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Cortical activity modulation by botulinum toxin type A in patients with post-stroke arm spasticity: Real and imagined hand movement

Tomáš Veverka [a,*], Petr Hluštík [a,c], Pavel Hok [a], Pavel Otruba [a], Zbyněk Tüdös [c], Jana Zapletalová [d], Alois Krobot [b], Petr Kaňovský [a]

[a] Department of Neurology, Faculty of Medicine and Dentistry, Palacký University and University Hospital, Olomouc, Czech Republic
[b] Department of Physiotherapy, Faculty of Medicine and Dentistry, Palacký University and University Hospital, Olomouc, Czech Republic
[c] Department of Radiology, Faculty of Medicine and Dentistry, Palacký University and University Hospital, Olomouc, Czech Republic
[d] Department of Biophysics, Biometry and Statistics, Faculty of Medicine and Dentistry, Palacký University and University Hospital, Olomouc, Czech Republic

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ABSTRACT

Background: Our aim was to use functional magnetic resonance imaging (fMRI) to compare brain activation changes due to botulinum toxin A (BoNT) application between two chronic stroke patient groups with different degree of weakness treated for upper limb spasticity.
Methods: Fourteen ischemic stroke patients with hand weakness and spasticity were studied. Spasticity was scored by modified Ashworth scale (MAS). FMRI was performed 3 times: before (W0) and 4 (W4) and 11 weeks (W11) after BoNT application. Group A: 7 patients (2 males, 5 females; mean age 59.14 years) with hand plegia, who imagined moving fingers. Group B: 7 age-matched patients (6 males, 1 female; mean age 59.57 years) able to perform sequential finger movement.
Results: BoNT transiently lowered MAS in W4 in both groups. In group A, activation of the frontal premotor cortex dominated and persisted for all three fMRI sessions whereas the ipsilesional cerebellum and cortex bordering bilateral intraparietal sulcus activation changed over time. Between-session contrasts showed treatment-related activation decreases in the mesial occipitoparietal and lateral occipital cortex. In group B, brain activation was markedly reduced after BoNT (W4). Whereas some of these areas manifested only transient reduction and expanded again at W11, in others the reduction persisted.
Conclusion: Study of two age-matched groups with mild and severe weakness demonstrated different effects of BoNT-lowered spasticity on sensorimotor networks. Group A performing movement imagery manifested BoNT-induced reduction of activation in structures associated with visual imagery. Group B performing movement manifested reduced activation extent and reduced activation of structures outside classical motor system, suggestive of motor network normalization.

1. Introduction

Stroke is the leading cause of disability worldwide and one of the most common causes of death [27]. Despite the progress in the stroke management, a majority of stroke survivors experience motor deficit with impaired function of upper extremity [21]. Ischemic lesion of pyramidal and parapyramidal tracts cause upper motoneuron syndrome (UMS) [38]. Negative signs (weakness, loss of dexterity) of UMS are crucial in determining the degree of movement deficit [22]. Nevertheless positive signs of UMS (especially spasticity) may play an important role. By Lance's historical definition, spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex [26]. Spasticity prevalence estimates range from 19% to 42.6% in stroke survivors [43,46]. It is generally recognized that poststroke spasticity (PSS) may interfere with voluntary movement [31]. Disability associated with PSS may undoubtedly affect patient's quality of life, increase caregiver and socioeconomic burden [57]. Current multidisciplinary approach to relieve focal spasticity combines physiotherapy with botulinum toxin A (BoNT-A) application. Numerous clinical trials have shown that BoNT-A is safe and effective way to reduce upper limb PSS [44,52]. Although BoNT-A acts primarily on muscle spindles there is growing evidence that BoNT-A also exerts central (remote) effects. BoNT-A affects intrafusal fibers as well as extrafusal ones and thus alters abnormal sensory input to the CNS via Ia afferents [36]. This is probably the mechanism how BoNT-A injected in the periphery can induce cortical reorganization [7]. This hypothesis has been supported by studies in focal dystonia [6,12,23,24]. We have consistently studied the neuroanatomical correlate of BoNT-related post-stroke spasticity relief using functional MRI (fMRI). In our previous

* Corresponding author at: Department of Neurology, University Hospital, I. P. Pavlova 6, 77520 Olomouc, Czech Republic. Tel.: +420 588 443 419; fax: +420 585 428 201.
E-mail address: veverka.tomas@seznam.cz (T. Veverka).

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studies we have provided evidence that effective treatment of upper limb spasticity is associated with dynamic changes at the level of the cerebral cortex [47,48]. The aim of the present study was to localize and analyze BoNT-related pattern of cerebral cortex activation during motor or mental tasks in patients with PSS.

2. Material and methods

Patients were studied using a previously published protocol [45]. The following text summarizes the methodology and highlights differences particular for the present study.

2.1. Patients

The patients were recruited in the Comprehensive Stroke Centre at Department of Neurology, University Hospital, Olomouc, Czech Republic. The study was conducted in accordance with the Declaration of Helsinki 1964 (in the latest revision in 2013) and it was approved by the institutional ethics committee.

Fourteen ischemic stroke patients with hand weakness and spasticity were studied. Group A consisted of 7 patients (2 males, 5 females; mean age 59.14 years, range 33–78 years, SD 16.94) with hand plegia, who imagined moving fingers. Group B consisted of 7 age-matched patients (6 males, 1 female; mean age 59.57 years, range 34–80 years, SD 16.93) able to perform sequential finger movement. All subjects were in the chronic stage of the ischemic stroke; the time from stroke onset to the study entry ranged from 3 to 83 months, the median was 10.5 months. Localization of the ischemic lesions were subcortical or corticosubcortical within the middle cerebral artery territory. Hand spasticity was clinically relevant and exceeded 1 on modified Ashworth scale (MAS) [4]. Exclusion criteria were: time after stroke onset less than 3 months; history of BoNT application or drugs affecting muscle hypertonus intake; severe cognitive deficit and severe depression, assessed using the MMSE [10] and Zung Self-rating Depression Scale [58], which could affect cooperation during the study protocol; and finally the magnetic resonance imaging exclusion criteria. The patients' characteristics are listed in Tables 1 and 2.

2.2. Clinical evaluation

Patients were clinically examined (after previous screening) at Week 0, when they were enrolled into the study and injected with BoNT, then at Week 4, four weeks following the injection of BoNT, when BoNT effect is assumed to be maximal, and at Week 11, three months after the BoNT injection, when peripheral BoNT effect was expected to wane.

Evaluation of spasticity using the modified Ashworth scale (MAS) was performed at each visit. The MAS was assessed separately for fingers and wrist and the values were averaged together (mean MAS). Further clinical investigations included following standardized scales were performed at study enrollment: the modified Medical Research Council (mMRC) [33] scale to test upper extremity strength; the National Institutes of Health (NIH) [5] stroke scale to assess neurological impairment, the Barthel index (BI) [28] and the modified Rankin Scale (mRS) [34] to assess disability.

2.3. Treatment

Enrolled patients were treated with BoNT injections into the muscles of the affected arm at Week 0 and then they underwent a dedicated physiotherapy protocol.

The injections were performed using the EMG guidance (Medtronic Keypoint, Alpine Biomed ApS, Denmark), preferably with electrical stimulation for localization of the muscle intended to be treated. The following muscles were always injected: flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), flexor digitorum superficialis (FDS), and flexor digitorum profundus (FDP). The dose of BoNT (BOTOX®; Allergan, Inc., Irvine, CA, USA) per muscle was 50 U. Such dose reflects current recommendation [52]. The BoNT was given consistently in a fixed dose per muscle basis in both groups.

The rehabilitation treatment started several days after the BoNT injection (W0). Initial inpatient physiotherapy (2–4 weeks) was followed by outpatient therapy until the third clinical and fMRI evaluation (total of 11 weeks). The patients underwent daily physiotherapy sessions, for a total of 1 h, using various techniques such as Bobath concept, proprioceptive neuromuscular facilitation (PNF), passive and active stretching and occupational therapy. Proper adherence to the physiotherapy protocol has been repeatedly checked every session within the whole study [25].

2.4. Tasks

Patients were scanned while performing imaginary or real finger movement with the impaired hand. Subjects with preserved finger movements (group B) performed sequential finger movements (Roland's paradigm) [35] at the rate of approximately 1 movement per second. Subjects with hand paralysis (group A) first trained the sequential finger movement with the non-paretic hand and then were asked to imagine performing the same movement with the impaired fingers in association with kinesthetic feeling [42]. Inside the bore of the scanner, the task was performed with eyes closed, instructions to start and stop task performance were signaled verbally (start/stop) in MR-compatible headphones. In a block paradigm, imagery or real finger movement alternated with rest (15 s). Each experimental run consisted of 12 repetitions of the same task-rest block pairs, for a total of 6 min. Each participant had two experimental runs with the impaired hand.

Table 1
Group A - demographic and clinical characteristics.

Patient	Sex	Age	Stroke onset to W0 (months)	Lesion	Affected hand	mRS	BI	Initial NIHSS	MMSE	Zung (SDS index)	mMRC (WF/WE)	mMRC (FF/FE)	Mean MAS (W0)	Mean MAS (W4)	Mean MAS (W11)
1	F	76	6	Thalamus, IC, insula	Left	4	45	7	24	65	1/0	1/0	3	1.75	2.5
2	F	78	5	Thalamus. IC	Right	4	60	10	N/A	49	0/0	0/0	3	2	3
3	F	44	83	FP lobe. insula	Right	2	95	4	29	39	2/1	2/1	2	1	2
4	F	64	6	Insula. BG. FT lobe	Right	3	70	8	N/A	63	0/0	0/0	2	1.25	1.75
5	M	68	9	Thalamus. BG. FT lobe. insula	Left	3	75	7	29	34	0/0	0/0	3	1.75	3
6	M	33	32	BG. IC	Left	3	70	5	28	59	2/1	2+/1	2	1	2
7	F	51	23	BG. insula. FT lobe	Right	3	65	9	N/A	43	0/0	0/0	3	2	2

Note: L = left; R = right; BG = basal ganglia; IC = internal capsule; F = frontal; T = temporal; P = parietal; NIHSS = NIH stroke scale; mMRC = modified MRC scale; BI = Barthel index; WE = wrist extensors; WF = wrist flexors; FE = finger extensors; FF = finger flexors; MAS = Modified Ashworth scale; and N/A = not applicable – the MMSE score could not be interpreted because of the presence of expressive aphasia.