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#### **Title Page:**

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# Contralateral Lumbar to Sacral Nerve Rerouting for Hemiplegic Patients after Stroke: A Clinical Pilot Study

3

#### 4 Abstract

5 BACKGROUND: Spasticity and muscle weakness are common severe neurologic 6 sequelae after stroke. Contralateral peripheral neurotization has been successfully applied 7 to promote motor function of the hemiplegic upper extremity in patients with central 8 neurological injury. Here we present the first report of contralateral lumbar to sacral 9 nerve transfer for the lower extremities in hemiplegic patients after stroke.

10 CASE DESCRIPTION: Two patients were enrolled in the study. The first is a 57-year-old 11 man who suffered from permanent muscle weakness in his left leg after right cerebral 12 infarction. The second patient is a 42-year-old man who had spasticity and hemiplegia in 13 both upper and lower limbs on the right 32 months after a left cerebral hemorrhage. Both 14 patients underwent contralateral lumbar to sacral nerve rerouting to improve lower-limb 15 motor function. 20 months after surgery, both patients experienced significant 16 improvement in ambulatory status.

17 CONCLUSION: Although long-term follow-up and a randomized controlled trial are 18 required, this study demonstrates the safety and possible benefits of contralateral lumbar 19 to sacral nerve transfer for hemiplegic patients after stroke. This novel surgical approach 20 could provide a new means for lower-limb motor functional recovery.

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- 22

23 Running Title: Contralateral peripheral neurotization for stroke

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25 KEY WORDS: Hemiplegia, Nerve Rerouting, Nerve Transfer, Spasticity, Stroke

Spasticity is a common symptom after stroke, arising in about 30% of patients, who are 27 left with physical disabilities, especially with lower-limb dysfunction.<sup>1-4</sup> Patients often 28 demonstrate abnormal hip adduction and develop knee stiffness and clubfoot, thus 29 significantly impairing ambulation, self-care ability and quality of life. Muscle weakness 30 with or without neuromuscular fatigue is another common post-stroke complication.<sup>5</sup> It 31 has been attributed to anatomical and physiological changes within the descending 32 pathway and the muscle.<sup>6-8</sup> Current strategies for treating hemiplegia and spasticity 33 secondary to stroke are mostly focused on physical rehabilitation and physiotherapy. 34 35 These may result in progress during early stroke recovery, but usually lead to little improvement in long term follow-up.9,10 Selective dorsal rhizotomy (SDR), which is a 36 standard treatment option for reducing spasticity in children with cerebral palsy,<sup>11-13</sup> has 37 been reported to be beneficial for improving ambulatory status for adult patients with 38 multiple spasticity causes.<sup>14-17</sup> Dorsal root entry zone (DREZ) lesioning is more effective 39 for reducing spasticity, but more destructive than SDR.<sup>18</sup> However, SDR or DREZ 40 lesioning procedures typically do not enhance the coordination or strength of the target 41 muscles. 42

We have previously reported that patients with chronic upper extremity hemiplegia 43 could improve arm and hand function even after significant rehabilitation with 44 contralateral C7 nerve transfer.<sup>19</sup> Animal experiments and TMS and fMRI findings in 45 patients have suggested that the mechanism for delayed recovery of motor function may 46 lie in new active connections between the contralesional hemisphere and the paralyzed 47 limb.<sup>19-21</sup> We believe that the similar approach can be used to treat lower limb paralysis. 48 In particular, animal experiments have confirmed the effectiveness and safety of 49 contralateral L6 neurotization for improving motor recovery of the hemiplegic hindlimb 50 after unilateral CNI in adult rats.<sup>22</sup> 51

Herein, we report the first two cases of lower extremity contralateral nerve reroutingfor hemiplegic patients after stroke. In these patients, we were able to increase the muscle

54 strength and decrease the spasticity of the affected leg after contralateral lumbar to sacral

55 nerve transfer.

56

#### 57 CLINICAL PRESENTATION

58 Patient Presentation

59 Case 1

A 57-year-old male presented to the limb function reconstruction clinic in Huashan 60 61 Hospital with a history of right medial frontal lobe cerebral infarction 6 years previous. 62 (Table 1) He suffered from left lower extremity weakness, with mild spasticity in the 63 upper extremity. He was bedridden for a long time and eventually ambulated with 64 difficulty using a crutch. He underwent a physical habilitation program but achieved no significant improvement after 1 year. His quadriceps muscles strength was Medical 65 Research Council (MRC) grade 4, while the biceps femoris, the gluteus maximus, and the 66 longus muscles of the sacrum, all had only MRC grade 2 strength or less. His Fugl-Meyer 67 lower-extremity scale score was 16. His upper-extremity modified Ashworth score (MAS) 68 was 1/5. (Table 2). 69

70

71 Case 2

A 42-year-old Male presented 32 months after left cerebral hemorrhage. He had spasticity and hemiplegia in both in his right upper and lower limbs. In addition, he had mild speech disorder. He was enrolled in our contralateral C7 transfer clinic trial program, and was satisfied with his upper-limb motor function improvement 12 months after surgery. Therefore, he returned to our clinic and requested the contralateral lumbar to sacral nerve transfer. He had severe spasticity in his leg, with a mean MAS score of 3/5 and Fugl-Meyer lower-extremity scale of 19.

79

80 Surgical Description

Electrophysiological evaluation and functional MRI were done to evaluate and 81 exclude other neurological diseases preoperatively. Volatile induction and maintenance of 82 anesthesia with sevoflurane inhalational anesthetic was applied. A longitudinal midline 83 incision was made on the back at approximately the L5 level. We performed standard L5 84 laminectomy, and decompression of the sacral bone to identify the L5 and S1 foramina 85 and nerve roots bilaterally. The spinal dura was incised longitudinally under the operating 86 microscope. The L5 and S1 sacral roots were identified using anatomical localization and 87 88 intraoperative electrophysiology. On both sides, the ventral (motor) root filaments were 89 separated from the dorsal (sensory) filaments and tested by electrophysiology. The dorsal 90 filaments remained intact while 50% of the ventral roots was transected. Microanastomosis was created between the contralateral L5 and paralyzed S1 by suturing 91 50% of the proximal contralateral lumbar ventral L5 to 50% of the distal ventral S1 nerve 92 root using 9-0 prolene (Figure 1). The dura was closed primarily, and the incision closed 93 in multiple layers. Due to laminectomy and dural opening, the patient underwent flat bed 94 rest for 30 days postoperatively, without spinal fixation. 95

96

97 Postoperative and Extended Recovery

Patients were prescribed routine physical and occupational therapy at our local 98 rehabilitation center one month post operation, including isometric muscle contraction 99 training in early stage and gait training in late stage. Robotic-assisted motor training was 100 101 also routinely used in our center, providing tactile feedback that kinetically and kinematically corrected the user's movement. Patients were followed up in the outpatient 102 103 clinic every three months. Follow-up variables and studies included lower limb muscle strength, range of motion, paresthesias, two-point discrimination, MAS, Tardieu Scale, 104 Fugl-Meyer lower-extremity scale, electromyography and fMRI. 105

Both patients experienced a transient decrease in muscle strength, which was characterized by a decrease in the strength of donor-side knee flexion, dorsiflexion, and plantarflexion, and mild soreness and discomfort. 3 months post operation, the muscle
strength of the healthy limb began to recover. 12 months post operation, the muscle
strength returned to preoperative levels and this was confirmed by electromyography. No
numbness or two-point discrimination impairment was observed.

At 18 months after surgery, the muscle strength of the first patient's affected limb significantly increased. Hip extension, knee flexion and ankle plantarflexion all recovered to MRC grade 3. At 20 months after surgery, this patient who was bed-bound prior to surgery had postoperative improvement in ambulatory status. There was no significant change in his upper-limbs.

117 The second patient showed mild decrease in spasticity on the first day after the operation. The spasticity returned to baseline in less than 1 month. At 16 months after 118 operation, coordinated movement of hip flexion, knee flexion and ankle dorsiflexion was 119 noticed. At 20 months after operation, the motor function of the affected limb was 120 significantly improved, including active hip abduction and flexion, and ankle flexion. His 121 Fugl-Meyer lower-extremity scale increased to 26. Functional magnetic resonance 122 imaging showed that when the right ankle was flexed and extended, there was 123 corresponding significant activation of the right parietal frontal lobe. (Figure 2B). 124 Compared to a pre-operative baseline, the activation zone had a statistically significant 125 increase in blood oxygen level dependent (BOLD) signal (p<0.001 corrected for 126 127 family-wise error, FWE), and was located in the bilateral medial superior frontal gyrus 128 (BA9) and right anterior cingulate cortex (ACC). (Figure 2C). Detailed follow-up assessment is found in table 2. 129

130

#### 131 DISCUSSION

132 Rationale for the study

Recent discoveries in stroke care has resulted in significant progress in the treatmentof the acute phase of stroke. Mortality in acute stroke has been greatly reduced, however,

the population of disabled stroke survivors has subsequently increased.<sup>23</sup> The range of 135 treatments available for poststroke disability has expanded considerably in recent decades, 136 including physical rehabilitation,<sup>24</sup> conventional medical management, intrathecal 137 baclofen (ITB) therapy, botulinum neurotoxin type A injection, SDR, DREZ, selective 138 neurectomy and tendon transfer.<sup>25</sup> Among these treatments, oral antispasmodics have 139 been most frequently used, especially baclofen. These medications may have adverse 140 effects and can be poorly tolerated.<sup>26</sup> ITB therapy is reported to be effective in reducing 141 spasticity, increasing motor strength and improving gait in ambulatory patients. <sup>27,28</sup> In 142 143 addition to its expense and potential complications, such as catheter dislodgement or breakage, dizziness and infection,<sup>29,30</sup> ITB therapy primarily effects tone and should not 144 improve motor function that is unrelated to spasticity, such as weakness and 145 incoordination.<sup>31</sup> Botulinum neurotoxin type A injection has been shown to be good for 146 focal spasticity but cannot be sustained for long periods. <sup>32</sup> SDR and DREZ lesioning 147 were discussed previously. Selective neurectomy has been performed mostly in 148 upper-limb spastic patients. <sup>33</sup> Tendon transfer has been used for muscle rebalancing. 149 Most of the existing therapies are focused on reducing spasticity and rebalancing the 150 antagonistic muscle groups, but weakness remains difficult to treat. Moreover, because of 151 the central nervous system injury, it is hard to improve coordination and flexibility within 152 current approaches. 153

In our previous study, we successfully improved hemiplegic upper limb function and 154 coordination after stroke using contralateral seventh cervical nerve transfer (grafting the 155 contralateral C7 nerve from the nonparalyzed side to the paralyzed side).<sup>19</sup> We inferred 156 157 that the replacement of the nonfunctional C7 nerve root with a healthy contralateral C7 root in affected limb can establish a functional connection between the affected limb and 158 the contralateral hemisphere (i.e., the ipsilateral hemisphere of the affected limb). The 159 success of this method is based on two basic conditions. One is that the harvest of the 160 contralateral donor nerve does not cause long-term functional impairment. The second is 161

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that the brain has certain has plasticity and is able to acquire control of bilateral limbs.

Historically, therapeutic ventral rhizotomy has been used to treat patients with spastic paralysis, but it has been abandoned because of resultant muscle atrophy and loss of function.<sup>16,34</sup> As a result, SDR was developed and used for treatment of severe spasticity. Recently, ventral rhizotomy was reported for treatment of dystonia together with SDR in 2 studies.<sup>35,36</sup> It is unclear whether it is safe to cut the ventral root, but weakness and injury from this is a significant concern.

The difference between our surgery and ventral rhizotomy mainly lies in the degree 169 170 of neurotomy. Ventral rhizotomy was performed typically approximately from L1-S1 in order to prevent compensation and decrease the muscle tone. Because the motor function 171 of the C7 nerve largely overlaps with that of the other four nerves that give rise to the 172 brachial plexus, severing this nerve usually results in only transient weakness and 173 numbness in the ipsilateral upper extremity.<sup>19,37</sup> Similarly, the sacral plexus emerges from 174 the lumbar and sacral vertebrae (L4-S4) with significant overlap.<sup>38</sup> The nerves have 175 compensatory mechanisms, <sup>38</sup> but for the sake of safety, with electromyography 176 conformation, only 50% contralateral L5 ventral root was dissected as donor site, and 50% 177 S1 ventral root of the affected limb was chosen as the destination. 178

179

180 Selectivity and Monitoring

L5 and S1 were chosen based on two criteria. First, L5 and S1 are in the middle of 181 182 the sacral plexus, which allows for more redundancy in function by surrounding nerve roots. Second, Xiao and Du have reported successful restoration of bladder control in 183 patients with spinal cord injury by establishing a somatic-autonomic reflex pathway 184 through lumbar-to-sacral ventral root nerve rerouting.<sup>39</sup> More than 80% of 110 patients 185 with spinal cord injury using ipsilateral L5-S2/3 transfer to restore the bladder reflex, 186 achieved continence, without long-term extremity weakness. Although negative results 187 were reported in several subsequent studies, including a double-blinded randomized 188

controlled trial,<sup>40</sup> only one long-term complications was identified, a child with new 189 persistent foot drop after surgery. Most of the patients reported weakness of lower 190 extremity muscle groups at 1 month post-op and they returned to baseline strength by 12 191 months.<sup>41,42</sup> We treated adult stroke patients, who had more fully-developed nervous 192 systems, and during the procedure, electromyography stimulation was used to confirm 193 redundant function in adjacent nerve roots. However, permanent foot drop was still our 194 main concern, so we put particular emphasis on stimulation results for both candidates of 195 196 the divided L5 root, choosing to transfer the root division that was less involved in ankle 197 dorsiflexion. Second, the main function of the lower limbs is standing and walking. And the most basic requirements for standing and walking are hip and knee stability and 198 199 flexion, which require gross muscle power rather than the fine motor control of the hand in the upper extremity.<sup>43</sup> Both L5 and S1 innervate muscles for abduction and lateral 200 rotation of the hip, flexion of the knee, and plantarflexion and dorsiflexion of the ankle. 201 L5 contributes more to dorsiflexion of the foot, while S1 contributes more towards 202 plantarflexion and eversion of the ankle.<sup>38</sup> As there would be a certain time of weakness 203 of affected muscle groups after neurotomy, we attempted to maximize foot function by 204 using the S1 root as the recipient; using L5 as the donor root allowed us to maximize foot 205 stability and function in the contralateral leg during the early stages of recovery 206 post-operatively. 207

208

209 Functional Performance

Although both of our patients recovered impressive function of their hemiplegic leg, the manner of their improvement differed. At 20 months after surgery, patient 1, who had primarily weakness, achieved significant muscle power increase in the glutei muscles, biceps femoris, peroneus longus and brevis muscles and also regained the ability to walk without walker. This recovery was gradual and in accordance with the usual pattern of nerve regeneration.

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Patient 2, who had spastic dysfunction of the leg, had a biphasic recovery. Initially, 216 immediately post-operatively we noticed reduced decreased spasticity and significant 217 improvement in ambulatory status. This is due to cutting of the S1 root, which contains 218 nerve fibers that maintain muscle tone. However, the spasticity reappeared less than 1 219 month after surgery. The second, more delayed recovery phase showed an improvement 220 in muscle strength, coordination and motor function, which was manifested as synergistic 221 motion appearance of hip flexion, knee flexion and ankle dorsiflexion. This coordinated 222 223 movement of the lower extremity muscles was first noticed about 16 months after surgery 224 and it improved with rehabilitation, which may reflect the time course of regeneration of the contralateral nerve fibers into the affected limb nerves. Although the spasticity 225 226 improved, it did not result in an outcome that was as good as expected from SDR alone. Since SDR also requires laminectomy and dural opening, we propose to perform 227 contralateral lumbar to sacral nerve transfer simultaneous with SDR for severely spastic 228 patients with hemiplegia in the future. 229

Clinical improvement was associated with electromyography results and fMRI data. 230 Activation of the contralesional hemisphere generated by extension and flexion of the 231 ankle of the paralyzed leg was increased at 20 months after surgery compared to baseline, 232 which suggests that new neural pathways were successfully established. Additionally, the 233 bilateral medial superior frontal gyrus and right ACC were significantly more activated 234 compared to preoperative baseline. The medial superior frontal gyrus is thought to play a 235 role in executive mechanisms, and is crucially involved in self-generated action and 236 self-reflection.<sup>44,45</sup> The ACC projects to the thalamus and other cortical neurons, and also 237 sends descending projections to affect spinal cord sensory transmission.<sup>46</sup> It is believed to 238 play an important part in the coordination of motor behavior.<sup>47</sup> Changes in these regions 239 in our patients after contralateral nerve transfer may reflect successful integration of the 240 injured leg, or strengthening of bilateral motor pathways in the supplemental motor areas. 241 These observations warrant further study. 242

243

244 Limitations

The primary limitation of this study is its small size. However, the two patients enrolled had different pathologies, ischemic stroke and hemorrhagic stroke, as well as different clinical manifestations of muscle weakness and spasticity. Although we demonstrated good clinical outcomes without long-term complications in two patients, further clinical trials are required to confirm the safety and effectiveness of the procedure. In addition, stroke is a heterogenous disease and different lesions may require different surgical or non-surgical approaches.

252

#### 253 CONCLUSION

This report demonstrates the safety and efficacy of contralateral lumbar to sacral nerve transfer for hemiplegic patients after stroke. This procedure provides a new method for lower-limb motor functional recovery. Further research, including long-term follow-up and randomized controlled trial, is required.

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382 Figure legends:

Figure 1 A, diagram of contralateral lumbar to sacral nerve transfer for hemiplegic 383 patients after stroke. B-E, Intraoperative photographs of a contralateral L5 nerve root 384 transfer. B, after laminectomy was performed, the S1 root of the affected limb and the 385 contralateral L5 nerve root were exposed. C, The ventral root of S1 was evenly divided 386 into two branches. D, stimulation (arrow) of both 50%-root divisions confirmed 387 redundant function, the division that was less involved in ankle dorsiflexion was chosen. 388 389 E, microanastomosis was created between 50% of the proximal contralateral lumbar 390 ventral L5 and 50% of the distal ventral S1 nerve root.

391

Figure 2 Activation patterns revealed by right ankle dorsiflexion in patient 2 (left cerebral hemorrhage). Results are superimposed on the reconstructed cortical surface of the MNI template brain. A, baseline. B, 20 months post operation. C, differences between post operation and baseline using a 2-sample t-test (p<0.001 FWE corrected). Red indicates increased activation after surgery and rehabilitation.

Case	Current	Sex	Time of	Cause	Chief	Donor	Recipient
No.	Age, y		Injury,		Complaint	Root	Roots
			у			(Side)	(side)
1	57	male	6	right	weakness	50%	50%
				cerebral		L5(Right)	S1(left)
				infarction			×
2	42	male	2.6	left cerebral	spasticity	50%	50%
				hemorrhage		L5(left)	S1(Right)

Table 1. Population and Clinical Data

y=year

Case	Time Points	Fugl-Meyer	MA	Donor	Recipient side		
No.		lower-extremit	S	site			
		y scale		glutei	glutei	biceps	peroneu
				muscle	muscle	femoris	s longus
				s power	s power	power	power
1	Preoperation	16/34	0/5	M5	M1	M2	M1
	1 months	16/34	0/5	M4-	M1	M2	M1
	after op.						
	20 months	27/34	0/5	M5	M3	M3	M3
	after op.						
2	Preoperation	19/34	3/5	M5	M1	M1	M2
	1 months	19/34	3/5	M4	M1	M1	M2
	after op.						
	20 months	26/34	2/5	M5	M3-	M3	M3
	after op.						

Table 2. Details of functional results in patients who underwent contralateral lumbar to sacral nerve transfer procedure

op.=oreration

## ACCEPTED MANUSCRIPT





# Highlights:

- Spasticity and muscle weakness are common severe neurologic sequelae after stroke.
- We firstly report contralateral lumbar to sacral nerve transfer for the lower extremities in hemiplegic patients after stroke.
- This new surgical technique could provide a new method for lower-limb motor functional recovery.

CER MARINE CR.

## Abbreviations:

ACC: Anterior cingulate cortex

DREZ: Dorsal root entry zone

FWE: Family-wise error

ITB: Intrathecal baclofen

MRC: Medical Research Council

SDR: Selective dorsal rhizotomy