

# Analysis on the MRI Results of Neonatal Brain with Different Levels of Bilirubin

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LU ZHONGXING

Changzhou Maternal And Child Health Care Hospital

✉ szdxlzx@126.com *Corresponding Author*

ORCID: <https://orcid.org/0000-0002-4383-1475>

SHOULING DING

Paediatric Department of Taicang First People's Hospital

FEN WANG

Paediatric Department of Taicang First People's Hospital

Haitao Lv

Soochow University Affiliated Children's Hospital

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## Abstract

Numerous studies have focused on abnormal changes in craniocerebral MRI in neonates at severe bilirubin levels, and no abnormal changes have been reported at moderate and low levels, and the abnormal changes are related to gestational age, birth weight and bilirubin levels And other factors. Here, by analyzing the neonatal craniocerebral MRI manifestations at different levels of bilirubin, it is found that at moderate and low levels of bilirubin, the neonatal cranial MRI has abnormal changes, and the craniocerebras at severe bilirubin levels MRI abnormal changes were not statistically significant, and were not significantly related to gestational age, birth weight, and bilirubin levels. This suggests that neurotoxicity may occur at low and medium levels of bilirubin.

## Introduction

The accumulation of bilirubin in the body, causing xanthochromia of skin and organs, is the most common clinical problem in the neonatal period<sup>[1]</sup>. Mainly, with the high accumulation of unconjugated bilirubin, severe patients may suffer from bilirubin encephalopathy, which will cause permanent damage to the basal ganglia, hippocampus, hypothalamus, cerebellar neurons, etc. Clinical manifestation includes lethargy, poor response, fever, apnea, convulsion and so on. Magnetic resonance imaging (MRI) has proved to be highly sensitive in bilirubin encephalopathy. MRI: high stripy signals of globus pallidus and subthalamic nucleus can be detected in early T1WI, high stripy symmetric signals of globus pallidus can be detected in later T2WI<sup>[2-3]</sup>. However, bilirubin encephalopathy caused by bilirubin only accounts for a small part of neonate hyperbilirubinemia, most of them have no clinical manifestation except jaundice. Then, whether these high accumulation of bilirubin will cause brain damage to neonates or not? Is there any difference of brain damage caused by different levels of bilirubin with the high accumulation of bilirubin? For answering these questions, we examined the brain MRI of neonates with different levels of bilirubin levels, and the MRI results are as followed:

## Materials And Methods

### Clinical Data

Retrospectively analyzed 103 neonates(51 boys and 52 girls) without manifestation of bilirubin encephalopathy, who had been hospitalized in Neonatology Department of Taicang First People's

Hospital from March 2013 to September 2015. Gestational age of them ranges from 31+6 weeks to 43+1 weeks (in average,  $38.14 \pm 2.21$  weeks), birth weight from 1.55 kg to 5.00 kg (average,  $3.18 \pm 0.64$  kg), 26 pre-term neonates and 77 full-term neonates. These neonates were divided into three groups based on their levels of serum bilirubin concentration, 16 cases in mild group (TSB:  $0.0 \sim 229.0 \mu\text{mol/L}$ ), 49 cases in moderate group (TSB:  $229.0 \sim 342.0 \mu\text{mol/L}$ ) and 38 cases in severe group (TSB  $\geq 342.0 \mu\text{mol/L}$ ). Possible disease, such as toxic cerebral hypoxia damage, hepatolenticular degeneration, was excluded, which had similar MRI manifestation of bilirubin encephalopathy<sup>[2]</sup>.

## Methods and Criteria

### Methods

A Siemens Skyra 3.0T superconductivity magnetic resonance scanner and new Tim4G platform equipped with 20 units of high-density matrix head and neck joint coils. Before MRI scanning, the neonate patients were accepted a routine sedation, kept in supine position and been warm.

T1WI (TR=477 ms, TE=15 ms), T2WI (TR=4060 ms, TE=120 ms), matrix  $256 \times 256$ , slice thickness 5 mm, gap 0.4 mm. Coronal scanning was done for all neonate patients. The MRI scan sequences and parameters were as follows: T1WI (TR=450 ms, TE=10 ms), T2W1 (TR=4200 ms, TE=98 ms), matrix  $220 \times 256$ , slice thickness 5 mm, gap 1.5 mm.

### Criteria for Diagnosis

All MRI results were jointly written and analyzed by two radiologists who did not know the clinical history of patient.

MRI: high stripy signals of globus pallidus and subthalamic nucleus detected in T1WI, or high stripy symmetric signals of globus pallidus detected in T2WI or uneven signal of basal ganglion was regards as abnormality. No above-mentioned manifestation was regarded as normality. and heterogenous signal intensity of basilar on T2W1<sup>[2-3]</sup>.

### 1.2.3 Brainstem Auditory Evoked Potential (BAEP)

BAEP examination was done for the 103 neonate patients. Passed the examination was regarded as

normality, failed the examination was regarded as abnormality.

#### Statistical Method

Data analysis was performed by the use of SPSS 23.0 statistical software. Each measuring parameter was expressed by Mean±SD() and t-tests (multi-group comparisons), while each counting parameter was expressed by rate and c<sup>2</sup> tests(comparisons among groups). P<0.05, the difference is statistically significant.

### Results

#### 2.1.1 Comparison of the bilirubin values of three groups

Table 1

<b>Group</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>Bilirubin value</b>	171.99±33.50	293.98±32.09	375.59±34.25
<b>t</b>	20.54	64.13	67.59
<b>P</b>	0.00	0.00	0.00

The comparison of bilirubin values of the three groups of neonates (P<0.01) indicates the difference is statistically significant.

#### 2.1.2 Comparison of brain MRI results of the three neonates groups

Table 2

<b>Group</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>Normal</b>	11	41	30
<b>Abnormal</b>	5	8	8
<b>c<sup>2</sup></b>		1.579	
<b>P</b>		0.454	

The comparison of brain MRI results of the three neonates groups (P<0.05) indicates that the difference is not statistically significant.

#### 2.2.1 Comparison of the bilirubin values between the pre-term group and the full-term group

Table 3

<b>Group</b>	<b>Pre-term</b>	<b>Full-term</b>
<b>Bilirubin value</b>	289.70±85.38	310.36±72.32
<b>t</b>		-1.20
<b>P</b>		0.232

The comparison of the bilirubin values between pre-term group and full-term group (P<0.05) indicates that the difference is not statistically significant.

#### 2.2.2 Comparison of MRI results between pre-term group and full-term group

Table 4

Group	Pre-term	Full-term
Normal	18	64
Abnormal	8	13
$\chi^2$		2.31
P		0.16

The comparison of brain MRI results between prem-term group and full-term group ( $P \geq 0.05$ ) indicates that the difference is not statistically significant.

### 2.3.1 Two groups divided based on the weight of 2500g

Table 5

Group	2500g	$\geq 2500g$
Weight	2.04 $\pm$ 0.21	3.39 $\pm$ 0.46
t		-18.85
P		0.00

The weight comparison of the two groups ( $P \leq 0.01$ ) indicates that the difference is statistically significant.

### 2.3.2 Comparison of MRI results of the two neonates groups divided based on the weight of 2500g

Table 6

Group	2500g	$\geq 2500g$
Normal	10	72
Abnormal	6	15
$\chi^2$		3.42
P		0.09

The comparison of brain MRI results of two neonates groups ( $P \leq 0.05$ ) indicates that the difference is not statistically significant.

### 2.4 Comparison between normal and abnormal MRI bilirubin values

Table 7

Group	Normal (n=82)	Abnormal (n=21)
bilirubin value	305.55 $\pm$ 74.54	303.56 $\pm$ 83.04
t		0.11
P		0.92

The comparison of bilirubin values between the two groups ( $P \leq 0.05$ ) indicates that the difference is not statistically significant.

### 2.5 Comparison of abnormal MRI signal values of globus pallidus on T1WI in mild, moderate and severe groups and comparison of these abnormal MRI signal values with normal MRI signal values

Table 8

Group	n	Mean signal value of left globus pallidus	Mean signal value of right globus pallidus
Normal group <sup>1</sup>	82	892.03 $\pm$ 132.54	878.65 $\pm$ 126.43
Mild group <sup>2</sup>	5	956.85 $\pm$ 245.87	942.06 $\pm$ 232.60
Moderate group <sup>23</sup>	8	1056.23 $\pm$ 254.21	1032.32 $\pm$ 222.32
Severe group <sup>23</sup>	8	1246.03 $\pm$ 278.46	1239.03 $\pm$ 288.53

The comparison of normal group signal values with that of mild group ( $p < 0.05$ ), with that of moderate group and with that of severe group ( $p < 0.01$ ) indicates that the difference is statistically significant; 2. The comparison of signal values between mild and moderate groups ( $p < 0.05$ ) and between mild group and severe group ( $p < 0.01$ ) indicates that the difference is statistically significant; 3. The comparison of signal values between moderate group and severe group ( $p < 0.05$ ) indicates that the difference is statistically significant.

2.6 Comparison of hearing screening results for neonates patients with abnormal MRI in three groups and comparison of hearing screening results between neonates patients with abnormal MRI and normal MRI.

Table 9

Group	Normal MRI 82	Abnormal MRI in mild group5	Abnormal MRI in moderate group8	Abnormal MRI in severe group8
Normal	67	3	4	2
Abnormal	15	2	4	6
%	18.29	40.00	50.00	75.00
Review abnormality after one month	0	0	1□12.50□	2□25.00□

## Discussion

Neonatal jaundice is the most common clinical manifestation occurred in neonate period, which is mainly caused by the increase of serum bilirubin in neonates. In the prenatal period, due to the hypoxic environment, the amount of red cells is increased and the hemoglobin content in the fetal is high. After birth, due to the hyperoxic environment, the survival time of red blood cell becomes short. The fetal hemoglobin is gradually converted to adult hemoglobin producing a large amount of bilirubin, which exceeds the ability of liver to treat bilirubin. When bilirubin levels are above  $139\mu\text{mol/L}$ , skin or organ xanthochromia may appear, that is called neonate jaundice. It has been previously thought if the concentration of bilirubin in the blood is above  $342\mu\text{mol/L}$ , serious damage to nervous system for the neonates may occur and the acute stage manifestation of acute bilirubin encephalopathy (ABE) or chronic kernicterus appears<sup>[4]</sup>. Brain damage caused by neonatal hyperbilirubinemia (NHB) is not always reversible, may lead to cerebral palsy and hearing loss. The most common type of nerve injuries are the sequelae of severe neurological dyskinesia and hearing impairment. <sup>[5-8]</sup>. Chronic bilirubin encephalopathy or kernicterus mainly affects subcortical regions,

such as globus pallidus, hypothalamus, substantia nigra, cerebellar dentate nucleus, or hippocampus. Although, the underlying mechanisms are still unknown<sup>[9-10]</sup>. Most of ABE neonatal patients still have a chance to be recovered by timely treatment of reducing serum bilirubin levels, while only a few suffer from sequelae, like kernicterus.

The feature of MRI manifestation to bilirubin encephalopathy is the high signal of globus pallidus in the acute stage of T1-weighted imaging (T1WI). With the development of the disease, it has changed from the high signal in acute stage of T1WI to the high symmetric signal of bilateral globus pallidus and subthalamic nucleus in chronic stage and FLAIR sequence signal<sup>[11-13]</sup>. Since in the neonatal period the basal ganglia nerve cells have strong physiological and biochemical metabolism and the oxygen consumption is increasing, especially, the middle and later part of the globus pallidus is the most sensitive<sup>[14]</sup>. This leads to the selectively deposition of serum bilirubin in the globus pallidus, the middle and later part of the globus pallidus is more sensitive<sup>[15-17]</sup>. Besides, it will cause the damage to neurons and glial cells, the apoptosis of neurons and the change of glial cells' mitochondria function<sup>[18-19]</sup>. Basal ganglia pallidus injury caused by hyperbilirubinemia can be efficiently detected by MRI. The high and symmetric signal of bilateral T1WI pallidal is an important imaging feature of neonatal ABE, while the change from high signal of T1WI to high signal of T2-weighted imaging (T2WI) is the imaging feature of nuclear jaundice on MRI, indicating neuronal cell necrosis and poor prognosis. Presently, the mechanism of MRI signal change still remains unclear. This may be related to the reduction of the T1 value, which is caused by the deposition of bilirubin in glial cells and the destruction of bilirubin to nerve cell membrane<sup>[20]</sup>.

Most of the MRI results mentioned above were obtained from brain MRI findings of the severe or profound NHB patients with bilirubin encephalopathy or non-bilirubin encephalopathy. So far, there is no report about whether the MRI results of mild and moderate NHB patients without bilirubin encephalopathy manifestation are abnormal. Therefore, this study retrospectively analyzes the bilirubin level and MRI results of 103 patients with jaundice in order to understand whether there is abnormal brain MRI at different bilirubin levels, as well as whether there is statistical difference of

abnormal brain MRI results in bilirubin levels, gestational age, and birth weight.

It is reported in literature that some mild levels of bilirubin could cause temporary or permanent neurological sequelae under the condition that a certain level of bilirubin is considered as being safe by people<sup>[21]</sup>. Based on total serum bilirubin concentration(TSB), the 103 patients in our research were divided into three groups, including 16 cases in the mild group (TSB: 0.0—229.0 $\mu$ mol/L), 49 cases in the moderate group (TSB: 229.0—342.0 $\mu$ mol/L) and 38 cases in the severe group ( TSB  $\geq$ 342.0 $\mu$ mol/L). There were 21 cases with abnormal MRI results, which consisted of 5 cases in mild group, 8 cases in moderate group and 8 cases in severe group. The comparison of TSB among the three groups  $P < 0.01$  indicated that the difference was statistically significant, whereas, the comparison of abnormal brain MRI results among the three groups  $P > 0.05$  indicated that the difference was not statistically significant. This pointed out that bilirubin brain nerve damage may occur in patients without the manifestation of ABE even in low level of bilirubin, and the rate of MRI abnormality is not rising with the rising of bilirubin level. The study findings are not consistent with the reports of Changjun Ren et al. that the higher the total bilirubin level is, the higher the proportion of abnormal MRI is<sup>[22]</sup>. We think that low number of cases in the mild group may also be an important factor. Under Taoka et al.'s follow-up of the observed subjects for 2 years, it was found that the infants had been developing normally whether the high symmetric T1WI signal was demonstrated in GP and STN regions or not. In accordance with reports in the literature, it may be related to the development of gray matter ball in GP and STN after the birth of neonates<sup>[23-26]</sup>. Besides, lots of literatures have reported that this manifestation is one of the brain MRI findings of nuclear jaundice<sup>[27-30]</sup>. Along with the extensive clinical application of MRI, the manifestation is becoming more and more common in neonates, and normal neonates. Thus, some scholars recently have raised different opinions<sup>[22-24]</sup>. For example, Hrris et al.<sup>[31]</sup> reported that high symmetric signal in the globus pallidus region of four 5-21 day neonates with acute kernicterus has disappeared during the follow-up. This manifestation was thought transient, had no correlation with the prognosis of the patients. This manifestation also appeared in the cases of neonatal hypoxic ischemic encephalopathy,

hypoglycemia and other cases [32-33].

In this study, the neonate patients, who has high signal of globus pallidus in T1WI or T2W1, caused by the diseases of neonatal hypoxic ischemic encephalopathy, hypoglycemia, hepatolenticular degeneration and other diseases, have been excluded. In this study, 12 cases of the 21 patients with MRI abnormalities were followed up for one month, and 9 cases of the 21 patients were followed up for 3 months. 6 cases of patients had normal brain MRI results in the 1 month later reexamination. 3 cases of patients had not been reexamined of the MRI, one of the 3 cases had neurological abnormalities 2 months later, who was delivered with gestational age 40 weeks, birth weight 3.31kg, clear amniotic fluid, the Apgar score 8 at 1 min and 9 in 5 mins, maximum bilirubin value 327.3 $\mu$ mol/L, and uneven signal of the brain MRI in bilateral basal ganglia region. However, one case of this study showed no brain MRI abnormalities with maximum bilirubin value 502.3 $\mu$ mol/L, birth weight 3.05 kg, gestational age 36+3 weeks, clear amniotic fluid and the Apgar score 9 at 1min, 9 in 5 mins. In addition, another case in the study may have ABE with gestational age 40+4 weeks, birth weight 3.5 kg, amniotic fluid in III meconium-stained during birth, the Apgar score 9 at 1 min, 9 in 5 mins, the maximum bilirubin value 130.4 $\mu$ mol/L, and high symmetric T1WI signal of bilateral basal ganglia indicated by his brain MRI. The high symmetric signal of bilateral globus pallidus is not unique to the neonatal ABE, it can also be seen in some neonatal patients with hypoxic ischemic encephalopathy<sup>[34-35]</sup>, or even in normal neonates<sup>[36]</sup>. But the MRI manifestations of hypoxic ischemic encephalopathy(HIE) involved more extensive scope, which was characterized by internal capsule, the putamen and the thalamu, and accompanied by cortical and subcortical, deep leukoplakia plaque abnormal signals, diffuse brain edema, intracranial hemorrhage, and so on. These accompanied manifestations were scarcely appeared in bilirubin encephalopathy<sup>[37]</sup>. Without the medical history, signs of hypoxic ischemic encephalopathy and the above MRI manifestations, the symmetric T1WI high signal was demonstrated in bilateral basal ganglia of the child brain MRI. Blood brain barrier injury, might be caused by anoxia or other factors in antepartum and intrapartum, increased the permeability of blood brain barrier, resulting in the increasing of free bilirubin to enter

into brain tissue through the injured blood-brain barrier and to deposit in the basal nerve nucleus, cerebral ganglia, subthalamic nucleus, parietal nucleus, ventricular nucleus, caudate nucleus, cerebellum, oblongata, cerebral cortex and spinal cord. Accordingly, the utilization of oxygen in brain tissue was inhibited, leading to brain damage [38-39]. It is also believed that bilirubin deposition cause the influx of neuron cells  $Ca^{2+}$  and stimulate the increase of proteolytic enzyme activity, leading to neuronal apoptosis<sup>[36]</sup>.

It has been reported in many studies that the occurrence of neonatal BE is related to the factors of gestational age, birth weight, bilirubin binding state and bilirubin level, etc. <sup>[18]</sup> In this study, 103 patients were divided into preterm group (26 cases) and full-term group (77 cases), observing the comparison of bilirubin values ( $289.70 \pm 85.38$  vs  $310.36 \pm 72.32$ ,  $P = 0.232$ ) of the two groups and the MRI abnormal result ( $P = 0.16$ ) of the two groups was  $P \geq 0.05$ , the difference was not statistically significant, which indicated that there may be no difference in the toxicity of bilirubin to central nervous system between pre-term group and full-term group without BE clinical manifestation. Moreover, it was not case that premature infants with younger gestational age were more susceptible to bilirubin toxicity. The analyses of this result may be as follows: (1) Premature delivery patients, who are usually admitted to be in hospital after birth, are treated for jaundice in time during hospitalization. While, full-term infants are admitted to be in hospital only when their bilirubin value reaches a higher level. On the one hand, high level of bilirubin could easily cause nerve damage by through the blood brain barrier; on the other hand, the longer the high level of bilirubin remains in the body, the more neurotoxicity of bilirubin is. (2) The statistical analysis in this study may be biased, on account of the fewer cases of pre-term delivery group, especially lack of pre-term patients less than 31 weeks of gestational age due to obstetric factors. Meanwhile, we also observed whether there was statistical difference between birth weight and brain MRI abnormality of the jaundice patients. Based on birth weight, 103 patients were divided into two groups, one group birth weight  $< 2500g$  (16 cases, including 6 abnormal cases) and the other group birth weight  $\geq 2500g$  (87 cases, including 15 abnormal cases). The comparison of brain MRI abnormality of the two groups was  $P = 0.09$ ,  $P > 0.05$ ,

the difference was not statistically significant .

In addition, the comparison of bilirubin value between abnormal MRI group and normal MRI group was ( $303.56 \pm 83.04$  vs  $305.55 \pm 74.54$ ,  $P=0.92$ ,  $P>0.05$ ), the difference was not statistically significant, which indicated that there was no obvious difference in bilirubin level between abnormal MRI group and normal MRI group of jaundice patients without ABE.

At the same time, we measured the T1WI signal values of the patients with abnormal brain MRI and the signal values of the patients with normal brain MRI in the three groups, and performed statistical comparison, which showed that the T1WI signal values of the patients with abnormal MRI were all higher than those of the patients with normal MRI ( $P<0.05$ ), and the T1WI signal values of the patients with MRI abnormalities in the three groups also had statistically difference ( $P<0.05$ ). With the increase of serum bilirubin level, the T1WI signal value of the patients with MRI abnormalities also increased, which was consistent with the report of Yan Ruifang et al <sup>[40]</sup> that there was a linear correlation between the mean signal value of globus pallidus and serum total bilirubin levels in the lesion group. This indicated that with the rising of bilirubin level, the more bilirubin deposited on neuron such as globus pallidus, the more serious damage would be made to nerve tissue such as neuron.

We performed hearing tests for the 103 patients with BAEP<sup>[41]</sup> devices, it was found that 15 cases of 82 patients with normal MRI results were abnormal, accounting for 18.29%. In the mild group 2 cases of 5 patients with abnormal MRI were abnormal, accounting for 40.00%. In the moderate group 4 cases of 8 patients with abnormal MRI were abnormal, accounting for 50.00%. In the severe group 6 cases of 8 patients with abnormal MRI were abnormal, accounting for 75.00%. After one month followed-up, the reexamination found that the patients with hearing abnormalities in the MRI normal group and the mild group were all returned to normal level, and 1 case in the moderate group and 2 cases in the severe group were remained abnormal. This result indicated that, on the one hand, the BAEP abnormal rate of the patients with abnormal MRI was higher than that of the patients with normal MRI, and the BAEP abnormal rate of the patients with abnormal MRI increased with the

increase of bilirubin level. It also shows that with the increase of bilirubin, the hearing damage is more obvious<sup>[42]</sup>. On the other hand, it also proved the application value of MRI in neonatal jaundice patients, which could timely detect the abnormalities of central nervous system of the patients with jaundice, and provide imaging evidence for early diagnosis and early intervention.

In conclusion, in the presence of certain factors, central nervous system damage may also occur at low level of bilirubin and be appeared abnormality on MRI. Meanwhile, MRI can also be used to provide early imaging signs for the judgment of central nervous system damage to NHB neonatal patients without clinical manifestations of ABE, and offer clues for early treatment and early intervention so as to prevent the occurrence of severe brain tissue damage and over-treatment of the patient who only has hyperbilirubinemia<sup>[43]</sup>.

### Limitations Of The Present Study

Although the findings of this study indicate that in babies with jaundice, the brain MRI may show abnormal changes at mild and moderate levels of bilirubin, and there is no statistically significant difference between brain MRI abnormalities in the severe group, Our results have been affected by a number of issues. First, we failed to measure the free bilirubin levels, internal environmental conditions such as serum albumin levels, pH values, etc. of the jaundice newborns participating in the study at that time, so it cannot be said with certainty that the baby's brain was exposed to biliary red crossing the blood-brain barrier Prime type. Secondly, the sample size in this study is relatively small, especially in the mild group and the sample size is less than 2500g. Finally, the craniocerebral pathology test of newborn animal Jaundice model is lacking to validate our findings. This will be an issue that we need to address in this type of research in the future.

### Abbreviations

ABE : acute bilirubin encephalopathy

TSB : total serum bilirubin

MRI: Magnetic resonance imaging

NHB : neonatal hyperbilirubinemia

ABE : acute bilirubin encephalopathy

T1WI :T1-weighted imaging

T2WI :T2-weighted imaging

## Declarations

These authors have contributed equally to this work.

Compliance with Ethical Statements: The study was approved by the Ethics Committee of the First People's Hospital of Taicang City.

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Figures

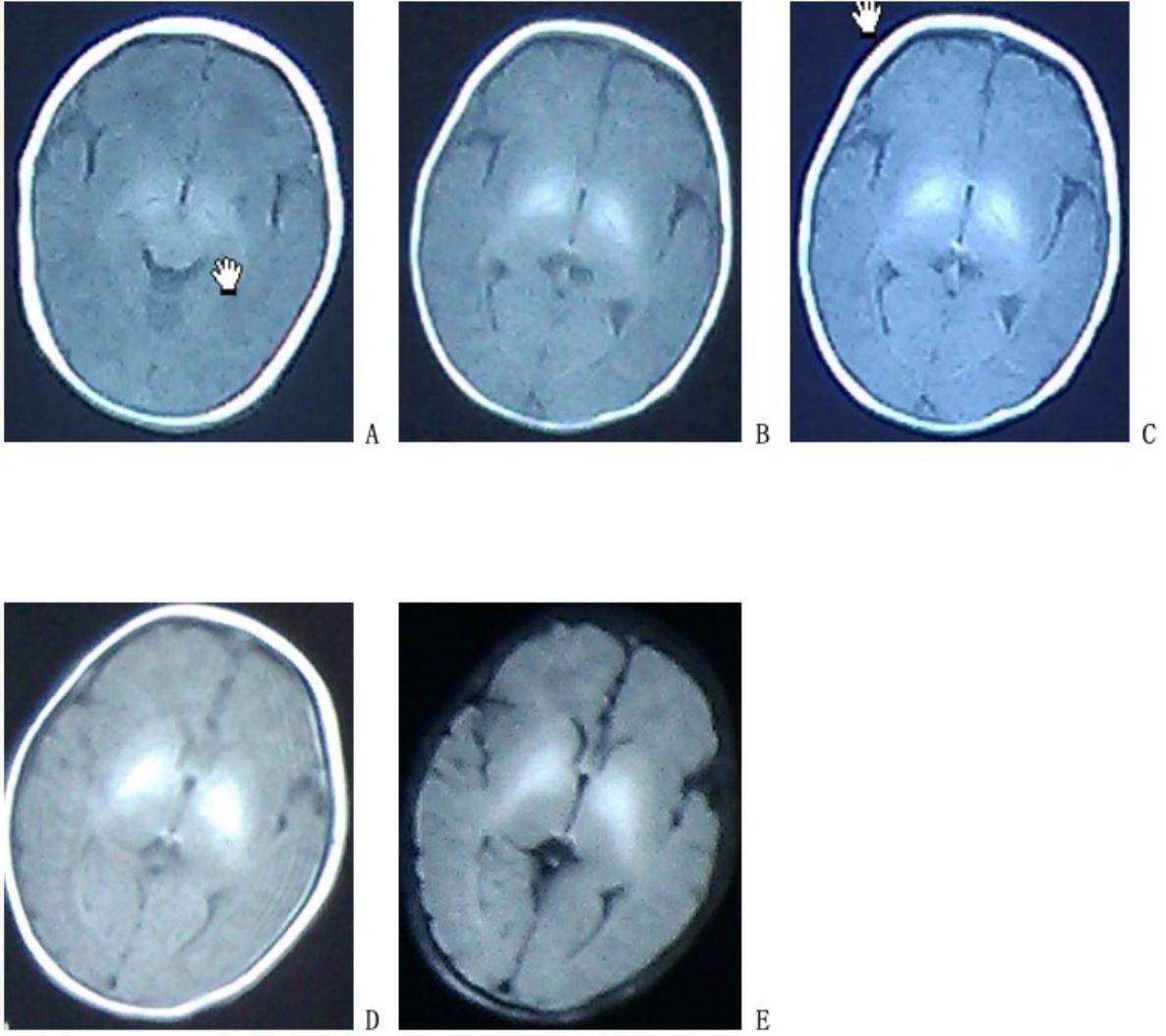


Figure 1

MRI pictures. A normal B mild C moderate D severe E T2WI manifestation