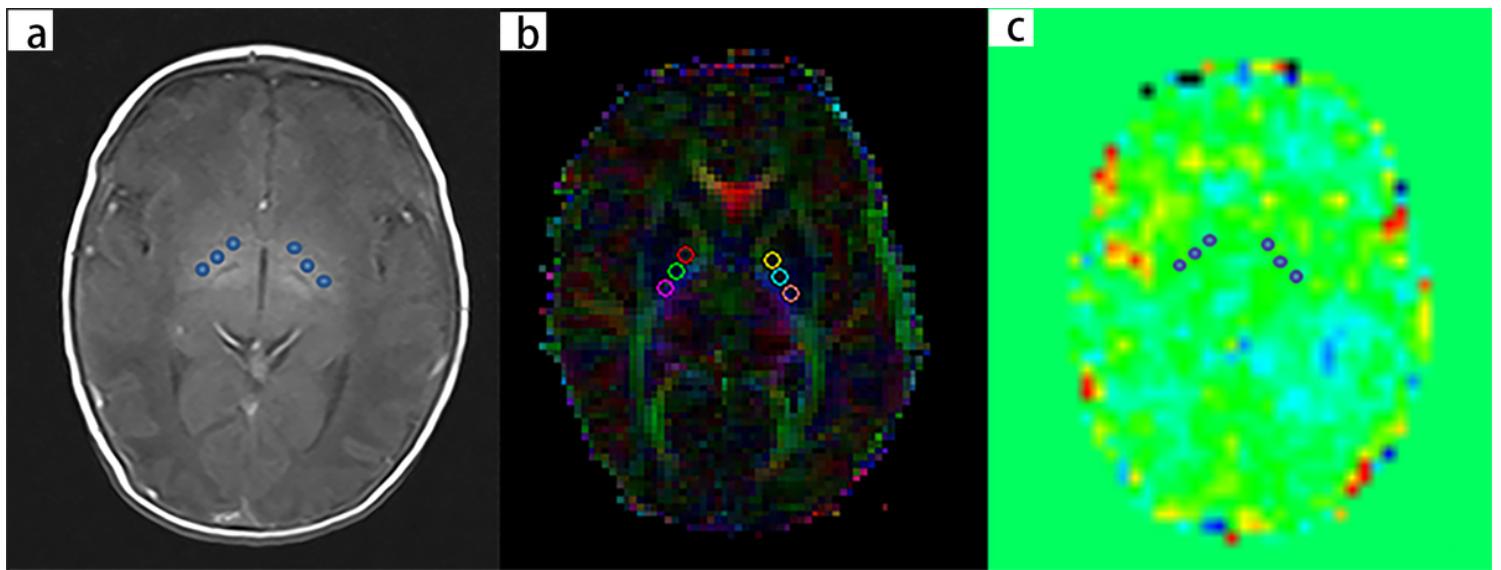


Figure 1

The method of manual ROIs. a: T1WI image; b: DTI image; c: ASL image. Three symmetrical ROIs were located on both sides of the globus pallidus respectively from anteromedial to posterolateral on T1WI image, DTI image and ASL image.

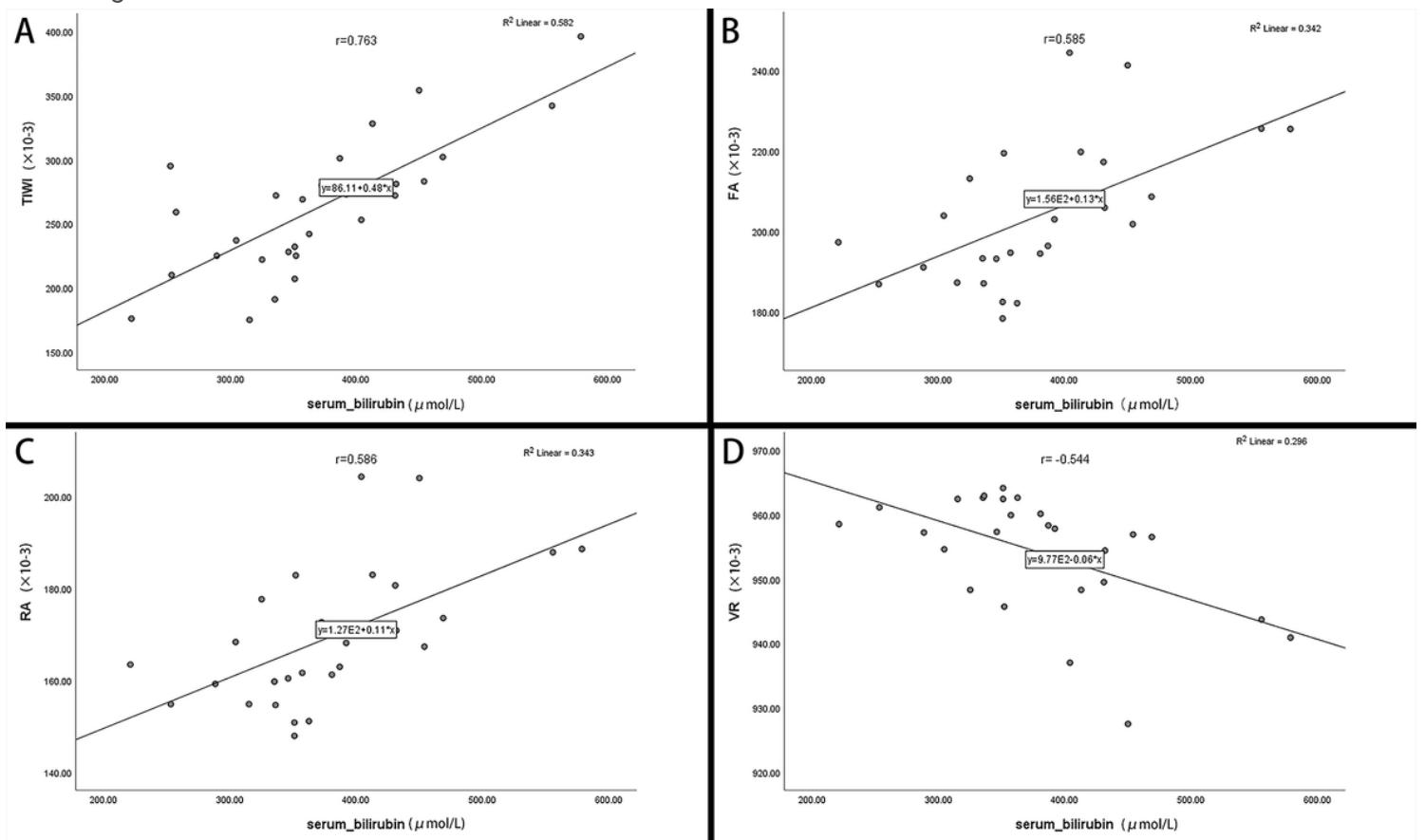


Figure 2

The correlation between serum bilirubin and MRI parameters. The A, B, C, D represented the T1WI, FA, RA, and VR respectively.

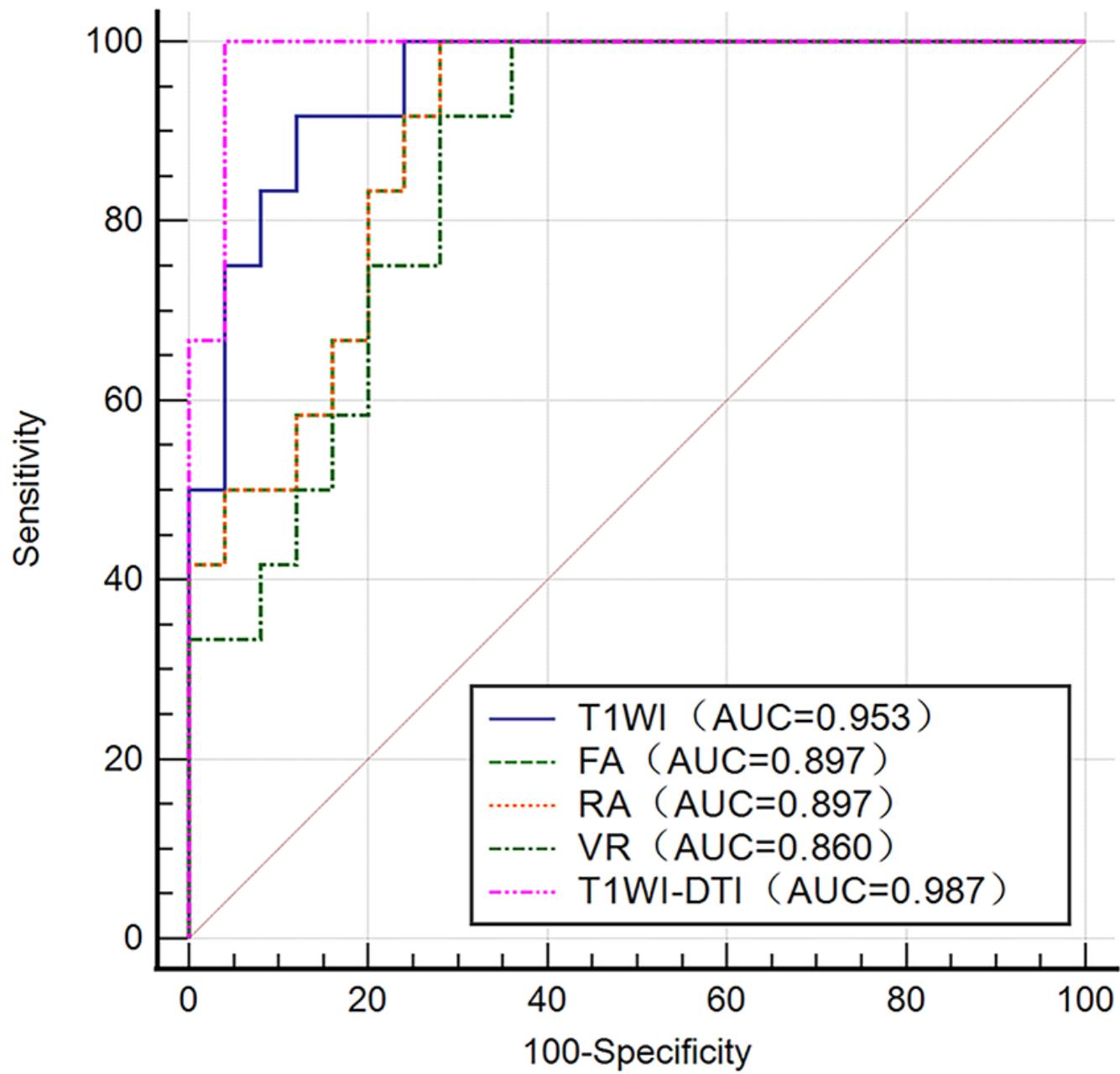


Figure 3

ROC curves for T1WI, FA, RA, VR, and T1WI-DTI. T1WI: T1 weighted imaging, FA: fractional anisotropy, RA: relative anisotropy, VR: volume ratio, T1WI-DTI: the diagnosis method combined T1WI, FA, RA and VR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table3.docx](#)