Journal of the Neurological Sciences 319 (2012) 89–95

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

BoNT-A related changes of cortical activity in patients suffering from severe hand paralysis with arm spasticity following ischemic stroke

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ARTICLE INFO

Article history:
Received 7 December 2011
Received in revised form 19 April 2012
Accepted 2 May 2012
Available online 9 June 2012

Keywords:
Stroke
Arm spasticity
Functional MRI
Botulinum toxin

ABSTRACT

Background: Investigations were performed to localize and analyze the botulinum toxin (BoNT-A) related changes of cerebral cortex activation in chronic stroke patients suffering from severe hand paralysis with arm spasticity. Effects on task- related cerebral activation were evaluated by functional magnetic resonance imaging (fMRI).

Methods: 14 patients (5 males, 9 females, mean age 55.3 years) suffering from upper limb post-stroke spasticity were investigated. The change of arm spasticity was assessed by using the modified Ashworth scale (MAS). FMRI sessions were performed before (W0), four weeks (W4) and 11 weeks (W11) after BoNT-A application. Patients were scanned while performing imaginary movement with the impaired hand. Group fMRI analysis included patient age as a covariate.

Results: BoNT-A treatment was effective in alleviation of arm spasticity. Mean MAS was at Week 0: 2.5 (SD 0.53), at Week 4: 1.45 (SD 0.38), at Week 11: 2.32 (SD 0.44).

Task-related fMRI prior to the treatment showed extensive activation of bilateral frontoparietal sensorimotor cortical areas, anterior cingulate gyrus, pallidum, thalamus and cerebellum.

Effective BoNT-A treatment (W4) resulted in partial reduction of active network volume in most of the observed areas, whereas BoNT-free data (W11) revealed further volume reduction in the sensorimotor network.

On direct comparison, significant activation decreases associated with BoNT-A treatment were located in areas outside the classical sensorimotor system, namely, ipsilesional lateral occipital cortex, supramarginal gyrus and precuneus cortex. On comparison of W4 and W11, no activation increases were found, instead, activation further decreased in ipsilesional insular cortex, contralesional superior frontal gyrus and bilateral frontal pole.

Conclusions: Whole brain activation patterns during BoNT-A treatment of post-stroke arm spasticity and further follow up document predominantly gradual changes both within and outside the classical sensorimotor system.

1. Introduction

Stroke is a leading cause of disability in Western countries [1]. Up to two thirds of stroke survivors experience impaired function and spasticity of the upper limb, and the impairment of the wrist and fingers is prevailing compared to proximal shoulder muscles [2,3].

The degree of muscle weakness is crucial in determining the degree of movement deficit, but spasticity may also contribute [4,5]. Spasticity frequently causes problems of common daily activities, hygiene, nursing care and also physiotherapy [6]. A recent prospective study has found a spasticity prevalence rate of 38% one year after stroke [7].

Recommended treatment strategies to relieve spasticity combine physiotherapy procedures with Botulinum toxin A (BoNT-A) application. [8,9]. BoNT-A acts at the neuromuscular junction and the mechanism of action on muscle spindles has been well described [10,11]. There is small but growing evidence that BoNT-A also exerts effects through supraspinal mechanisms and can even affect cortical reorganization [12]. The hypothesis of central reorganization following BoNT-A treatment has been supported by studies using neurophysiological and imaging methods in patients with focal dystonia [13–17]. Most of previous fMRI studies in stroke patients have described changes in task-related cortical activity following physiotherapy treatment, e.g., constraint-induced therapy [18]. Only several studies reported cortical changes after BoNT-A injections into the spastic muscles [19,20].

In two previous pilot fMRI studies, we have hypothesized that BoNT-A treatment can relieve focal spasticity through dynamic changes at multiple levels of motor system, presumably including cerebral cortex

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doi:10.1016/j.jns.2012.05.008

[21,22]. These processes have been reflected in the changes of cortical activation during motor and mental tasks. Nevertheless, the results of these pilot studies have been limited by the small number of subjects.

The aim of our present study was to localize and analyze the BoNT-A related changes of cerebral cortex activation in chronic stroke patients suffering from severe hand paralysis with arm spasticity.

For that, we designed a protocol involving three serial fMRI sessions. This approach allowed documenting the whole brain activation pattern during treatment of spasticity and further follow ups.

2. Material and methods

2.1. Patients

The study has been approved by the institutional ethical committee, and all subjects gave written consent for the study in accordance with Declaration of Helsinki.

Study group consisted of 14 premorbidly right-handed patients (5 males, 9 females, mean age 55.3 years, range 22–78) with chronic ischemic stroke in the middle cerebral artery territory. Ischemic lesions were subcortical or corticosubcortical. The time from stroke onset to the study entry ranged from 3 to 83 months, the median was 7 months.

All patients suffered from distal arm plegia and spasticity of upper extremity following ischemic stroke at 1+ and higher of modified Ashworth scale (MAS) [23]. Severity of hand paralysis measured using modified Medical Research Council scale (mMRC) [24] ranged from 0 to 2+, which did not allow the patients to perform an overt hand motor task. Enrolled patients were naive to BoNT-A and drugs affecting muscle hypertonus. Exclusion criteria were time after stroke less than 3 months, severe cognitive deficit and severe depression, assessed using the MMSE [25] and Zung Self-rating Depression Scale [26], which could affect cooperation during the study protocol; and finally the magnetic resonance imaging exclusion criteria. The patients' characteristics are listed in Table 1.

2.2. Clinical evaluation

Patients were studied using a previously published protocol [22]. Patients were clinically examined (after previous screening) at Week 0, when they were enrolled into the study and injected with BoNT-A, then at Week 4, four weeks following the injection of BoNT-A, when BoNT-A effect is assumed to be maximal, and at Week 11, three months after the BoNT-A injection, when peripheral BoNT-A effect was expected to wane.

Several standardized scales were used: the Modified Ashworth Scale (MAS) to evaluate spasticity; the modified Medical Research Council (mMRC) scale to test upper extremity strength; the National Institutes of Health (NIH) [27] stroke scale to assess neurological impairment, the Barthel Index (BI) [28] and the modified Rankin Scale (mRS) [29] to assess disability. The MAS was assessed separately for fingers and wrist and the values averaged together.

2.3. Task

Patients were scanned while performing imaginary finger movement with the impaired hand. As demonstrated previously, kinesthetic imagery of finger movements evoked activation in the same cortical areas as those associated with performed movements [30]. Each subject first trained a sequential finger movement with the non-paretic hand (Roland's paradigm) [31] at the rate of approximately 1 movement per second and then was asked to imagine performing the same movement with the impaired fingers in association with kinesthetic feeling [32]. 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 of finger movement alternated with rest (15 s). Each experimental run consisted of 12 repetitions of the same imagery-rest block pairs, for a total of 6 min. Each participant had two experimental runs with the impaired hand. Like the behavioral assessments, the functional MRI examinations were done at Week 0, Week 4, and at Week 12.

2.4. Treatment

The patients were treated with BoNT-A injections into the muscles of the affected arm at Week 0. The injections were done using EMG guidance (Medtronic Keypoint, Alpine Biomed ApS, Denmark) and electrical muscle stimulation. These muscles were always treated: flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP). When there was a need for additional injections into other muscles of the upper limb to relieve the spasticity effectively, these were injected using the same technique: flexor pollicis longus (FPL) in two patients, biceps brachii (BB) in one patient and pronator teres (PT) in two patients were injected. The dose of BoNT-A (Botox®) per muscle was 50 U (therefore 100 U in biceps brachii). The effect of BoNT-A treatment was tested using both clinical (MAS) and imaging assessments.

Table 1
Demographic and clinical characteristics.

Patient	Sex	Age	Stroke onset to W0 (months)	Lesion	Affected hand	mRS	BI	NIHSS	MMSE	Zung SDS index	mMRC (WF/WE)	mMRC (FF/FE)	Mean MAS (W0)	Mean MAS (W4)	Mean MAS (W11)
1	M	31	7	Thalamus, IC, BG	Left	3	90	5	30	34	1+/0	1+/1+	3	1.5	2.5
2	M	22	3	BG, IC	Right	3	85	8	29	30	0/0	0/0	3	1	2.5
3	F	74	3	BG, insula, thalamus, FT	Left	4	40	9	24	45	0/0	0/0	3	2	3
4	F	76	6	Thalamus, IC, insula	Left	4	45	7	24	65	1/0	1/0	3	1.75	2.5
5	F	78	5	Thalamus, IC	Right	4	60	10	N/A	49	0/0	0/0	3	2	3
6	F	44	83	Insula, FP	Right	2	95	4	29	39	2/1	2/1	2	1	2
7	F	64	6	Insula, BG, FT	Right	3	70	8	N/A	63	0/0	0/0	2	1.25	1.75
8	F	25	11	Thalamus, IC, BG	Left	3	80	5	29	64	1/0	0/0	2.5	1.5	2.5
9	M	68	9	Thalamus, BG, FT, insula	Left	3	75	7	29	34	0/0	0/0	3	1.75	3
10	F	69	4	BG, insula, thalamus	Right	3	80	6	27	48	0/0	0/0	2	1	2
11	M	33	32	BG, IC	Left	3	70	5	28	59	2/1	2+/1	2	1	2
12	M	67	64	Insula, FT	Right	2	95	6	N/A	50	2/1	2/1+	2	1.25	2
13	F	51	23	BG, insula, FT	Right	3	65	9	N/A	43	0/0	0/0	3	2	2
14	F	73	7	IC, F	Right	2	100	3	25	40	2+/2	2+/2	1.5	1.25	1.75

Note: L = left; R = right; BG = basal ganglia; IC = internal capsule; F = frontal lobe; T = temporal lobe; P = parietal lobe; 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; N/A = not applicable – the MMSE score could not be interpreted because of the presence of expressive aphasia.