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Why do stroke patients with negative motor evoked potential show poor limb motor function recovery?

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Research Highlights

(1) Results from this study showed that the fractional anisotropy values in the cerebral peduncle in patients with negative motor evoked potentials after cerebral infarction decreased most obviously within 1–3 months after disease onset, and the drop critical value of fractional anisotropy value of 0.36 occurred during this time period, indicating poor limb motor function recovery.
(2) Patients with negative motor evoked potentials after cerebral infarction presented with a ken area of the cerebral peduncle on the affected side at 6 months after disease onset, and even worse outcomes in the subsequent months until 12 months, with a lower limit value of area asymmetry of 0.83, indicating poor limb motor function recovery.

Abstract

Negative motor evoked potentials after cerebral infarction, indicative of poor recovery of limb motor function, tend to be accompanied by changes in fractional anisotropy values and the cerebral peduncle area on the affected side, but the characteristics of these changes have not been reported. This study included 57 cases of cerebral infarction whose motor evoked potentials were tested in the 24 hours after the first inspection for diffusion tensor imaging, in which 29 cases were in the negative group and 28 cases in the positive group. Twenty-nine patients with negative motor evoked potentials were divided into two groups according to fractional anisotropy on the affected side of the cerebral peduncle: a fractional anisotropy < 0.36 group and a fractional anisotropy ≥ 0.36 group. All patients underwent a regular magnetic resonance imaging and a diffusion tensor imaging examination at 1 week, 1, 3, 6 and 12 months after cerebral infarction. The Fugl-Meyer scores of their hemiplegic limbs were tested before the magnetic resonance and diffusion tensor imaging tions. In the negative motor evoked potential group, fractional anisotropy in the affected cerebral peduncle declined progressively, which was most obvious in the first 1–3 months after the onset of cerebral infarction. The areas and area asymmetries of the cerebral peduncle on the affected side were significantly decreased at 6 and 12 months after onset. At 12 months after onset, the area asymmetries of the cerebral peduncle on the affected side were lower than the normal lower limit value of 0.83. Fugl-Meyer scores in the fractional anisotropy ≥ 0.36 group were significantly higher than in the fractional anisotropy < 0.36 group at 3–12 months after onset. The fractional anisotropy of the cerebral peduncle in the positive motor evoked potential group decreased in the first 1 month after onset, and stayed unchanged from 3–12 months; there was no change in the area of the cerebral peduncle in the first 1–12 months after cerebral infarction. These findings confirmed that if the fractional anisotropy of the cerebral peduncle on the affected side is < 0.36 and the area asymmetries < 0.83 in patients with negative motor evoked potential after cerebral infarction, then poor hemiplegic limb motor function recovery may occur.

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Key Words

neural regeneration; neuroimaging; cerebral infarction; motor evoked potential; fractional anisotropy; cerebral peduncle; magnetic resonance diffusion tensor imaging; grants-supported paper; neuroregeneration

INTRODUCTION

Wallerian degeneration occurs in the pyramidal tract after cerebral infarction, which can negatively affect the restoration of limb movement. Fractional anisotropy of the cerebral peduncle on the affected side declines progressively after cerebral infarction in early stages, and cerebral peduncle atrophy in later stages can be detected by diffusion tensor imaging (DTI). Motor evoked potentials provide an objective quantitative index of reflecting the functional status and integrity of the pyramidal tract and can be used to probe the status of neurofunctional recovery after cerebral infarction.

It has been reported that secondary neuronal loss occurs in the ventral nucleus of the thalamus, brainstem and spinal cord after middle cerebral artery occlusion, and a decrease in fractional anisotropy values in relevant regions can be shown using DTI[1-4]. The fractional anisotropy value can reflect the integrity of pyramidal tract fibers. Lower fractional anisotropy values indicate worse myelin integrity, fiber density and parallelity[5-6].

Liang *et al* [7] have found that decreased fractional anisotropy signals from the internal capsule, cerebral peduncle, pons and medulla oblongata on the affected side can be observed on a DTI fractional anisotropy map from 1 to 12 weeks after middle cerebral artery occlusion. These signals are equivalent to the route of the pyramidal tract and the attenuation becomes more apparent with time. However, the scores of limb motor function (Fugl-Meyer scores; FM scores) become gradually and significantly higher from 1 to 12 weeks after illness. These findings conflict with the phenomenon that more obviously decreased fractional anisotropy values of the corticospinal tract after cerebral infarction leads to more severe impairment of motor function in the early stage and at 3 months after cerebral infarction[8]. The underlying reason for this contradiction requires further investigation.

Mark *et al* [9] studied the bilateral cerebral peduncle areas in 34 hemiplegic patients who suffered from supratentorial cerebral infarction for more than 1 year. They found that the size of the cerebral peduncle area on the affected side was just 72% of that on the contralateral side. Warabi *et al* [10] divided hemiplegic patients who suffered from cerebral infarction for more than 1 year into three groups according to the asymmetry ratio of the cerebral peduncle: < 0.6, = 0.6 and > 0.6[10]. The authors noted that 0.6 was considered as the critical value of cerebral peduncle area ratio, thus < 0.6 indicates that limb motor function could not be recovered, = 0.6 indicates that limb motor function could be recovered to some degree, and > 0.6 indicates that limb motor function could be well recovered. Atrophy of cerebral peduncle may occur as much as 1 year after cerebral infarction and the degree of atrophy is related to the recovery of limb motor function.

However, why does the cerebral peduncle atrophy occur within 1 year of cerebral infarction? What is the impact of cerebral peduncle atrophy on limb motor function recovery? All of these questions require further study. Motor evoked potentials, an objective quantitative index, can be used to reflect the functional status and integrity of the pyramidal tract and to speculate on neurofunctional recovery. The limb motor function of stroke patients with negative motor evoked potentials does not tend to exhibit good reco- very, a phenomenon that is reversed for patients with positive motor evoked potentials[11-13]. For patients with normal motor evoked potentials in the acute phase, neurofunctional deficit scores in the convalescent period were improved significantly

from the acute phase. For patients with abnormal motor evoked potentials, especially loss of motor evoked potentials in the acute phase, neurofunctional deficit scores in the convalescent period deteriorated or did not improve compared with the acute phase.

Motor evoked potential change and the Wallerian degeneration state after cerebral infarction depend on the extent and location of the primary lesion and the relationship with the pyramidal tract[11-14]. We hypothesize that changes in cerebral peduncle fractional anisotropy caused by Wallerian degeneration after cerebral infarction should be consistent with changes in motor evoked potentials (*i.e.*, the prognosis is poor when motor evoked potentials are negative, motor conduction time is prolonged and the fractional anisotropy value of the cerebral peduncle is decreased). Liang *et al* [7] reported that the fractional anisotropy value of the cerebral peduncle on the affected side progressively decreased in the 12 weeks following cerebral infarction, but limb motor function scores gradually increased, which conflicts with the conclusion that lower fractional anisotropy values indicate a poorer prognosis[8]. This result calls into question the relationship between the evaluation of the Wallerian degeneration state and limb motor function recovery after cerebral infarction using fractional anisotropy values.

There are two possibilities for any patient with limb paralysis after cerebral infarction who is tested using motor evoked potentials: positive or negative. However, the results of limb motor function recovery are completely different. The possibility that the cases selected by Liang *et al* [7] might only contain patients with positive motor evoked potential whose limb motor function score might be affected cannot not be excluded, which may lead to this contradiction. The fractional anisotropy changes in the cerebral peduncle in healthy volunteers has been studied and the lower limit value of fractional anisotropy of the cerebral peduncle in healthy volunteers is 0.36[15]. The relationship between the fractional anisotropy of the cerebral peduncle after cerebral infarction and changes in motor evoked potentials was determined in another study[16]; the results showed that changes in the fractional anisotropy of the cerebral peduncle after cerebral infarction were consistent with changes in motor evoked potentials. When the fractional anisotropy of the cerebral peduncle on the affected side is < 0.36, prognosis should be poor, particularly in patients with negative motor evoked potentials. However, the impact on prognosis when the fractional anisotropy of the ipsilateral cerebral peduncle is less than 0.36 needs to be further studied. There is a variation in the area of the cerebral peduncle in healthy volunteers, and the lower limit value of the cerebral peduncle area and asymmetry in this study was 0.84 cm^2 and 0.83[15].

When does the change in the cerebral peduncle area occur after cerebral infarction-caused Wallerian degeneration? What are the characteristics of cerebral peduncle area changes in patients with negative and positive motor evoked potentials? There have been no studies addressing these questions. Only by determining the precise time point after cerebral infarction at which the cerebral peduncle area is shrunk can we accurately evaluate the Wallerian degeneration state after cerebral infarction according to the cerebral peduncle area.

This study mainly investigated the relationship between characteristics of cerebral peduncle fractional anisotropy values and area on the affected side and limb motor function recovery in patients with negative motor evoked potential after cerebral infarction. It further investigated the effects of the lower limit value of the cerebral peduncle on limb motor functional recovery in these patients.

RESULTS

Quantitative analysis of subjects

Sixty-three patients with cerebral infarction were included in this study. Of them, five were lost, one died and the remaining 57 patients received motor evoked potential detection within 24 hours after a diffusion tensor imaging examination. Twenty-nine patients were confirmed with negative motor evoked potential results (negative group) and 28 with positive results (positive group). The negative group was subdivided into two groups according to fractional anisotropy of the cerebral peduncle (< 0.36 and ≥ 0.36). All 57 patients were included in the final analysis.

Baseline analysis of subjects

There were no significant differences in cerebral infarction patients' age, gender and other indices between patients with negative and positive motor evoked potentials ($P > 0.05$; Table 1).

Cerebral peduncle fractional anisotropy value and area and hemiplegic limb's Fugl-Meyer scores in the negative group at different time periods

There were no statistically significant differences in ce-

rebral peduncle fractional anisotropy value and area, or in the hemiplegic limb's Fugl-Meyer scores in the negative group at 1 week and at 1, 3, 6, and 12 months after cerebral infarction. In these patients, fractional anisotropy of the cerebral peduncle and asymmetries on the affected side decreased progressively with time. The fractional anisotropy of the cerebral peduncle decreased slowly except in the first 3 months. Cerebral peduncle area on the affected side and its asymmetry declined significantly after cerebral infarction at the 6- and 12-month points compared with previous stages (P < 0.05). At 12 months after cerebral infarction, the area asymmetry of the cerebral peduncle on the affected side was significantly lower than the lower limit of 0.83[15] (Table 2). Typical MRI results are shown in Figure 1.

Hemiplegic limb Fugl-Meyer scores in the negative group at different time periods

There was no statistically significant difference in hemiplegic limb Fugl-Meyer scores between the fractional anisotropy < 0.36 group and the fractional anisotropy ≥ 0.36 group at either 1 week or 1 month after cerebral infarction. The Fugl-Meyer scores in the fractional anisotropy ≥ 0.36 group were gradually and significantly higher than in the fractional anisotropy < 0.36 group at 3–12 months (P < 0.05; Table 3).

Cerebral peduncle fractional anisotropy value and area and hemiplegic limb's Fugl-Meyer scores in the positive group at different time periods

There were periodic significant differences in cerebral peduncle fractional anisotropy on the affected side, cerebral peduncle asymmetries and the hemiplegic limb's Fugl-Meyer scores (P < 0.05). The cerebral peduncle fractional anisotropy and asymmetries in the positive group decreased significantly 1 month after cerebral infarction (P < 0.05).

Cerebral peduncle fractional anisotropy and asymmetries at the 1-week time point were significantly lower than in the other time periods (P < 0.05). There was a significant difference in the hemiplegic limb's Fugl-Meyer scores at the 1-week and 1-month points after cerebral infarction compared with other time periods (P < 0.05) and no significant differences were detected at the 3-, 6- and 12-month time points (Table 4).

Table 1 Baseline analysis of subjects

Item	Negative motor evoked potential (n = 29)	Positive motor evoked potential (n = 28)	t	χ^2	P
Age (mean±SD, year)	66.3±13.3	70.6±9.55	1.349		0.189
Male	16(55)	13(46)		0.436	0.509
Female	13(45)	15(54)		0.436	0.509
Hypertension	13(45)	9(32)		0.967	0.325
Hyperlipemia	12(41)	11(39)		0.026	0.872
Diabetes mellitus	4(14)	1(4)		1.860	0.173
Smoke	10(34)	10(36)		0.009	0.922
Drinking	10(34)	10(36)		0.099	0.922
Cardiopathy	3(10)	1(4)		1.002	0.317

Independent sample t-test and chi-square test were used. The data with the exception of age are expressed as n (%).

Table 2 Cerebral peduncle fractional anisotropy (FA) value, area, asymmetry and Fugl-Meyer (FM) scores in patients with negative motor evoked potential at different time periods

Time after cerebral infarction	FA of cerebral peduncle on the affected side	FA of cerebral peduncle on the healthy side	FA asymmetry	Cerebral peduncle area on the affected side (cm^2)	Cerebral peduncle area on the healthy side (cm^2)	Area asymmetry	FM scores
1 week	0.42±0.11	0.55±0.08	0.79±0.26	1.18±0.22	1.21±0.21	0.98±0.06[a]	5.04±0.19
1 month	0.37±0.06[a]	0.55±0.08	0.69±0.16[a]	1.18±0.22	1.21±0.21	0.98±0.06	5.24±0.91
3 months	0.33±0.05[ab]	0.55±0.08	0.63±0.15[a]	1.18±0.22	1.21±0.21	0.98±0.06[c]	5.58±4.13
6 months	0.31±0.06[ab]	0.55±0.08	0.58±0.15[ab]	1.02±0.17[ab]	1.21±0.21	0.85±0.10[ab]	6.52±6.63
12 months	0.28±0.07[abc]	0.55±0.08	0.52±0.16[ab]	0.88±0.18[abc]	1.21±0.21	0.73±0.14[abc]	7.10±8.12
F	14.767	0.034	15.556	15.87	1.806	18.447	0.882
P	0.000	0.998	0.000	0.000	0.171	0.000	0.476

[a]P < 0.05, *vs*. 1 week after cerebral infarction; [b]P < 0.05, *vs*. 1 month after cerebral infarction; [c]P < 0.05, *vs*. 3 months after cerebral infarction. Data were expressed as mean ± SD. Repeated measures analysis of variance was used. FM scale is a measure of limb function, with higher scores reflecting greater function (maximum 66). Each movement tested is given a score of 0 (movement cannot be performed), 1 (reduced strength, speed, amplitude or precision) or 2 (normal).

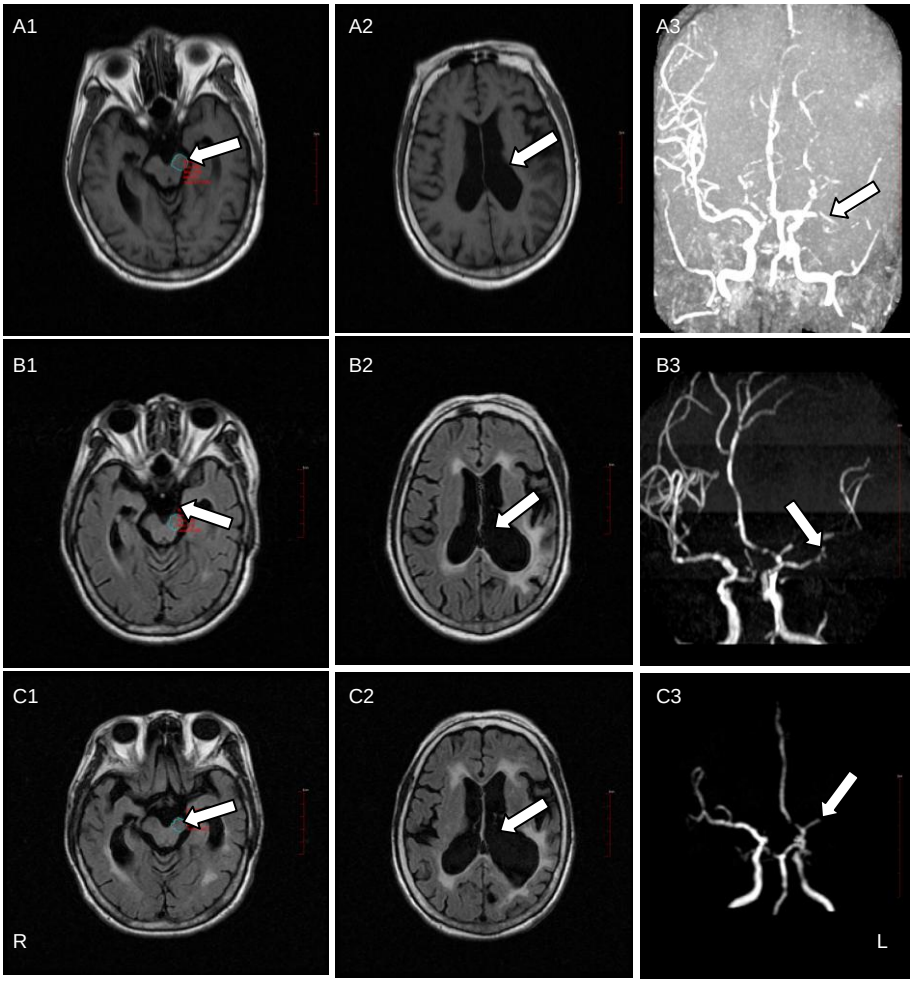

Figure 1 MRI manifestation of a 69-year-old male patient with negative motor evoked potentials after cerebral infarction.

The patient was hospitalized for the right limb fatigue for 1 day and negative motor evoked potentials were detected. A1–A3, B1–B3, C1–C3 indicate changes in the cerebral peduncle area, lateral ventricle magnetic resonance angiography and middle cerebral artery angiography images at 1, 6 and 12 months after cerebral infarction. The cerebral peduncle area on the affected side was shrunken at 6 months after cerebral infarction (B1) and the shrinkage was more obvious at 12 months (C1). The lateral ventricle on the affected side was gradually enlarged (A2–C2) and the middle cerebral artery imaging (A3–C3) gradually became worse (A3–C3).

The arrows from left to right in each panel indicate the cerebral peduncle, lateral ventricle and the blood supply in the middle cerebral artery.

Table 3 Fugl-Meyer (FM) scores in the fractional anisotropy (FA) < 0.36 and ≥ 0.36 groups at different time periods

Group	1 week		1 month		3 months		6 months		12 months	
	n	FM score	*n*	FM score	*n*	FM score	*n*	FM score	*n*	FM score
FA < 0.36	6	5.00±0.00	10	5.00±0.00	16	4.00±0.00[a]	21	4.00±0.00[a]	25	4.00±0.00[a]
FA ≥ 0.36	23	5.00±0.00	19	5.37±1.11	13	7.34±5.68	8	13.12±10.36	4	26.50±5.75

All data were expressed as mean ± SD. [a]$P < 0.05$, *vs*. FA ≥ 0.36 group. An independent-sample *t*-test was used.

Cerebral peduncle fractional anisotropy value between affected and healthy sides

Fractional anisotropy values on the affected side were lower than on the healthy side in the negative group at each period ($P < 0.05$). There was a statistically significant difference in fractional anisotropy value between the affected and healthy sides of the cerebral peduncle at each period except for the 1-week time point ($P < 0.5$; Table 5).

Table 4 Cerebral peduncle fractional anisotropy (FA) value, area, asymmetry and Fugl-Meyer (FM) scores in patients with positive evoked potential at different time periods

Time after cerebral infarction	FA of cerebral peduncle on the affected side	FA of cerebral peduncle on the healthy side	FA asymmetry	Cerebral peduncle area on the affected side (cm^2)	Cerebral peduncle area on the healthy side (cm^2)	Area Asymmetry	FM scores
1 month	0.45±0.07[a]	0.51±0.06	0.88±0.15[a]	1.18±0.19	1.19±0.20	1.00±0.12	52.17±4.81[a]
3 months	0.45±0.06[a]	0.51±0.06	0.88±0.13[a]	1.18±0.20	1.19±0.20	1.00±0.12	64.71±2.79[ab]
6 months	0.46±0.07[a]	0.52±0.05	0.88±0.15[a]	1.18±0.20	1.19±0.20	1.00±0.12	66.00±0.00[ab]
12 months	0.46±0.06[a]	0.51±0.07	0.90±0.15[a]	1.18±0.20	1.19±0.20	1.00±0.12	66.00±0.00[ab]
F	51.683	0.406	4.790	0.008	0.002	0.040	1.323
P	0.000	0.803	0.006	1.000	1.000	0.997	0.000

[a]*P* < 0.05, *vs*. 1 week after cerebral infarction; [b]*P* < 0.05, *vs*.1 month after cerebral infarction. Data were expressed as mean ± SD, *n* = 28. Repeated measures analysis of variance was used.

DISCUSSION

Characteristics of cerebral peduncle fractional anisotropy and limb motor function recovery among patients with cerebral infarction under different conditions of motor evoked potential

Experimental results from this study showed that the fractional anisotropy of the cerebral peduncle on the affected side decreased progressively and hemiplegic limb motor function recovery was poor in the negative motor evoked potential group. However, fractional anisotropy of the cerebral peduncle on the affected side decreased transiently and remained unchanged, and limb motor function recovery was better in the positive motor evoked potential group.

Motor evoked potentials reflect the functional status of the pyramidal tract. The absence of motor evoked potentials does not mean that the pyramidal tract is blocked completely; it may be the result of the cortex not being stimulated enough to excite the postsynaptic potential of the corresponding spinal cord motor neuron, therefore absence of motor evoked potentials does not mean that limb motor function is irreparable[11-13, 17-18]. The present experimental results showed that the fractional anisotropy of the cerebral peduncle on the affected side decreased progressively in the negative group in the first 12 months, while the Fugl-Meyer scores on the affected side tended to increase gradually but not significantly. These results suggest that there were some patients whose limb motor function recovered in this research group, which contradicts the findings from other studies[3, 5-7, 19-20]. A large amount of evidence has demonstrated that fractional anisotropy values in the affected corticospinal tract decrease progressively while Fugl-Meyer scores significantly improve in the first 6 months after cerebral infarction in the middle cerebral artery distribution area[3, 5-7, 19-20]. This phenomenon occurs mainly because in the previous studies the middle cerebral artery distribution area was the only factor considered during patient selection and the influence of lesions on pyramidal tract function was not fully taken into account. Results from this study showed that there were significant differences in Fugl-Meyer scores 1 week and 1 month after cerebral infarction compared with other periods in the positive group. However, Fugl-Meyer scores were not significantly different after 3 months between each period and were maintained at a relatively high level, and limb motor function in the positive group recovered and was close to the normal level at 3 months. These findings indicate that the previous conclusion about Fugl-Meyer scores indicating a change in characteristics of the pyramidal tract based on the distribution area of vessels after cerebral infarction, the only factor for patient selection, was not rigorous[3, 5-7, 19-20].

Table 5 Cerebral peduncle fractional anisotropy (FA) on both affected and healthy sides at each period

Group	Item	*n*	1 week	1 month	3 months	6 months	12 months
Negative motor evoked potential	FA on the affected side	29	0.42±0.11[a]	0.37±0.6[a]	0.33±0.06[a]	0.31±0.06[a]	0.28±0.07[a]
	FA on the healthy side	29	0.55±0.08	0.55±0.08	0.55±0.08	0.55±0.08	0.55±0.08
Normal motor evoked potential	FA on the affected side	28	0.52±0.08	0.45±0.07[a]	0.45±0.06[a]	0.46±0.07[a]	0.46±0.06[a]
	FA on the healthy side	28	0.53±0.07	0.51±0.06	0.51±0.06	0.52±0.05	0.51±0.07

[a]*P* < 0.05, *vs*. cerebral peduncle FA in the same group at the same time point (paired sample *t*-test). All data were expressed as mean ± SD. There were 29 patients in the negative motor evoked potential group and 28 patients in the positive motor evoked potential group.

This problem will lead to false positive results in that when fractional anisotropy of the cerebral peduncle on the affected side decreases progressively, limb motor function score increases gradually.

In the previous studies, the concept of a lower limit value was not proposed and the fastest drop period was not described. This is because most previous studies focus on observation within 3 months and in the chronic stage of cerebral infarction (6–24 months), but a dynamic observation of fractional anisotropy of the cerebral peduncle on the affected side in the same group of patients was lacking[5-7, 19-21].

Results from this study showed that fractional anisotropy of the cerebral peduncle on the affected side in the negative motor evoked potential group decreased most obviously in the first 3 months, and the lower limit value of fractional anisotropy of the cerebral peduncle on the affected side was 0.36. The fractional anisotropy of the cerebral peduncle on the affected side decreased to 0.37 after 1 month, which was close to the normal value of 0.36[15]. However, fractional anisotropy of the cerebral peduncle on the affected side at 3 months after cerebral infarction was 0.33, which is lower than the lowest value (0.36) from the healthy subjects. These findings further confirm that the lower limit value in the negative motor evoked potential group occurred from 1 to 3 months after cerebral infarction. There was no lower limit value on fractional anisotropy of the cerebral peduncle on the affected side in the positive motor evoked potential group.

Wallerian degeneration of cortical spinal cord tract was divided into four stages by scholars[21-23]: The first stage was at 1–4 weeks after cerebral infarction, and there was only neuraxial physical degradation with slight myelin biochemical changes. The second stage was at 4–14 weeks; the myelin protein was damaged at this time and the myelin lipid was still intact with increased lipid/protein ratio and hydrophobic organization. The third stage occurred up to 12 months after cerebral infarction, where degenerative tissue became hydrophilic, and myelin lipids were also damaged with neuroglia hyperplasia. The fourth stage occurred about 12 months to several years after cerebral infarction, and the major change was the atrophy of the cerebral peduncle. The stages of Wallerian degeneration after cerebral infarction described by Wang and colleagues[14] were different from Kuhn's findings in terms of the time at which each stage occurred, and the same in terms of the pathologic changes in each stage. Wang and colleagues[14] suggested that the first stage was 3–4 weeks after stoke, the second stage from 4 to 10 weeks, the third stage from 10 to 14 weeks, and the fourth stage from 4 to 12 months.

Results from this study showed that the duration of the fractional anisotropy drop occurred mainly during the second or third stage of pathological Wallerian degeneration. The time of the lower limit value shown by our data was consistent with that of the second or third stages of Wallerian degeneration described by Wang and colleagues[14]. Many studies have confirmed that the time of each period described by Wang and colleagues[14] is more reasonable[24-29]. The persistent decline of fractional anisotropy of the cerebral peduncle on the affected side in patients with negative motor evoked potentials after cerebral infarction reflects the whole process of secondary fiber decomposition and destruction of the cerebral peduncle, which is consistent with the course of disease.

However, in patients with positive motor evoked potentials, changes in fractional anisotropy of the cerebral peduncle on the affected side was not consistent with the pathological course of Wallerian degeneration[22-23]. There was a statistically significant difference in fractional anisotropy of the cerebral peduncle on the affected side between 1 month and 1 week after cerebral infarction, and no significant difference was found between 1 month and other time periods.

The fractional anisotropy of the cerebral peduncle on the affected side at 1 week after cerebral infarction was significantly different from other time periods (1 month to 1 year after cerebral infarction), but it was similar to that on the healthy side at 1 week after cerebral infarction. From 1 to 12 months after cerebral infarction, the fractional anisotropy of the cerebral peduncle on the affected side was lower than on the healthy side. The primary reasons are as follows: at 1 week after cerebral infarction, Wallerian degeneration occurs in only a small amount of pyramidal tracts and this process is mainly biochemical changes; at 1 month after cerebral infarction, this disease worsens greatly and the whole pathological process of Wallerian degeneration is finished with time. This process leads to the fractional anisotropy of the cerebral peduncle on the affected side at each time period always being lower than that on the healthy side, but the progressive decrease in fractional anisotropy on the healthy side is not present because of the extremely limited number of degenerative fibers. At 1 week after cerebral infarction, the fractional anisotropy of the cerebral peduncle on the affected side in

patients with negative motor evoked potentials is lower than that on the healthy side, which occurs possibly because a large amount of fibers began to present with Wallerian degeneration.

The large amount contributes to a significant difference in fractional anisotropy of the cerebral peduncle between healthy and affected sides. Thus, when studying Wallerian degeneration of the pyramidal tract on the affected side in patients with cerebral infarction, vascular distribution area cannot be considered as the only condition because the fractional anisotropy of the cerebral peduncle on the affected side when negative motor evoked potentials occur is greatly different from when positive motor evoked potentials occur, leading to inaccurate outcomes.

The relationship between the lower limit value of cerebral peduncle fractional anisotropy and limb motor function recovery in the negative group

The present experimental results showed that fractional anisotropy of the cerebral peduncle on the affected side in the negative group was < 0.36, which suggests poor hemiplegic limb motor function recovery. From Table 3, we can know that when motor evoked potentials were negative and the fractional anisotropy of cerebral peduncle on the affected side was < 0.36, the Fugl-Meyer scores from disease onset to end remained at a stable level. From the third month, Fugl-Meyer scores in the ≥ 0.36 group gradually increased and were different from that in the < 0.36 group, which suggests that when motor evoked potentials are negative and the fractional anisotropy of the cerebral peduncle on the affected side is < 0.36, limb motor function recovery on the affected side is impossible, while when the fractional anisotropy of the cerebral peduncle on the affected side is ≥ 0.36, limb motor function will recover to some degree.

Evidence exists that hemiplegic limb motor function recovers to different degrees within 1 year[30-32], which is consistent with the present findings regarding negative motor evoked potential from the ≥ 0.36 group and stable Fugl-Meyer scores from the < 0.36 group. This suggests that all stages of Wallerian degeneration have been accomplished and may continue to worsen[33-34], which indicates that there is a poor prognosis of motor function recovery in this group.

The relationship between the changes in cerebral peduncle area on the affected side and limb motor function recovery in the negative group

The cerebral peduncle area on the affected side began to become smaller 6 months after cerebral infarction and the patients' conditions became more serious. If the asymmetries of the cerebral peduncle area < 0.83 after cerebral infarction, then hemiplegic limb motor function recovery tended to be poor. Table 2 shows that cerebral peduncle atrophy began at 6 months after cerebral infarction, but the asymmetry of the cerebral peduncle area (0.85 ± 0.10) was not lower than the normal lower limit (0.83)[15], while the asymmetry of the cerebral peduncle area on the affected side decreased and was below the lowest limit (0.83) after 12 months. From the point of view of the asymmetry of the cerebral peduncle area, cerebral peduncle atrophy in the negative group had begun at 6 months after cerebral infarction. A diminished cerebral peduncle area and an expanded ipsilateral lateral ventricle can be seen in the present experimental data.

The figure of the patient with middle cerebral artery occlusion at M1 shows that cerebral peduncle atrophy occurred at 6 months and was more obvious at 12 months with more severe occlusion of the artery, while a diminished cerebral peduncle area was found only 1 year later[21, 35-37]. It has been reported in China that cerebral peduncle atrophy of patients with cerebral vascular disease can occur at 9 months after cerebral infarction[38].

Our study showed that cerebral peduncle atrophy can occur at 6 months after cerebral infarction, and the occurrence time was consistent with the Wallerian degeneration time at the fourth stage described by Wang *et al* [14] (several months to 12 months). Several respects were similar to those reported by Wang and colleagues[14].

There were obvious shortcomings about their study from 9 months, for exmple that the normal lowest limit of the cerebral peduncle area should not be suitable for Wallerian degeneration state evaluation after the cerebral infarction, but only for a self-control study. In addition, cerebral peduncle area changes are vulnerable to age and brain lesion position, *i.e*., cerebral peduncle areas in aging people are smaller than in young people and cerebral peduncle areas in patients with leukoaraiosis and Binswanger are smaller than in healthy people[39-43].

The asymmetry of the cerebral peduncle area clearly reflects the status of the area ratio variation of the cerebral peduncle, and is not influenced by age and the symmetry of brain lesions[39-43]; this makes it suitable for judging Wallerian degeneration at stage 4[22-23]. There was no statistically significant difference in asymmetry of the cerebral peduncle area between 1 and 3 months after cerebral infarction, but a significant difference was found between 3 and 6 months after cerebral infarction,

suggesting that asymmetry of the cerebral peduncle area was synchronized with the change in the area of the cerebral peduncle. From Table 2, we know that the asymmetry of the cerebral peduncle on the affected side at 6 months after cerebral infarction was 0.85, while our present results showed that the lower limit value of the cerebral peduncle area was 0.83. This result suggests that most fibers in the pyramidal tract had just begun to enter into Wallerian degeneration at stage 4; more fibers in the pyramidal tract had entered into Wallerian degeneration at stage 4 at 12 months because the area asymmetry was 0.73, which is much lower than the normal lower limit of area asymmetry. This also suggests that Wallerian degeneration at stage 4 does not begin at 1 year after cerebral infarction.

The asymmetry of the cerebral peduncle area reported by scholars outside China from 1 year to several years after stroke was from 0.60 to 0.72, and limb motor function recovery was poor[9-10]; we found a similar value of 0.73 at 12 months after cerebral infarction. This also indicates that the lower limit value of cerebral peduncle area asymmetry appears between 6 and 12 months after cerebral infarction.

There are shortcomings in this study. First, the paralysis degree and area asymmetry condition could not be affirmed at onset; second, hemiparalysis itself was an indicator of poor prognosis, *i.e*., 0.6 was lower than 0.83, as patients with stroke whose area asymmetry was lower than 0.83 tended to have a poor prognosis; lastly, Wallerian degeneration degree and speed depended on primary lesion degree, location and relationship with the pyramidal tract after cerebral infarction[9, 14, 24-28].

The criteria for selecting patients in this study lacked much variation in terms of lesion degree, location and relationship with the pyramidal tract. The cerebral peduncle critical ratio level of 0.6 put forward in Warabi's study should be suitable to patients following a stroke after more than 1 year in our view, but not for patients who had had a stroke within 1 year. We note that if the asymmetry of the cerebral peduncle area after illness declined gradually even lower than the lower limit (0.83), limb motor function recovery would be poor, and the reason for the poor prognosis needs to be further investigated.

Experimental results showed that there were no statistical differences in cerebral peduncle area and area asymmetry between different stages in patients with positive motor evoked potential, and the quantity of pyramidal tract fibers in which Wallerian degeneration occurred was not enough to cause a cerebral peduncle area change.

Taken together, (1) the fractional anisotropy of the cerebral peduncle on the affected side declined progressively, and this decline peaked at 1–3 months after cerebral infarction, during which the critical point of fractional anisotropy drop appeared when motor evoked potentials were negative. (2) The fractional anisotropy of the cerebral peduncle on the affected side in patients with negative motor evoked potentials after cerebral infarction was lower than the normal lower limit value of 0.36, indicating that hemiplegic limb motor function recovery was poor. (3) Cerebral peduncle area atrophy on the affected side was noticeable starting at 6 months after cerebral infarction and deteriorated further up to 12 months after; area asymmetry was lower than 0.83 at 12 months, indicating that hemiplegic limb motor function recovery was poor. (4) The fractional anisotropy value of the cerebral peduncle decreased within 1 month and stayed unchanged in subsequent months after cerebral infarction in patients with positive motor evoked potentials, and there was no change in cerebral peduncle area from the beginning to the 12th month after cerebral infarction in these patients.

SUBJECTS AND METHODS

Design

A concurrent, non-randomized, controlled trial.

Time and setting

This study was performed in Xiaolan Hospital of Southern Medical University, China from September 2009 to September 2011.

Subjects

Sixty-three patients with acute cerebral infarction in the middle cerebral artery who received treatment in the Department of Neurology, Xiaolan Hospital of Southern Medical University, China between September 2009 and September 2010 were included in this study. Clinical observation was successfully performed in 57 of them.

Diagnostic criteria of acute cerebral infarction

The diagnostic criteria of acute cerebral infarction formulated by Compilation Committee of Chinese Cerebrovascular Disease Prevention Guidelines[44] are as follows: (1) acute onset; there may be a transient ischemic attack before the onset in some patients. (2) The severity of disease reaches its peak level almost in a

few hours or days, and some of symptoms may be progressive or fluctuated. (3) Focal neurofunctional deficit symptoms and signs. (4) Cerebral infarction confirmed by skull CT scan or MRI examination.

Inclusion criteria of selected subjects

(1) Cerebral infarction of middle cerebral artery and accepting the same therapeutic plan. (2) Time limited to 1 week after cerebral infarction. (3) The subjects have good compliance and can cooperate with investigator's follow-up study. (4) No contraindications for MRI examination.

Exclusion criteria of selected subjects

(1) Without hemiplegia. (2) Unstable vital signs. (3) With complications.

Ethical issues

This study was consistent with the *Declaration of Helsinki* and international ethical guidelines for biomedical research involving human subjects as well as *Administrative Regulations on Medical Institution* [45]. The study plan and possible risk factors were communicated to subjects before the commencement of the study and informed written consent was obtained from each subject.

Methods

MRI scanning and limb motor function evaluation

T1 and T2 weighted imaging, diffusion weighted imaging, fluid attenuated inversion recovery (FLAIR) and DTI sequences were obtained with a 1.5 T GE Signal System MR scanner (GE Medical Systems, Milwaukee, WI, USA). Scanning was performed according to the following parameters: T1 FLAIR: repetition time (TR) 2 000/echo time (TE) 24 ms, number of excitations (NEX) = 2; T2 weighted imaging (TR 3 800/TE 120 ms); FLAIR (TR 9 000 / TE 120 / T12 200 ms, NEX = 2, field of view (FOV) = 24 cm × 24 cm). DTI used echo planar imaging with the following parameters: TR 10 000/TE 115 ms, matrix = 128 × 128, NEX = 2, FOV = 24 cm × 24 cm, slice thickness = 5 mm, intersection gap 1 mm, *b* value (diffusion factor) 1 000 s/mm^2. DTI data were processed with software provided by the MRI scanner manufacturer and fractional anisotropy images were obtained.

Fractional anisotropy values of the left and right cerebral peduncle were measured using Basser's method in which the region of interest was defined as a circle or ellipse of 34 mm^2 and the fractional anisotropy ratio was defined by ipsilesional/contralesional side[46-47]. The cerebral peduncle areas were measured according to the method described by Mark *et al* [9].

The brightness level in the MRI was adjusted to ensure that the margins of the midbrain were clearly visible. The axial level showing the greatest expansion of the cerebral peduncle was identified on the MRI scans. The medial boundary of the cerebral peduncle was determined by connecting the oculomotor nerve sulcus to the lateral sulcus of the midbrain at the level of the optic chiasm. The cross-sectional area (cm^2) of the cerebral peduncle was measured on both sides with the software provided with the MRI scanner for calculating area (GE Medical Systems. The peduncular asymmetry ratio was calculated by the peduncular area ipsilateral to the infarction divided by the peduncular area contralateral to the infarction[9, 39].

DTI examinations were performed at 1 week, 1, 3, 6 and 12 months. The affected limbs of all patients were evaluated according to Fugl-Meyer scores before DTI examinations. Higher Fugl-Meyer scores (total score = 66 points) indicated better limb motor function. A score of 0 represents no limb movement, 1 poor muscular strength, poor motor velocity, amplitude or accuracy, and a score of 2 indicates normal movement[48].

Detection of motor evoked potentials

The motor evoked potential was detected at 24 hours after the first DTI examination through the use of 4-channel Nicolet Viking Quest EMG Laptop (Nicolet Biomedical, Madison, WI, USA). A Cadwell MES-10 magnetic stimulator (Cadwell Laboratories, Kennewick, WA, USA) connected with an 8-shaped coil was used. According to the methodology described by Arac *et al* [49], motor evoked potential was detected with the following parameters: bandpass, 2 000–3 000 Hz; gain, 100–500 μV; scan speed, 5 ms; electrical resistance, < 10 MΩ; number of superimpositions, 6 times. The record electrode was AgCl circular electrode (Madison). The stimulus position was 2 cm lateral to Cz. Single pulse stimulation was used and stimulus intensity was 40% (1.5 T) at the beginning on both sides till the output was 15–20% of supraliminal stimulus.

If a motor evoked potential wave could not be recorded on the patient's abductor pollicis brevis muscle, the stimulus intensity was gradually increased to 100% of output. If the motor evoked potential wave could still be recorded, then the recording electrodes were moved to the abductor digiti minimi muscle and the above-mentioned stimulus processes were repeated. If the motor evoked potential could not be recorded, the patient would be considered as motor evoked potential deficient. If the motor evoked potential wave could be

recorded, then the patient would be considered as motor evoked potential positive.

Statistical analysis

The measurement data were expressed as mean ± SD and count data were expressed as a percentage. All data were statistically processed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Paired sample or independent sample *t*-tests were used for comparing the mean differences between groups. Repeated measures analysis of variance was used to compare differences between each period in patients with cerebral infarction. Chi-square tests were used for comparing the difference in count data across groups. A level of $P < 0.05$ was considered statistically significant.

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