

1 BRIEF COMMUNICATIONS – SHORT SUMMARY

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3 Trans cranial magnetic resonance–guided focused ultrasound is a recently introduced
4 incisionless treating option for essential tremor and tremor-dominant idiopathic Parkinson
5 disease. There is preliminary evidence that it may result in a promising effective treatment
6 option for other movement disorders too. Here, we report on two patients with
7 multiple sclerosis with medication refractory debilitating essential tremor comorbidity who
8 successfully underwent unilateral Vim tcMRgFUS thalamotomy for tremor control. Patients’
9 clinical condition and expanded disability status scale scores showed no changes during the
10 1-year follow-up period with no evidence of multiple sclerosis activity or progression.

11 BRIEF COMMUNICATIONS – MAIN TEXT

12

13 **INTRODUCTION**

14 Trans cranial magnetic resonance–guided focused ultrasound (tcMRgFUS) has emerged as an
15 incisionless, safe (1, 2), accurate(3) and effective brain ablation technique for the treatment of
16 medication refractory essential tremor (ET) and Parkinson disease’s tremor. There is also
17 preliminary evidence that tcMRgFUS ventral intermediate (Vim) thalamotomy may result in
18 a promising effective treatment option for other tremors (4), including multiple sclerosis-
19 associated tremor (5).

20 Here, we describe two cases of multiple sclerosis (MS) patients with medication refractory
21 debilitating ET that successfully underwent unilateral Vim tcMRgFUS thalamotomy by using
22 a 1.5 Tesla magnetic resonance (MR) unit for procedure guidance(6).

23

24 **METHODS**

25 *Case presentation*

26 **Case 1** - A 71-years-old right-handed man, with a family history of tremor, was diagnosed
27 with ET because of the onset of postural and kinetic tremor of both hands when he was 30.
28 Ten years later, successively the onset of walking difficulties and fatigue, following a
29 complete diagnostic workup, MS was diagnosed. While clinical course was characterized by
30 few relapses with a mild increase of disability (motor and sensory impairment), without
31 cerebellar signs and symptoms, tremor which poorly responded to medical treatments
32 severely limited many daily activities (Table 1).

33 **Case 2** - A 44-years-old man with ET familiarity, that started complaining of tremor during
34 adolescence when he worked as a mechanic. MS disease onset was characterized by right
35 lower limb paresis at the age of 29. During the following years he experienced severe and

36 frequent relapses determining brainstem involvement with ophthalmoparesis, pyramidal signs
37 with mild paresis of the upper limbs and a more severe paresis of the legs limiting the
38 autonomy of the patient requiring cans to walk. Due to neuroradiological and clinical
39 evidence of disease activity, he started monthly natalizumab infusion. At the time of the visit
40 before FUS treatment, tremor involved arms, tongue, voice, and head, making him unable to
41 wash himself or use utensils or to hold an object (Table 1). An axial tremor was also present
42 particularly in standing position. ET first line treatments were not tolerated by the patient.
43 Botulinum neurotoxin (BoNT), transcranial magnetic stimulation and transcranial direct
44 current stimulation were ineffective.
45 Both patients refused deep brain stimulation (DBS) while they both agreed to undergo
46 unilateral tcMRgFUS Vim ablation.

47

48 **RESULTS**

49 Patient in case 1 underwent tcMRgFUS left thalamotomy in late October 2018 (Figure 1 and
50 Figure 2). After the tcMRgFUS treatment patient tremor recovered almost completely in the
51 correspondent arm and remained stable at the 1-year follow up visit (Table 1). Furthermore,
52 patient clinical condition and expanded disability status scale (EDSS) scores showed no
53 changes during the follow-up period and he was considered in a no evidence of disease
54 activity status (NEDA-4).

55 Patient in case 2, underwent tcMRgFUS left thalamotomy in early November 2018 (Figure
56 2). From a clinical point of view there was a reduction of the postural component of the
57 tremor despite no changes of the cerebellar tremor at the right arm (Table 1). The patient and
58 his relatives reported a slight improvement in the possibility to handle an object (i.e. to light
59 up a cigarette). After treatment the patient continued natalizumab infusion as usual with no

60 clinical or MRI patterns suggestive for disease activity or progression. At 1-year follow-up he
61 was considered as NEDA-4 status.

62

63 **DISCUSSION**

64 The cases we presented show that, also in patients with MS, unilateral tcMRgFUS ablation of
65 the Vim nucleus may be a safe and effective treatment option for ET. In both cases tremor
66 was a symptom already present when MS was diagnosed. Though this finding is an important
67 element from tremor etiopathogenesis perspective, our major concern in treating MS patients
68 was the risk of a modification of the clinical course of MS. Not only clinical or
69 neuroradiological sign of disease activity or progression following FUS treatment was not
70 observed, but patient in case 2 continued his therapy with natalizumab at the usual regimen
71 supporting the hypothesis that the FUS-induced controlled thalamic thermal ablation does not
72 influence patient's immune system activity and it doesn't change the clinical course of the
73 demyelinating disease nor the efficacy of the medication in preventing relapses.

74 Only one report exists in English literature about tcMRgFUS performed on an MS patient
75 with medically refractory right-hand mixed tremor (5). In this study a reduction of the CRST
76 score of the treated hand of 79.3% (from 29 at baseline to 6) persisting for 1 year, has been
77 reported. Both these preliminary experiences seem to support the use of tcMRgFUS for the
78 treatment of tremor in MS patients.

79 Anyhow there are still some open clinical questions to be addressed. As previously
80 discussed(5), one crucial point to be considered when generating a therapeutic lesion in a
81 brain that is already damaged by a chronic demyelinating process is that the reduced brain
82 network efficiency may influence the clinical outcome as well as the severity of transient side
83 effects commonly reported in the first weeks after the tcMRgFUS procedures. We do also
84 agree about the importance of a very careful selection and accurate intraprocedural clinical

85 evaluation. It is also worth noting, that our patients did not show worsening pyramidal or
86 sensory symptoms after the procedure, nor they had any mood or cognitive impairment at
87 subsequent follow ups. These elements, together with any changes in the therapeutic response
88 to the administered drugs, are critical and deserve great attention in MS patients.

89

90 **CONCLUSIONS**

91 MS is one of the commonest non-traumatic invalidating disease affecting young adults.

92 Already in itself characterized by a considerable high societal costs per patient (7, 8), not

93 rarely MS might be associated with other embarrassing and disabling diseases such as ET.

94 Since medication effectiveness on tremor is very limited, this symptom remains challenging

95 even considering other treatment options (BoNT, DBS).

96 Furthermore, many MS patients are often reluctant to undergo conventional surgery. In this

97 scenario, tcMRgFUS should be investigated as an alternative treatment option to assess the

98 safety and long-term clinical outcomes in larger patient samples including not only patients

99 with ET and MS as a comorbid condition, but also those with MS-associated tremor.

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