

Dynamic assessment of punctate white matter damage in premature infants based on conventional MRI and apparent diffusion coefficient value

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Research article

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Abstract

Background The purpose of this study was to observe the distribution of punctate white matter damage (PWMD) in premature infants and the signal characteristics of conventional and diffusion weighted imaging MRI. To explore the application value of routine MRI and ADC value in evaluating white matter damage in premature infants. **Methods** A total of 218 premature infants were enrolled from the Affiliated Hospital of Qingdao University and divided into a case group (n=110) and a control group (n=108). ADC values of lesions in white matter, areas around lesions (within 5 mm) and contralateral areas of mirror images were measured. ADC values of the same areas were reexamined and measured after 5-7 weeks. ADC values were measured in normal appearing areas of the case group and control group. **Results** 1. A total of 390 white matter lesions were found in 110 children in the case group. 324 lesions (83.1%) had a hyperintense signal in T1WI, 352 (90.3%) had a hyperintense signal in diffusion weighted imaging (DWI), 326 (83.5%) had a hyperintense signal in fluid-attenuated inversion recovery (FLAIR), and 118 (30.3%) had a low signal on T2WI. 2. The ADC value in the lesion was significantly lower than that in the surrounding area and the contralateral area, and the ADC value in the surrounding area was also lower than that in the contralateral area. At the time of reexamination, the ADC value of the lesions was still significantly lower than that of the surrounding and contralateral areas of the lesion. In the case group, the ADC values of the normal area in the bilateral centrum ovale and in the splenium of the corpus callosum were lower than those in the control group. **Conclusion** In the early stage, (within 7 days), DWI was the most sensitive to detecting lesions, and the detection rate of lesions on T1WI was the highest as time went on. By measuring the ADC value, we can find the damage in the surrounding area of the lesion and the damage in the normal area which can not be detected on a conventional MRI sequence.

Background

In recent years, the incidence of premature infants domestic and abroad has increased annually [1-3]. With the progress of diagnosis and treatment, the survival rate of critically premature infants has been significantly improved, but serious neurological sequelae of some children have caused serious impacts on society and their families, and white matter damage is one of the main forms of damage. The prognosis of diffuse white matter damage is poor, and the incidence is relatively low, while the incidence of punctate white matter damage is high, which is the main type of white matter damage in premature infants. At present, MRI has become the main diagnostic method of white matter damage, and DWI can detect the occurrence of white matter damage earlier than conventional MRI [5] and can detect cytotoxic brain edema caused by white matter damage. However, the T2 transmission effect of DWI may lead to a false-positive diagnosis. The diagnostic physicians can only use the naked eye to judge the damaged area and normal area on the DWI sequence, so there will inevitably be errors among different physicians. The ADC value can quantitatively analyze the diffusion ability of water molecules in lesions to quantitatively assess the degree and extent of white matter damage. When white matter damage occurs, the diffusion of water molecules is limited, and the ADC value of lesions decreases [6-7]. In this study, we

mainly discussed the signal and distribution characteristics of white matter damage in premature infants and the changes in ADC values in lesion and normal white matter areas.

Methods

1.1 Research objective

We enrolled premature infants born in the Affiliated Hospital of Qingdao University from October 2015 to May 2019. Premature infants with gestational age less than 34 weeks or body weight less than 2 kg were routinely examined by MRI. Premature infants whose mothers have high risk factors, such as hypertension, diabetes, infection and so on, should also undergo MRI. Cranial magnetic resonance examination (including T1WI, T2WI, FLAIR, DWI) was completed within 10 days after birth. The MR images of each patient were evaluated by three doctors. A total of 110 premature infants with white matter damage on the conventional MR sequence were selected as the case group (n=110), and 108 premature infants with normal performance on the conventional MR sequence were selected as the control group. There were 64 males and 46 females in the case group, with an average gestational age of 33.6 ±1.3 weeks. There were 66 males and 42 females in the control group, with an average gestational age of 34 ±1.6 weeks. There was no difference in gender, examination time or gestational age between the two groups (P > 0.05).

1.2 MRI scanning

All subjects completed routine MRI examinations within 10 days after birth, and their ADC values were measured. Five to 7 weeks later, the patients with PWMD were reexamined by routine MRI examination (average age 42 ±6 days), and the ADC values of the corresponding sites were measured again.

Scanning parameters and equipment include the GE3.0T magnetic resonance instrument, and the scanning parameters were as follows: T1WI (TR: 1708 ms, TE: 10 ms, including sagittal and axial scanning, slice thickness: 4 mm, slice gap 0.5 mm, NEX: 2). T2WI (TR: 3580 ms, TE: 104 ms, axis scanning, slice thickness: 4 mm, slice gap: 0.5 mm, NEX: 2). FLAIR (8402 ms, TE: 131 ms, axis scanning, 4 mm, slice thickness: 0.5 mm slice gap, NEX: 2). DWI (EPI-SE, TR=2120 ms, TE=63 ms, b values were 0 and 1000 s/mm². axis scanning, slice thickness: 4 mm, slice gap: 0.5 mm).

1.3 Measurement of ADC values

The DWI image was converted to an ADC image by Functiontool software of GE magnetic resonance workstation. The ADC value of the corresponding area was measured by three experienced physicians and the average value was taken.

Case group: The ADC value of each lesion was measured at the first MRI scan, and its average value was calculated as the ADC value of the lesion area. The ADC value of three points was measured in the range of 5 mm around each lesion, and then the average value was calculated as the ADC value around the lesion. The ADC value of the normal area of the contralateral cerebral hemisphere was measured in each

lesion, and the average value was taken as the ADC value of the contralateral region. The ADC values of the above parts were measured according to the same method when MRI results were reexamined. The ADC values were measured at three points in the bilateral centrum ovale, bilateral corona radiata, bilateral optic radiation, splenium of the corpus callosum and posterior limb of the internal capsule. Then, the average ADC value was taken as the ADC value of the bilateral centrum ovale, bilateral corona radiata, bilateral optic radiation, splenium of the corpus callosum and posterior limb of the internal capsule.

Control group: The ADC values were measured at three points in the bilateral centrum ovale, bilateral corona radiata, bilateral optic radiation, splenium of the corpus callosum and posterior limb of the internal capsule. Then, the average ADC value was taken as the ADC value of the bilateral centrum ovale, bilateral corona radiata, bilateral optic radiation, splenium of the corpus callosum and posterior limb of the internal capsule.

1.4 Statistical methods

SPSS 19.0, independent sample T-test, paired sample T-test, and chi-square test were used. A $P < 0.05$ was considered statistically significant.

Fig 1, 2 As shown by the black arrow, the lesions showed a hyperintense signal in DWI and a decreased signal on ADC, and the range of some lesions on ADC was slightly larger than that on DWI (as shown by the white arrow); Fig 3-5 The lesions showed a hyperintense signal in T1WI and FLAIR and a low signal on T2WI (indicated by the black arrow); Fig 6, 7 and 8 The abnormal signal on DWI, ADC and T1WI disappeared at the time of reexamination; Fig 9 The ADC value in the focus (white circle) of a child was $1.08 \times 10^{-3} \text{ mm}^2/\text{s}$, the average ADC value of three points (red circle) in the 5 mm range (black circle) around the lesion was $1.58 \times 10^{-3} \text{ mm}^2/\text{s}$, and the ADC value in the contralateral area of the lesion was $1.72 \times 10^{-3} \text{ mm}^2/\text{s}$.

Results

2.1 Distribution characteristics of lesions

A total of 390 lesions were found in 110 children with white matter damage, and their distribution in the white matter is shown in Table 1. There were 315 (80.8%) lesions in the central area (bilateral optic radiation, corona radiata I area, centrum ovale, paraventricular white matter, posterior limb of internal capsule, splenium of corpus callosum). There were 75 lesions (19.2%) in the peripheral area (bilateral frontal-parietal-temporal-occipital lobe white matter).

Table 1 Distribution of lesions in different brain regions of the case group

| Position | Number of lesions | Percentage |
|---|-------------------|------------|
| Apparent radiation | 114 | 29.2% |
| Corona radiata | 116 | 29.7% |
| Centrum ovale | 35 | 9% |
| Parasomal white matter of lateral ventricle | 14 | 3.6% |
| White matter of frontal lobe | 25 | 6.4% |
| White matter of parietal lobe | 28 | 7.2% |
| White matter of temporal lobe | 9 | 2.3% |
| White matter of occipital lobe | 13 | 3.3% |
| Paraventricular white matter | 10 | 2.6% |
| Posterior limb of internal capsule | 6 | 1.5% |
| Paraventricular posterior horn | 18 | 4.6% |
| Splenium of corpus callosum | 2 | 0.5% |
| Total | 390 | 100% |

2.2 Signal characteristics of lesions

The average age at the initial examination was 7 days. The signal characteristics of 390 lesions in 110 children are shown in Table 2. Among them, there were 286 lesions (73.3%) with a hyperintense signal in both T1WI and DWI, 38 lesions (9.7%) with a hyperintense signal in T1WI and an equal signal on DWI, 66 lesions (16.9%) with a hyperintense signal in DWI and an equal signal on T1WI. Seventy-two children were scanned within 7 days after birth, with a total of 262 lesions. Thirty-eight children were scanned within 7 to 10 days after birth, with a total of 128 lesions (Table 2). The detection rate of lesions on the DWI sequence was the highest in children examined within 7 days after birth, and the detection rate on the T1WI sequence was the highest in children examined more than 7 days after birth. The chi-square test showed that the differences were statistically significant (Tables 3 and 4). At the time of reexamination, 352 hyperintense lesions on the DWI sequence disappeared (100%), and 314 of 324 hyperintense lesions on the T1WI sequence disappeared (96.9%).

Table 2 Number of abnormal signals on different sequences at the initial examination (number, percentage of lesions)

| Inspection time | Number of children | Number of lesions | Hyperintense signal in T1WI | Low signal in T2WI | Hyperintense signal in FLAIR | Hyperintense signal in DWI |
|------------------|--------------------|-------------------|-----------------------------|--------------------|------------------------------|----------------------------|
| Within 7 days | 72 | 262 | 204(77.9%) | 48(18.3%) | 220(84%) | 246(93.9%) |
| More than 7 days | 38 | 128 | 120(93.8%) | 70(54.7%) | 106(82.8%) | 106(82.8%) |
| Total | 110 | 390 | 324(83.1%) | 118(30.3%) | 326(83.5%) | 352(90.3%) |

Table 3 Chi-square test for the number of abnormal signals on T1WI, FLAIR and DWI sequences in children examined within 7 days of birth

| | Signal | | |
|------------------------------|---------------------|---------------------|-------|
| | Hyperintense signal | Hyperintense signal | Total |
| Magnetic resonance sequences | | | |
| T1WI | 204 | 58 | 262 |
| FLAIR | 220 | 42 | 262 |
| DWI | 246 | 16 | 262 |
| Total | 670 | 116 | 786 |

There was no significant difference between T1WI and FLAIR sequence ($P = 0.75$). There was significant difference between DWI and T1WI sequence ($P < 0.001$). There was significant difference between DWI and FLAIR sequence ($P < 0.001$).

Table 4 Chi-square test for the number of abnormal signals on T1WI, FLAIR and DWI sequences in children examined 7

| | | days after birth | | |
|------------------------------|-------|---------------------|---------------------|-------|
| | | Signal | | |
| | | Hyperintense signal | Hyperintense signal | Total |
| Magnetic resonance sequences | T1WI | 120 | 8 | 128 |
| | FLAIR | 106 | 22 | 128 |
| | DWI | 106 | 22 | 128 |
| Total | | 332 | 52 | 384 |

Comparing T1WI with FLAIR and DWI sequences, the difference was statistically significant (P=0.006).

2.3 ADC value measurement

2.31 Comparison of ADC values in lesion area, surrounding lesion and mirrored contralateral region

The ADC value of the lesion area was significantly lower than that of the surrounding area and the contralateral area of the lesion (Table 5), and a T-test of paired samples showed that the difference was statistically significant (P < 0.01). The ADC value of the surrounding area was lower than that of the contralateral area, and a T-test of paired samples showed a significant difference (P = 0.021).

At the time of reexamination, the ADC value in the lesion area increased significantly, while the ADC value in the surrounding and contralateral areas decreased. The differences were statistically significant. The ADC value in the area around the lesion was still significantly lower than that in the surrounding area and the contralateral area. The T-test of paired samples showed a significant difference (P < 0.01); the ADC value in the area around the lesion was also lower than that in the contralateral area, and the T-test of paired samples showed a significant difference (P = 0.015).

Table 5 The apparent diffusion coefficients ($\times 10^{-3} \text{ mm}^2/\text{s}$, $\bar{x} \pm s$) of lesions, surrounding lesions and contralateral area, and P values of differences between the two scans

| | Lesion area | Perilesional area | Contralateral area |
|-------------|--------------|-------------------|--------------------|
| First scans | 1.049+ 0.246 | 1.532+ 0.201 | 1.571+ 0.178 |
| Review | 1.408+ 0.189 | 1.444+ 0.204 | 1.466+ 0.220 |
| P value | 0.0001 | 0.0001 | 0.0001 |

2.32 Comparison of ADC values between the normal area of the case group and the control group

The ADC values of the normal area, bilateral centrum ovale and splenium of corpus callosum in the case group were lower than those in the control group (Table 6). Independent sample T tests showed that the differences were statistically significant (P=0.01; P=0.003).

Table 6 The apparent diffusion coefficients ($\times 10^{-3} \text{ mm}^2/\text{s}$, $\bar{x} \pm s$) in normal areas of the case group and the control group, and the P values between the two groups

| | Centrum ovale | Corona radiata | Apparent radiation | Splenium of corpus callosum | Posterior limb of internal capsule |
|---------------|---------------|----------------|--------------------|-----------------------------|------------------------------------|
| Case group | 1.820+ 0.112 | 1.878+ 0.097 | 1.522+ 0.097 | 1.191+ 0.103 | 1.204+ 0.104 |
| control group | 1.854+ 0.076 | 1.861+ 0.088 | 1.531+ 0.080 | 1.232+ 0.096 | 1.212+ 0.080 |
| P value | 0.010 | 0.16 | 0.468 | 0.003 | 0.360 |

Discussion

With the increasing application of MRI in premature infants, reports of punctate white matter damage in premature infants are increasing year by year. The main manifestations of punctate white matter damage were dotted, linear and clustered hyperintense signals in DWI. Over time, a hyperintense signal in T1WI appeared in the corresponding parts, with or without low signals on T2WI [8]. Most of the abnormal signals disappeared after 3 to 4 weeks of birth, and a small number of children eventually developed periventricular leukomalacia (PVL) [9]. Because the brain of premature infants is still immature, it is susceptible to various risk factors. Moreover, the metabolism of deep white matter is higher, and the density of cerebrovascular matter decreases temporarily at 28 to 36 weeks of gestation, so white matter is more vulnerable to damage in this period [10].

3.1 Distribution of lesions and characteristics of MRI signal

Punctate white matter damage in premature infants occurs mainly in the bilateral centrum ovale, bilateral corona radiata and bilateral periventricular areas. This study showed that most of the white matter damage was located in the bilateral corona radiata (29.7%), followed by bilateral optic radiation (29.2%), and the focus in the central area accounted for 80.8%. Comette et al. [11] showed that white matter damage in premature infants often distributes around the lateral ventricles and is located in the central region, which was consistent with the results of this study. Roelants [12] et al. showed that the glutamic compound increased significantly in the lesion area within 1 week of birth, leading to mast cell phagocytosis and gliocyte hyperplasia, thus reducing the water content in surrounding tissues and shortening the relaxation time of T1 and T2. Gomori [13] et al. believed that this signal change was caused by the decomposition products of red blood cells, but magnetic susceptibility-weighted imaging showed that there were no microhemorrhagic components in the lesions [14]. This study showed that DWI is more sensitive to lesion detection in the early stage, and over time, T1WI is more sensitive to lesion detection. Miller [15] et al. showed that the hyperintense signal in DWI indicates that the diffusion of intracellular water molecules is limited, so the lesions could be detected in the early stage, and this study showed that the detection rate of lesions by DWI is the highest within one week after birth. FLAIR is an important diagnostic index for punctate white matter damage because it has a high detection level and is similar to T1WI. The detection rate of T2WI is low in each period, so it can only be used as an auxiliary reference index.

3.2 Measurement of ADC value

The ADC value of the lesion was significantly lower than that of the surrounding area and the contralateral area. The ADC value of the lesion decreased significantly, suggesting that the pathological mechanism of the lesion was cytotoxic edema. Inder [16] et al. showed that children with bilateral paraventricular diffuse white matter damage showed symmetrical hyperintense signals in DWI, and the ADC value was lower than that of normal preterm infants of the same gestational age. Feldman [17] et al. found that the ADC value of children with white matter damage was significantly lower than that of normal newborns. The study by Tong Xin [18] et al. also showed that the ADC value of the brain white matter damaged area was significantly lower than that of surrounding areas and lower than that of normal premature infants. Their results were consistent with this study. However, their results showed no difference in ADC values between the surrounding area of the lesion and normal preterm infants. Although no abnormal signal was found in the surrounding area of the lesion in conventional sequence and DWI in this study, the ADC value of the surrounding area was lower than that of the contralateral areas of the lesion, suggesting that the damage range of white matter may be larger than that shown in conventional sequences. The area around the lesion we measured was only within 5 mm of the lesion, and the extent of white matter damage around the lesions remains to be further studied. Marin-Padilla [19] et al. found abnormal neurons in the cortex around the lesion by special pathological methods, which may be caused by white matter damage that affects the differentiation of cortical neurons.

This study showed that the ADC values in the normal areas of coronal radiata and splenium of corpus callosum in children with white matter damage were lower than those in normal preterm infants.

According to the results, it can be inferred that mild white matter damage may also occur in normal areas of conventional MRI. The structural integrity of white matter determines the neurobehavioral ability at the later stage [20], which is why many premature infants with mild white matter damage on early MRI scans show significant cognitive impairment at school age.

At the time of reexamination, the hyperintense signal in DWI of all lesions disappeared, and the ADC value increased, indicating that the lesions were recovering. The ADC values of the surrounding and contralateral areas decreased, indicating that the white matter of the brain was in the process of myelination. However, the ADC value in the lesion area is still significantly lower than that in the surrounding area and the contralateral area, and the ADC value in the surrounding area is also lower than that in the contralateral area, suggesting that the disappearance of abnormal signal in DWI does not mean the complete recovery of water molecular diffusion disorder. At this time, white matter damage may still exist, which is consistent with the results of Tong Xin [18]. When correcting gestational age to full term, Ramenghi [21] found that premature infants with focal white matter damage had cortical dysplasia by MR maturity score. Miller [22] showed that premature infants with focal white matter damage had myelination disorder by diffusion tensor imaging (DTI), even in children and adolescents; this abnormality still exists [23]. These results indicate that white matter damage in premature infants has an effect on the development of white matter. As a result, most children have mild cognitive impairment at a later stage [21]. Therefore, early and adequate intervention treatment for premature infants with white matter damage may help to improve their nerve development and alleviate symptoms.

Conclusion

In summary, focal white matter lesions in premature infants are predominantly located in the central region. The early stage is characterized by a hyperintense signal in DWI. Over time, the hyperintense signal in DWI gradually decreases, while the hyperintense signal in T1WI gradually increases. The ADC value showed that the range of white matter damage was larger than that shown by the conventional MRI sequence and could be used to evaluate the outcome of the lesion more accurately.

Abbreviations

PWMD (punctate white matter damage)

ADC(apparent diffusion coefficient)

FLAIR (fluid-attenuated inversion recovery)

PVL(periventricular leukomalacia)

Declarations

Ethics approval and consent to participate This study has been approved by the ethics committee of the Affiliated Hospital of Qingdao University. Informed consent was obtained from the parents of the infants.

Consent for publication The patient's parents have signed the written informed consent and allowed the publication of this article.

Availability of data and material All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests The authors declare that they have no competing interests.

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Authors' contributions JZ was a major contributor in writing the manuscript. CC, CD, MM analyzed MRI image and measure ADC value. HL was in charge of statistical analysis. XL was responsible for Article final verification and correspondence author. All authors read and approved the final manuscript.

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Figures

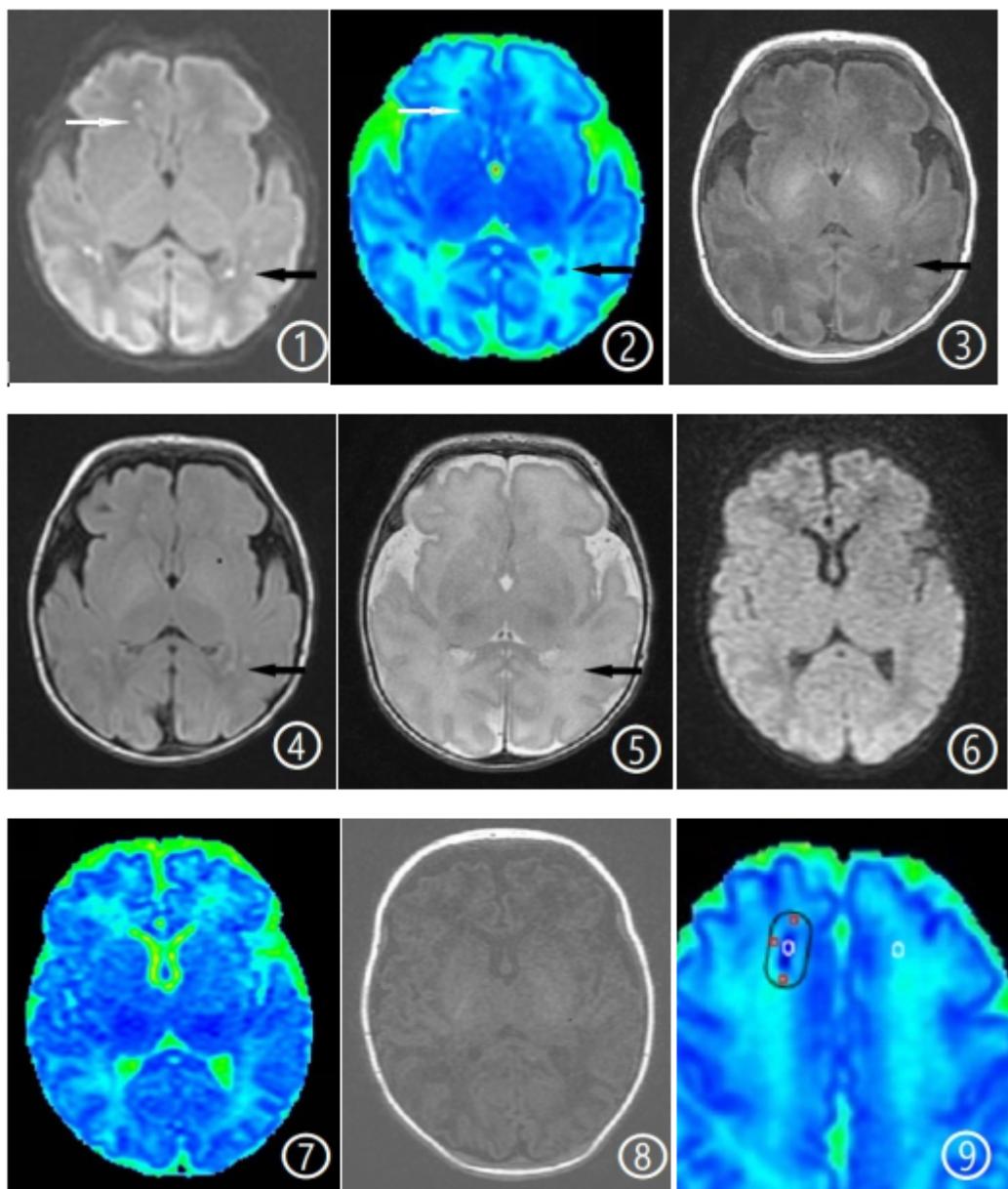


Figure 1

Fig 1, 2 As shown by the black arrow, the lesions showed a hyperintense signal in DWI and a decreased signal on ADC, and the range of some lesions on ADC was slightly larger than that on DWI (as shown by the white arrow); Fig 3-5 The lesions showed a hyperintense signal in T1WI and FLAIR and a low signal on T2WI (indicated by the black arrow); Fig 6, 7 and 8 The abnormal signal on DWI, ADC and T1WI disappeared at the time of reexamination; Fig 9 The ADC value in the focus (white circle) of a child was $1.08 \times 10^{-3} \text{ mm}^2/\text{s}$, the average ADC value of three points (red circle) in the 5 mm range (black circle) around the lesion was $1.58 \times 10^{-3} \text{ mm}^2/\text{s}$, and the ADC value in the contralateral area of the lesion was $1.72 \times 10^{-3} \text{ mm}^2/\text{s}$.