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Review Article

Relevant studies and latest developments in crossed cerebellar diaschisis

Xiao Wang, Jing-Liang Cheng, Yong Zhang, Ya-Nan Lin, Lu Yang

Department of MRI, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

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Abstract: Crossed cerebellar diaschisis refers to a phenomenon, in which blood flow and oxygen metabolism rate in the contralateral cerebellum decline due to supratentorial brain tissue damage. In 1914, the terminology "diaschisis" was proposed for the first time by a Swiss neurologist neurosis to describe some specific changes in focal brain injury. Thereafter, the detection of cerebral oxygen metabolic rate, cerebral glucose metabolic rate and other techniques has continuously been applied by scholars in performing in-depth studies of this phenomenon; thus, the phenomenon of crossed cerebellar diaschisis in humans has been confirmed. With the recent progress in research methods and the application of new imaging techniques, researchers have attained further insights into the mechanism of this phenomenon. In this study, the mechanism of crossed cerebellar diaschisis, the relationships between its occurrence and progress and related diseases, as well as the research progress in the imageological examination of this phenomenon, have been comprehensively reviewed.

Keywords: Crossed cerebellar diaschisis, cerebral infarction

Introduction

In 1914, Swiss neurologist, Constantin von Monakow, first proposed the term 'diaschisis' to describe specific changes in focal brain injury; and thus, explaining the phenomenon found in his experiments that contralateral cerebellar hemisphere hypoplasia occurred in juvenile cats after the removal of the cerebral cortex [1]. As early as 1870, Brown-Sequard reported the remote effect on focal brain injury, and found that remote regions exhibited excessive excitatory or inhibitory brain function disorders after focal brain injury. In 1935, a report exhibited that one patient with brain atrophy secondary to birth trauma was followed by crossed cerebellar atrophy, which confirms the hypothesis of crossed cerebellar diaschisis in humans.

Crossed cerebellar diaschisis (CCD) refers to the decline in blood flow reduction and metabolism rate in the contralateral cerebellum due to supratentorial brain tissue damage [2]. In 1980, Baron *et al.* first reported the phenomenon that blood flow was reduced and oxygen metabolic rate declined in the contralateral cerebellar hemisphere in patients with supratentorial infarction by applying noninvasive continuous inhalation of steady-state ^{15}O combined with positron emission tomography (PET) [3], Thereafter, scholars confirmed the existence of CCD using techniques that detect cerebral oxygen metabolic rates and cerebral glucose metabolic rates.

With the recent progress in research methods and the application of new imaging technologies, researchers have attained further insights into the mechanism of CCD. To date, most Chinese scholars believe that the mechanism of diaschisis may be due to the impact of primary lesion damage; in which brain tissue blood flow in remote nerve fibers-linked region suffer a secondary slowing down, resulting in the reduction of function in remote parts, and thus attributing diaschisis to the interruption of the neurological link [4, 5]. Furthermore, majority of scholars worldwide suggest that diaschisis is related to the following three factors [6]. (1) Inhibition of the nerve conduction pathway. Most studies suggest that damage in the cortical-pons-cerebellum (CPC) pathway can better

explain the occurrence of CCD after supratentorial infarction [7-9]. Since the CPC pathway is the main nerve fiber pathway connected to the contralateral cerebellar hemisphere, the inhibition of the CPC pathway is the anatomical basis of CCD occurrence [10]. The CPC pathway starts from the cerebral cortex, passes from the cortex to the ipsilateral pons, and goes to the contralateral cerebellar cortex [11, 12]. The frontoparietal cortex is the origin of the CPC pathway, while the projection of corticopons is mainly the excitatory impulse transmitting to the granule cells in the contralateral cerebellar hemisphere. Therefore, damage in the CPC pathway can lead to contralateral cerebellar dysfunction; namely, crossed cerebellar diaschisis. The corpus callosum may play a crucial role in the occurrence of connection dysfunction in the contralateral hemispheric cortex. (2) Changes in hemodynamics. After the occurrence of cerebral cortex infarction, hypoperfusion in lesions adjacent to the cortex can occur; which may be the result of the extension of the lesion of penumbra. Hemodynamic hypothesis can explain the ipsilateral brain connection dysfunction, but cannot make a reasonable explanation for chronic diaschisis and connection dysfunction in the contralateral cerebellar hemisphere, namely, crossed cerebellar diaschisis. (3) Delayed neuronal death. Experimental studies have revealed an abnormal radioactivity concentration in the ischemic ipsilateral caudate nucleus and putamen in a middle cerebral artery occlusion (MCAO) rat model, and that the ventral lateral nucleus of the ipsilateral thalamus also presented abnormal radioactivity concentrations after two weeks; suggesting the presence of delayed neuronal death outside the ischemic area.

Studies have revealed that CCD may be secondary to diseases in the cerebral cortex, basal ganglia and thalamus [13]. Among cortical lesions, CCD caused by lesions in the parietal lobe is the most serious, followed by lesions in the frontal and temporal lobes. Basal ganglia lesions are more likely to lead to CCD than lesions in the hypothalamus. Damage on the upper section of pons can also lead to CCD, while those in the middle and lower sections cannot. There is no necessary correlation between the nature of lesions and CCD. A literature has shown that the CCD phenomenon may occur in a variety of central nervous system lesions; among which, cerebral infarction have been mostly reported The frequency of CCD was highest after infarction in blood supplying areas by the middle cerebral artery, which was also the most serious [14]. Followed by epilepsy, cases of CCD caused by tumors, brain trauma and Moyamoya disease have also been reported.

Cerebral infarction

As noted above, most scholars believe that the interruption of the CPC pathway may be the mechanism of CCD occurrence. Nguyen *et al.* considered that the severity of CCD is relevant with the degree of influence on the CPC pathway of primary lesions [15]. Studies have shown that the CPC pathway is the most important nerve fiber pathway between the cerebral cortex and contralateral cerebellar hemisphere, which consists of pons fibres from the cortex focused inward the forelimb and hindlimb of the internal capsule to ipsilateral pons, as well as fibers from pons to the contralateral cerebellum. When neuronal axonal rupture or injury caused by various brain damage occur, Wallerian degeneration may appear in proximal axons of the damage zone and distal axons of the damage zone may gradually undergo degeneration and disintegration from close to far, resulting in pathway interruption. Hence, cortical excitatory impulses cannot be transmitted to the contralateral cerebellum. When nerve impulses transmitted into the contralateral cerebellum from the supratentorial brain tissue decline, CCD occurs and functional inhibition appears [16]. Therefore, the occurrence and development of CCD after cerebral infarction may be related to age, lesion area and location of the cerebral infarction, as well as paralysis, muscle strength and so on. All of those will be described in detail in the following.

To date, the relationship between cerebral infarction stage and CCD remains controversial. Clinical and experimental studies are mostly regarding the CCD phenomenon after the hyperacute and acute phase of cerebral infarction and chronic cerebral infarction is rarely involved in CCD. Kim *et al.* considered that CCD is more likely to appear within 30 days after ischemic infarction symptoms than after a month or longer [17]. During the long-term follow-up of 26 patients with cerebral infarction,

he found that the CCD phenomenon may occur from the 5th to the 1,825th day after infarction symptoms, and that it is a relatively persistent phenomenon. Shin *et al.* found that when a F-18 FDG PET examination was conducted on laryngeal cancer patients who suffered left middle cerebral artery infarction 20 years ago, hypoperfusion occurred in the left side supratentorial blood supplying area by the middle cerebral artery and contralateral cerebellum, and glucose metabolism rate declined; which confirms the CCD phenomenon [18]. Some researchers found by a focal cerebral ischemia rat model that the activity of the contralateral cerebellum and blood flow would quickly decrease, while the middle cerebral artery and carotid artery were blocked [16, 19]. CCD may also occur in the hyperacute stage after infarction in the blood supplying area by cerebral artery [20]. Some scholars have detected the CCD phenomenon in cases of single-side supratentorial infarction three hours after symptoms via PET, and pointed out that the occurrence of CCD may be related with the area of local brain tissue injury, but not with the severity of hypoperfusion [21]. Therefore, the relationship between cerebral infarction stage and the CCD phenomenon remains controversial and needs further more in-depth studies.

Lesion area refers to the accumulated range affected by local brain tissue injury. Fu *et al.* found that the occurrence of CCD is unrelated with lesion size and the extent of hypoperfusion in supratentorial cerebral infarction [22]. Kim *et al.* also believes that the lesion area on supratentorial brain tissue is unrelated with the occurrence of CCD, but once CCD occurs, even if the area of primary lesion is relatively small, it may also play an important role in determining the severity of CCD [17]. However, several studies have also shown that when the supratentorial infarct area is relatively larger and involved in 2-3 lobes of the brain, CCD more likely occurs after cerebral infarction. Some scholars believe that the larger the infarct area is, the more likely is CCD to occur [23, 24].

Takasawa *et al.* considered that the location of the lesion in brain tissue injury may be a major determinant of CCD [25]. According to the current report, the cerebral cortex (mainly frontal and parietal lobe), basal ganglia, internal capsule and pons are the sites of primary lesion; which are likely to cause the CCD phenomenon [26]. Among cortical lesions, CCD caused by lesions in the parietal lobe is most serious, followed by those in the frontal and temporal lobes. Basal ganglia lesions are more likely to lead to CCD than lesions in the hypothalamus. Damage on the upper section of pons can also lead to CCD, while those in the middle and lower sections cannot. There is no necessary correlation between the nature of lesions and CCD. After infarction in the blood supplying area of the deep branches of the middle cerebral artery (internal capsule, basal ganglia) and in the wider coverage of the cortex, both may present severe metabolic reduction in the contralateral cerebellum [27]. Some academics have suggested that the CCD phenomenon only appears when damages are limited to the hindlimb of the internal capsule [28]. Alex *et al.* found that the CCD phenomenon occurred in patients with unilateral thalamus infarction [29], which further confirms that CCD is not confined to occur only after infarction in a large region of blood supplying area of the middle cerebral artery.

Xiaofei Geng *et al.* found that CCD may be related to the occurrence of cerebral hemiplegia and muscle strength, which may also reflect the situations of CCD to some extent, but not the deciding factor [30]. Biersack *et al.* found that CCD occurs mainly in patients with hemiplegia after cerebral infarction, and most non-hemiplegia patients do not show CCD [31]. This suggests that CCD may be due to the decrease of stimulations of the spinal cord and cerebellum caused by paralysis in the corresponding brain lobe.

With the progress of in-depth studies on CCD phenomenon, people found that rehabilitation situations of cerebral infarction patients accompanied by CCD were inferior to patients with cerebral infarction alone, while areas of supratentorial infarction of patients that show the CCD phenomenon were larger [32]. Although there are currently no data and reports that confirm the association between hypoperfusion in the cerebellum caused by CCD and permanent supratentorial infarction, imaging changes due to chronic nerve block suggest that the prognosis of patients with cerebral infarction combined with CCD is poor [33]. Furthermore, the CCD phenomenon can ebb in patients with good prognosis after reperfusion and vice versa. Takasawa *et al.* found that after

reperfusion of thrombolytic therapy, CCD phenomenon in patients with smaller infarct area can be gradually restored, and this rehabilitation situation is closely related to clinical outcome [25]. All these evidences above suggest that CCD is not only an associated symptom of cerebral infarction, but an important indicator of the therapeutic effect, function recovery and prognosis of patients with cerebral infarction.

As early as 1999, Seitz *et al.* [34] followed-up seven cases of patients with hemiplegia after cerebral infarction, and considered that the distant affected area induced by infarction anatomically overlap functional recovery regions; while local cerebral tissues in infarction patients may be related to the rehabilitation of motor function. Seitz conducted a PET test on seven cases of primary cerebral infarction patients, and results revealed that injury-related network anatomically overlap the rehabilitation-related network. In recent years, researchers have started to use Single-Photon Emission Computed Tomography (SPECT) and PET technology to study the post-infarction CCD phenomenon from various aspects. Bruine *et al*. found that the CCD phenomenon is significantly associated with hypoperfusion in supratentorial tissues, and the persistence of CCD indicated a poor prognosis and sustainable supratentorial tissue damage [35]. Some scholars have proposed that CCD may be a quantitative index for the evaluation of cerebral dysfunction after infarction [36]. In the subacute stage of cerebral infarction, for the location and extent of ischemic brain involved in CPC pathways, CCD phenomenon may provide valuable diagnostic cues [37, 38]. Watanabe *et al.* found that the severity of CCD was closely related to hemiplegia [39].

Some acute CCD symptoms are secondary to stroke and status epilepticus, which are reversible [40]. Acute and chronic CCD are different. After acute cerebral infarction, excitatory stimulations from the cerebral cortex to the cerebellum decrease, resulting in reduced excitability of cerebellar Purkinje cells, thereby causing acute CCD. When excitatory stimulations were accepted by cerebellum recovery, acute CCD can be quickly reversed [41]. However, persistent CCD was an irreversible process that can lead to neuronal degeneration, and caused the affected cerebellar hemisphere to atrophy. Controversies remain regarding whether the post-infarction CCD phenomenon can ebb over time. The third view was that not only would CCD not ebb with the improvement of infarction symptoms, but it would become more severe [42]. In summary, cerebral infarction can cause similar changes in the remote region where nerve fibers are linked to. Therefore, ischemic penumbra should be actively saved, and distant perfusion and metabolic reduced area should be focused on in clinical treatment.

Epilepsy

Massaro *et al.* conducted an MRI examination for a female patient diagnosed with persistent epilepsy, and found that the left temporal parietal, occipital cortex, left thalamus and right cerebellum grew restricted diffusion in large areas on DWI, which confirmed to be epileptic active status secondary to CCD [43]. After antiepileptic treatment, EEG examination revealed a remission of symptom; however, the patient continued to manifest mild aphasia and right hemiplegia, and the original site of restricted diffusion displayed an improvement on DWI. He also [43] suggests that epilepsy can render synaptic excitability to continue to increase, which passes to the contralateral cerebellum through the CPC pathway. Thus, excessive excitability caused the CCD phenomenon, while energy metabolism and cerebral blood flow increased; and hyperintense signals were revealed on DWI [44-46]. The causes for those may be hypoxia caused by failure in the regulation of energy metabolism and cerebral blood flow, which result in increased anaerobic glycolysis, followed by sodium-potassium pump deactivation and cytotoxic edema [47]. Although the CCD phenomenon after epilepsy can be attributed to injuries in the cerebral cortex and damage to neural connections, early damage may only be a functional impairment and an increase of excitatory signaling of the cerebral cortex. Dysfunction of the contralateral remote area caused by restricted cerebral cortex lesions indicates the mechanism of CCD after epilepsy. Clinical neuropathologic studies have confirmed that disinhibition of cortical neurons can lead to increased neuronal excitability in remote regions [48, 49]. Both above mechanisms can induce neurotoxicity injuries of brain cells, which can be found via imaging.

For the CCD phenomenon secondary to persistent epilepsy, signal enhancement may be seen

in the following parts in imaging examination: pulvinar thalami, caudate nucleus, putamen, globus pallidus and pad of corpus callosum; while the affected area shows angiectasis [50]. These symptoms are usually reversible, but sometimes these may be irreversible and lead to sustained damage. In status epilepticus, glutamic acid production increases which induces desensitization of γ-aminobutyric acid (GABA), and therefore sustains neuronal excitability and increase cerebral metabolic oxygen demand; and ultimately, the CPC pathway is damaged due to failure of compensation for excessively increased metabolic demand [51]. Whereas in patients with temporal lobe epilepsy, dorsal thalamus nucleus plays an important role in the process of transferring excitatory stimulation from the injured cerebral cortex to distant parts [52]. In short, in patients in status epilepticus, the CCD phenomenon and thalamus signal enhancement may be due to hyperactivity in the cortex of primary epileptic focus, and dysfunction of the pathway.

Brain trauma

A study found that unilateral focal brain trauma can lead to the reduction of metabolic rate in the contralateral cerebellum, with or without dysfunction and other symptoms [53]. Pathophysiological studies suggest that this phenomenon is induced by the inhibition of neural excitability transmitted through the CPC pathway to the pontine nuclei, which originates from primary supratentorial brain trauma lesions; but it remains inconclusive whether this is reversible. In CCD after traumatic brain injury, early pathology presents cerebellar atrophy, but this may be due to the sustained irreversible reduction of brain blood flow force caused by nerve degeneration; and this is quite contrary with the results of scholars' studies [54]. Some scholars believe that chronic irreversible cerebellar hypometabolism may be a secondary result of degenerative diseases. In addition, sustained changes may appear in the early stage, in which only changes in metabolism occur and that this is a reversible process. Brain trauma lesions in the cerebral cortex or its adjacent area may lead to crossed contralateral cerebellar metabolic reduction. However, complex brain trauma patients may show exceptions. CCD phenomenon is common in patients with severe brain trauma, which indicate that severe brain injury may be the primary cause of CCD. In addition, brain trauma patients with single lesions are more likely to show crossed contralateral cerebellar hypometabolism. In brain trauma patients with multiple lesions, larger lesions play a leading role for CCD [54]. Overtime, as brain trauma develops and outcomes, the metabolic rate of the cerebellum may also change with anatomic changes and interaction among lesions. The association between diffuse brain trauma and contralateral cerebellar metabolic abnormalities has not been reported, or maybe its manifestations of cerebellar metabolic abnormalities are different with those of single focus, which is because diffuse cerebellar lesions offset metabolic changes caused by each other. Therefore, obvious CCD phenomenon is rarely seen in patients with diffuse brain injury. If diffuse injury occurs in white matter fibers, the block of specific nerve impulses sent to the pontine nuclei from the original lesion would not occur. This can further explain the aforementioned phenomenon. Therefore, in brain trauma patients with diffuse axonal injuries, this "neutralizing effect" of crossed cerebellar hypometabolism is more common than in patients with simple brain injury. In summary, CCD phenomenon can also occur in patients with brain trauma, may be seen in patients with single or multiple lesions, but could not be seen in brain trauma patients with diffuse axonal injury. The clinical significance and its impact on the prognosis of CCD phenomenon after traumatic brain injury need further research and discussion.

Brain tumor

Glioma can cause a decreased rate of glucose metabolism in the contralateral cerebellum, suggesting that brain tumors can also be complicated by CCD. Since tumors in the frontal lobe are most common. In the same region, the cerebellar glucose metabolic rate is higher in malignant tumors than in poorly differentiated tumors [55]. The highest is that malignant tumors are primary in the frontal lobe and is involve in the parietal lobe, while extending to the midline; causing damage to all nerve bundles in the prefrontal, premotor and motor cortex that belong to the CPC pathway [56]. Since peritumoral edema surrounding well-differentiated glioma is more common than that of poor-

ly differentiated glioma, and different from the characteristic of metabolic abnormalities, in addition to the tumor occurrence site, the occurrence of CCD is related to the size of tumors rather than tumor metabolic abnormalities. In a study on a group of brain tumor patients after operation, researchers found that the CCD phenomenon may be related to the tumor itself, as well as surgery-induced brain damage. However, determining when the CCD phenomenon would occur in cancer patients remains to be studied. CCD in some patients may ease or disappear in a few days, but in some may aggravate or persist. According to the biological characteristics of the tumor, with the proliferation of tumor cells, edema formation, infiltration, and expansion of tumor invasion, CCD phenomenon may persist over time. Thus, the CCD phenomenon may be used as the indirect indicator of the evaluation of tumor infiltration and proliferation without changes in tumor metabolic parameters.

As early as 1990, some scholars reported that in a case of Sturge-Weber syndrome (SWS) patients, cerebral blood flow decreased while both brain tissue in the primary tumor area and contralateral cerebellum were affected; suggesting that a congenital ischemic disease can also cause the CCD phenomenon [57]. Masaaki *et al.* have also reported that in a rare case of adult Moyamoya disease in a patient, CCD occurred secondary to revascularization [58]. In a ^{123}I-IMP SPECT examination 17 months after operation, researchers found hyperperfusion in the right frontal and temporal lobe of the patient and significant reduction of blood flow in the left cerebellum. There are evidences that Moyamoya disease patients after revascularization may grow symptomatic cerebellar hyperperfusion, and primary vascular abnormalities in such patients can explain this phenomenon. Cianfoni *et al.* reported that they found the CCD phenomenon in encephalitis patients through MRI examination [59]. O'Gorman [60] also reported the existence of the CCD phenomenon in a case of 8-year-old patients with sickle cell anemia using arterial spin labeling magnetic resonance technique. CCD phenomenon has been repeatedly reported to be found in adult cerebral infarction, epilepsy, migraine, encephalitis and brain tumors; and reports on pediatric patients are relatively few. Diseases in which available literature have reported the discovery of CCD include cerebral infarction, seizures, encephalitis, migraines and damage on the chronic single side of the brain. Koy *et al.* reported that they found a left cerebellar diaschisis in a case of a three year-old child patient following the event of non-spasm status epilepticus in the right cerebral hemisphere [61]. CCD phenomenon is relatively rare in children's disease. In adult patients with cerebral infarction, the severity of CCD can be used as a quantitative indicator of long-term damage evaluation. However, for children patients, the relationship between CCD and prognosis of diseases remain unclear, the age when brain injury occurs may be an important factor of secondary lesions in the cerebellum [62], and the extent of damage to immature brain tissues caused by this phenomenon is less than that to adult brain tissues.

Imageologic tests

Since 1914, the concept crossed cerebral diaschisis was first proposed, ^{131}Xe, ^{123}I-IMP labeled PET, SPECT and perfusion-weighted imaging (PWI), diffusion tensor imaging (DTI), and other imaging techniques are used for the inspection of CCD to assess regional cerebral blood flow, oxygen metabolic rate and oxygen uptake score, and other parameters [63, 64]; among which, the more commonly used are SPECT and PET. In 1980, Baron [65] using PET confirmed the reduction of cerebral blood flow and the decrease of oxygen metabolic rate in the contralateral cerebellum in supratentorial infarction patients. This phenomenon was later confirmed by researchers applying SPECT perfusion imaging in a variety of diseases including internal capsule/basal ganglia infarction, brain tumor, spinocerebellar degeneration, Alzheimer's disease, epilepsy and progressive supranuclear palsy [66] CCD phenomenon can occur in the acute and chronic phase of cerebral infarction. Thus, SPECT was used to detect the CCD phenomenon in the acute phase (5-30 hours), subacute phase (5-15 days) and chronic phase (13-56 days) of infarction [67]; and the positive rate of CCD in each phase is over 60%. Some scholars found CCD in a patient 20 years after a cerebral vascular accident using F18-FDG-PET test. This case also shows that brain damage after the acute phase is irreversible and is of great significance for the research of

clinical changes and mechanisms of cerebral blood flow and perfusion in nuclear medicine.

The first discovery of the CCD phenomenon via MRI originated from Stubgen's report in 1995 [68], when conducting routine MRI examinations for a 32-year-old pregnant woman suffering from recurrent anxiety. Abnormal signals were discovered in the brain cortex and contralateral cerebellum, and it is considered as reversible excitatory cell damage. Thereafter, with the development of MRI technology, a variety of advanced new imaging technologies were also applied to explore the CCD phenomenon.

Perfusion-weighted imaging (PWI)

PWI is an inspection technique that noninvasively provides brain microcirculation status. This technique can be used to reflect the blood perfusion of local tissues and organs and microvascular distribution, and analyze hemodynamic and functional changes. The two main imaging methods are as follows: dynamic susceptibility contrast (DSC) and arterial spin labeling (ASL). The former is relatively more commonly applied including four parameters: (1) relative cerebral blood volume (rCBV), refers to the relative cerebral blood volume in interested regions including large blood vessels and capillaries; (2) relative cerebral blood flow (CBF), refers to the relative cerebral blood flow passing through the interested regions in unit time; (3) mean transit time (MTT), refers to the time for blood to flow through the blood vessels, mainly reflecting the time required for the contrast agent passing through the capillaries; (4) time to peak (TTP), refers to the time for the contrast agent to reach the highest concentration, mainly reflecting the time needed for blood flow to reach the interested regions [69]. The performances of CCD in PWI are prolonged TTP and reduction of cerebral blood flow. Thus, PWI is more increasingly used in clinical practice with its simple operation, no radiation, and higher spatial resolution. In recent years, ASL has emerged as a newly non-invasive magnetic resonance technique using free diffusing water as its endogenous contrast agents. It was the very technique that O'Gorman applied to successfully reveal the CCD phenomenon in a case of eight-year-old sickle cell anemia patient [60].

Diffusion-weighted imaging (DWI)

Currently, diffusion-weighted imaging (DWI) is the best way to invasively detect the diffusion movement of water molecules in living tissue. Its image is constructed according to the signal intensity reflecting the speed of water molecule diffusion movement in tissues. DWI image signal consists of the intensity of water molecule diffusion and T2 values of detected living tissues. The existence of T2 transmission effect in the image, to a certain extent, increases the incidence of false-positive rates; and therefore, the PWI image does not reflect the speed of diffusion movement in living tissues. The introduction of the concept of apparent diffusion coefficient (ADC) value and ADC map can eliminate this effect. Edgar *et al.* found in the DWI examination for episodic epilepsy patients that restricted diffusion occurred in the patient's left frontal and parietal lobes, the occipital cortex, left thalamus and right cerebellum; suggesting the existence of epilepsy-related CCD phenomenon [70]. Two weeks later, PWI examination was conducted again for the patient, and the high signal disappeared.

Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) is a magnetic resonance technique for the description of the direction characteristics of water molecule diffusion, which is performed by calculating the diffusion degree of water molecules and diffusion direction; and it can indirectly evaluate the integrity of white matter fibers. DTI is gained by applying a plurality of gradient fields of non-linear directions on the basis of MRI. DTI not only reflects the overall situation, but also reflects the directivity of water-restricted diffusion [71]; and it is currently the only non-invasive method for effectively detecting and tracking fiber tracts of white matter.

The commonly used parameters of DTI include: fractional anisotropic (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), relative anisotropy (RA) and volume ratio (VR).

ADC and FA are relatively extensively applied. (1) The unit of ADC values is mm^2/s. It can exhibit the diffusion speed and range of different water molecules in magnetic resonance diffusion-weighted imaging, but it cannot distinguish the direction of diffusion [72]. The ADC value is proportional to the content and diffusion capacity of free water molecules in tissues, reflects the overall diffusion speed of water molecules in brain tissues, is mainly closely related to vasogenic edema, cytotoxic

edema and the structural integrity of cells, and it can display the micro-structure information inside and outside cells. (2) FA refers to the ratio of anisotropic components of diffusion tensor in total diffusion tensor, which reflects the degree of anisotropy of water molecules in diffusion in brain tissues [73]. FA values range from 0 to 1, where 0 represents the greatest degree of isotropic diffusion, while 1 represents the greatest degree of anisotropic diffusion. FA values and its changes are related with the following factors: integrity of the myelin, compactness and parallel of the fibers, and FA value is not the same in different parts of the white matter. For example, the fiber bundle arranged in neat rows and represents a well-integrity of axonal structure has high anisotropy. This is because water molecules that move parallel to compactly arranged white matter fiber tracts have the fastest diffusion speed, suggesting that the partial axonal structures of brain tissues have well-integrity and the strongest conductivity. Then, the contrast is that the degree of anisotropy of the disorganized white matter fiber bundle is low, mainly due to the loss of directionality and consistency of the arrangement of nerve fiber bundles caused by diseases.

Due to its capacity of reflecting the integrity of white matter fiber tracts, DTI has been more widely used clinically including the evaluation of cerebral infarction, brain tumor, diffuse axonal injury and primary or secondary white matter lesions, etc. [74, 75] Stenset *et al.* confirmed the existence of diaschisis in the ipsilateral hemisphere via DTI technique [76]. They measured FA values of the bilateral white matter in patients with left side cerebral infarction. FA values of the white matter in left hemisphere were significantly lower than in the right hemisphere. Jinna Kim *et al.* conducted DTI inspection on 23 patients with chronic cerebral infarction and measured FA values. They found that FA values in contralateral brain tissues were significantly lower than in the affected side; thus, this further confirmed the value of DTI for detecting changes in fibres of corticocerebellar tracts in CCD patients after cerebral infarction [12].

In recent years, due to the advances in cerebral hemodynamics, through the metabolic measurement technique and imaging technique, people made great progress in the study on the mechanism and clinical treatment of diaschisis; which explained many clinical problems through the application of this theory. This theory has certain significance in the clinical diagnosis and treatment of CCD, and has a certain influence in the rehabilitation process of patients with cerebral infarction. Early recognition and treatment of CCD is of great help for the improvement of focal neurological damage and functional recovery after cerebral injuries.

Disclosure of conflict of interest

None.

Address correspondence to: Jing-Liang Cheng, Department of MRI, The First Affiliated Hospital of Zhengzhou University, No. 1 of Jianshe East Road, Erqi District, Zhengzhou 450052, China. Tel: +86 13603863860; Fax: +86 0371-66913114; E-mail: jingliangchengdor@163.com

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