Giuseppe Messina, Michele Rizzi, Miryam Carecchio,
Roberto Cordella, Angelo Franzini

11 Movement Disorders: Dystonia

Different forms of dystonia, including primary focal and generalized dystonia and secondary dystonia due to ischemic or traumatic brain injuries generally respond poorly to medical and conservative treatments. Mobile forms of dystonia, characterized by twisting, repetitive movements which result in abnormal, often painful postures, are classified according to the anatomical distribution of abnormal movements (focal, segmentary, generalized), presence or absence of a clear etiology (idiopathic or secondary), and age at onset (early or late forms). Medical therapies include the use of triexylphenidyl, tetrabenazine, benzodiazepines and baclofen. Focal dystonias, such as writer's cramp, may also benefit from local botulinum toxin injections, but generalized forms cannot and often do not respond satisfactorily to medical treatment.

A great heterogeneity exists with regard to the etiology of abnormal fixed postures of several body segments: they may develop following different focal brain lesions involving the basal ganglia, be psychogenic, or occur in the context of the so-called fixed dystonia (FD) syndrome. The prominent clinical feature seen in FD is the permanent abnormal posture of the affected body segments that never revert to normal positions. Accordingly, it is important to differentiate it from segmentary spasticity, which shows a typical pattern of muscular involvement, and from primary forms of dystonia that tend to be mobile and lack, by definition, structural abnormalities on brain imaging. FD is clinically and often etiologically different from mobile dystonia because it is more frequently focal and less frequently segmentary. It often causes a significant level of functional impairment, also due to poor response to medical treatment (Schrug et al 2004). FD can be idiopathic or be part of other conditions including corticobasal degeneration, advanced-stage primary dystonia and causalgia-dystonia syndrome. FD can also be accompanied by severe psychiatric disorders, thus being frequently misdiagnosed as somatization disorder or psychogenic dystonia. Prognosis is poor. In a series, only 6% of patients reached remission, 25% improved and 33% continued worsening (Ibrahim et al 2009).

The main surgical options that can be offered to these patients are Deep Brain Stimulation (DBS) and Implantable Cortical Stimulation (ICS). DBS of the posteroventrolateral (somato-sensory) portion of both GPs is considered a well-established and effective surgical procedure for the treatment of primary and secondary generalized dystonia, as well as of primary cervical dystonia. In this chapter, we address the results of extradural ICS.

11.1 Overview

Fixed dystonia (FD), which is poorly responsive to DBS (Romito et al 2007, Lalli et al 2012), has been observed to improve in patients with thalamic hand syndrome and in post-stroke fixed postures (Franzini et al 2000). Good control of involuntary movements has been reported by one Japanese group (Katayama et al 2002, Yamamoto et al 2011): in 2 of 3 patients with hemichoreo-athetosis, 2 of 2 patients with distal resting or action tremor, and 1 of 3 patients with proximal postural tremor. Two patients with chronic pain had their dystonic posture improved (Nuti et al 2012). The acute effects of M1 ICS in a patient with spasmodic torticollis unresponsive to thalamotomy are on record (Canavero et al 2003). The theoretical basis of application of CS in dystonia relies on the modulatory role of the pre-motor or primary motor cortex on sensori-motor cortico-strio-pallido-thalamic circuits.

Two targets are possible for CS: the primary motor cortex (M1) or the premotor cortex (PMC). Both have been implicated in the genesis of dystonia by non-invasive CS studies (Khedr 2009; Murase et al 2005, Huang et al 2004).

We recommend localization of M1 by preoperative fMRI because of the frequent aberrant representation of the affected area resulting from abnormal intracortical plasticity underlying dystonia. The latter variable could thus affect the actual position and size of M1. We perform intra-operative EMG by delivering electrical current from various combinations of the epidural contacts, to ascertain which is capable, singly or in combination, to evoke motor potentials in the affected part of the body. Delivered current is gradually increased until motor potentials are recorded; partial or generalized seizures are not an uncommon occurrence, and they can be abolished either by local administration of cold saline or by IV diazepam. At the end of this procedure, the electrode can be secured to the burr-hole with a titanium miniplate. In case of a craniotomy, the electrode(s) can be directly sutured to the underlying dura mater. Surgery is then completed by subcutaneously tunneling the connection cable (in the lateral cervical region) to an infraclavicular pocket, where the IPG is positioned.

Our group has previously reported (Lalli et al 2012) an overall improvement in 7 patients affected by primary pure focal dystonia (6 with cervical dystonia ([Table 11.1](#)) and 1 with upper limb dystonia), who underwent extradural PMC ICS under general anesthesia.

Table 11.1:

	Patients number	BFMDRS improvement at 12 months	TWSTRS improvement at 12 months	QOLI improvement (SIP scale)
Neurostimulation group	6	17%	15%	50%

Cervical dystonia patients received a bilateral epidural cortical electrode implant of the PMC, the patient with limb symptoms a unilateral implant on the contralateral cortex. The target was set 2 cm anterior to the hand area in M1. The electrodes were all perpendicular to the precentral gyrus, after electrophysiological localization of the central sulcus (N20-P20 phase reversal). In cervical dystonia cases, monopolar stimulation was performed with 2 active contacts on the PMC (0-,1-, case +); in the upper limb dystonia patient, there were 3 active contacts (0-,1-,2-, case +). Stimulation was continuous for 24 hours. The improvement was rated by the Burke-Fahn-Marsden scale (BMFS) and by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and was observed after a 12-months' follow-up period. *No effect on dystonia was observed immediately upon start of stimulation.* There was an improvement on the BFMS at 6 months that remained unchanged at 12 months. ICS was substantially ineffective in the patients with a mainly fixed posture of the dystonic body segment. The patient with limb dystonia improved 51% at 1 year. Though non significant, *working visual memory, phonemic fluency, anxiety and depression showed an improvement.* We also found baseline (pre-operative) and bilaterally increased cortical metabolism in S1/M1 - as compared to controls- on ¹⁸F-fluoro- deoxy-glucose positron emission tomography (FDG PET). This metabolic increase was found to be reduced during a 12 month post-surgery follow up, suggesting a modulatory or rebalancing role of epidural stimulation on hyperactive S1/M1.

We (Messina et al 2012) then submitted 10 patients affected by secondary fixed dystonia (FD) of the upper limb to M1 ICS. Here, we include a further patient affected by an ischemic thalamic stroke, for a total of 11 cases. The rationale for M1 ICS was based on the hypothesis that an abnormal cortical representation of the affected body segment could follow deep brain lesions (Opavsky et al 2006). Also, we reported on a patient affected by fixed hemidystonia who was unresponsive to Gpi DBS but not to M1 ICS (Romito et al 2007). All patients treated were refractory to conventional medical and non-invasive treatments (benzodiazepines, baclofen, motor rehabilitation, and botulinum toxin injections) and did not fulfil the Fahn and Williams's criteria for psychogenic dystonia. All were severely disabled: 5 patients had fixed dystonia secondary to cortical or subcortical ischemic stroke; in 1 patient to birth anoxia; in 2 patients to iatrogenic post-surgical syndromes; in 1 patient to postencephalitic syndrome; in 1 patient to long-term neuroleptic treatment (tardive dystonia); and in the last patient secondary to brain trauma. A movement disorder neurologist evaluated all patients both pre-operatively and post-operatively. These evaluations confirmed the phenotypic characteristics of unilateral upper limb fixed dystonia, involving, with various degrees of severity, shoulder, arm, forearm, and hand. Polygraphic EMG recordings showed tonic muscular co-contractions in the affected muscles at rest in all patients. Extensive psychiatric examination excluded the diagnosis of psychogenic dystonia, and complex regional pain syndrome (CRPS)-associated dystonia.

11.1.1 Surgical Procedure

In all patients, a unilateral quadripolar paddle electrode (Resume II, Medtronic, Minneapolis, Minnesota) was positioned on the dural surface corresponding to the “hand-knob” area of M1 of the side contralateral to the affected upper limb. Surgery was performed under general anesthesia in all patients without curarization, under neuronavigation guidance (Stealth Station System, Medtronic, Minneapolis, MA, USA) and through intraoperative electromyography (EMG) for localization of the hand-knob area. A 3-cm skin incision was made 4 cm behind the coronal suture and 3 cm lateral from the midline. A burr hole was performed to expose the dura mater overlying the postero-medial portion of the central gyrus. After dural dissection, from the internal cranial bone, the quadripolar electrode was placed parallel to the premotor cortex and along its main axis (as indicated by the navigation system); when a motor response was unelicitable, we changed the orientation of the paddle electrode until recording the appropriate upper limb’s EMG responses (abductor pollicis brevis muscle). Muscular sites monitored intra-operatively with EMG were the orbicularis oris, brachioradialis, abductor pollicis brevis, rectus femori, tibialis anterior, and extensor digitorum brevis. After the electrode’s initial positioning, a set of stimulation trials was delivered to evoke EMG responses in the affected muscles, specifically in the abductor pollicis brevis. In all cases, electric stimulation through the epidural quadripolar strip (60 Hz, 1 ms pulse width) evoked selective motor response and EMG activation of hand and upper limb muscles with 4 to 7 mA (Fig.11.1). Every procedure was completed with the subcutaneous implantation of a single-channel IPG and its connection cable to the epidural electrode. The day after surgery, the IPG was activated in all patients, and stimulation parameters adjusted to the threshold for the elicitation of side effects (such as paresthesias) and to the clinical effects during follow-up.

Fig. 11.1: Intraoperative EMG showing activation of hand muscles after stimulation with epidural paddle electrode.

11.1.2 Assessment and Outcome

Patients were evaluated using the Disability of Arm, Shoulder and Hand (DASH) scale and the Short Form-36 Physical Activity subscale. 7 out of 11 patients evinced a >30% improvement on the DASH scale and an overall 70% increase on the latter. A postoperative CT scan was merged with the preoperative 3D MR scan and the correct positioning of the epidural electrode was confirmed in all patients ([Fig.11.2-11.3](#)). The postoperative course was uneventful in all but 1 patient, who required surgical evacuation for an acute epidural hematoma; after 6 months the whole system was re-implanted. No patient experienced seizures during parameters' search. The final stimulation parameters were set at the 6-month follow-up examination in all patients and the configuration was quadruple monopolar (Case as Anode, contacts 0,1,2, 3 as Cathodes). The follow-up ranged from 1 to 9 years. Periodic reassessment was carried out monthly in the first 6 months and then on a 6-month basis. The DASH Scale was employed, together with a self-report questionnaire to measure physical function and symptoms (SF-36). Higher DASH scale scores indicate greater disability. This scale focuses on the whole functionality of the affected segment of the body, better than more traditional scales employed for classical predominantly "mobile" dystonia. The overall degree of disability of patients was high due to total refractoriness to conservative treatment: an improvement of 30% of the DASH scores is thus significant and 7 patients reached this level of improvement at the latest follow-up ([Table 11.2](#)). The overall improvement on the SF-36 scale may indicate the high degree of interference resulting from this pathological condition on overall well-being. Although differences between pre- and postoperative DASH scores found in this series do not seem impressive if only numerical data are taken into account, nevertheless, even small changes in DASH score reflected a significant higher quality-of-life score ([Table 11.2](#)). Placebo effects cannot be discounted, but given refractoriness to conventional treatments this seems unlikely.

Fig. 11.2: 3-dimensional postoperative reconstruction showing the placement of the chronic leads over the motor cortex.

Fig. 11.3: *Top:* 3-dimensional reconstruction of the post-operative Computerized Tomography showing the contacts of the paddle electrode which allowed stimulation of contralateral hand muscle; above, an axial functional MRI image showing aberrant activation of hand motor cortex in the affected contralateral hand; *Bottom:* the affected hand of the patient before (left) and 4 months after MCS (right).

Rieu et al (2014) reported a double-blind, crossover, multicenter study involving 5 patients affected by dystonia secondary to focal post-ischemic basal ganglia (BG) lesions, who underwent extradural CS (Table 11.3). All the patients suffered from hemidystonia secondary to a basal ganglia vascular lesions. For every patient, two parallel quadripolar electrodes were positioned in the epidural space overlying both MI and PMC, parallel to the central sulcus, under neuronavigation guidance. The anode was positioned over the motor representation of the most affected limb on M1; PMC-wise, the electrodes were positioned over the superior and the middle frontal gyri. In all patients, post-operative CT confirmed optimal positioning of the electrodes. In this case series, the BFMS, the Ashworth scale for spasticity, Visual Analogue Scale (VAS) for Pain and SF-36 for quality of life were used for pre- and postoperative evaluations. After one month from implantation, patients were randomly assigned to two groups: stimulation-on and stimulation-off groups; such condition was maintained for three months; after a washout period of one month, a clinical evaluation was performed and the on-off condition was reversed; again, this was maintained for other three months and, then, a second follow-up was carried out. The above-mentioned scales scores were not significantly modified at any evaluation time, thus no patient benefited from the procedure. Given the study design and the negative results obtained, the Authors concluded that Class I evidence exists that epidural CS failed to improve dystonia secondary to BG lesions. This is untenable, since these patients presented with mobile rather than fixed dystonia, the sample size was limited (5 patients) and the follow-up period relatively short (3 months). Also in light of the slow build-up of effect, the 1-month intervals may have been too short

11.2 Conclusion

How CS achieves its results remains unknown, but similar arguments to Parkinson disease can be made (see Chapter 10). Increased M1 excitability has been demonstrated in patients with dystonia secondary to focal lesions of the basal ganglia and thalamus (Trompetto et al 2012). An involvement of cerebellar pathways should also be considered.

The generator of FD could be an increased thalamocortical drive resulting in hyperexcitability of the sensorimotor cortex; the overactivation of glutamatergic input to the cortex could be caused by an unbalance between the so-called direct and indirect corticonuclear pathways, although why in some patients this may result in fixed postures rather than typical mobile dystonic movements remains unexplained. In fact, according to the direct-indirect pathways theory, lesions localized in the motor portion of the thalamus (such as those found in 3 of our patients) would more likely suppress movements instead of increasing the thalamocortical drive. Moreover, not all patients affected by acquired basal ganglia lesions present with FD, and spasticity, tremor, myoclonus, and athetosis can develop as well. Complex interactions between

Table 11.2:

Pt nr.	Origin	Stimulation Parameters	DASH pre	DASH post	Improvement %	SF-36 Physical Activity Subscale pre	SF-36 Physical Activity Subscale post	SF-36 Mental Subscale pre	SF-36 Mental Subscale post	Follow-up
1	Striatal stroke	120 µs, 30Hz, 2.5V	86	57	34	0	85	64	88	36
2	Parieto-temporal stroke	90 µs, 50Hz, 3.5V	90.5	77.6	15.1	0	40	24	72	48
3	Temporo-occipital and thalamic stroke	120 µs, 50Hz, 3V	92	49.1	47	30	85	28	48	24
4	Viral meningitis	120 µs, 30Hz, 3.1V	72.4	64.2	12.4	10	75	36	60	24
5	Bulbopontine cavernoma	90 µs, 30Hz, 3V	32.5	18.1	44.4	20	65	36	44	24
6	Perinatal hypoxia	120 µs, 50Hz, 3V	48.3	30.8	36	75	100	40	52	24
7	Neuroleptic-induced dystonia	90 µs, 50Hz, 3.3V	87.1	28.4	67	0	95	4	100	24
8	Thalamic oligoastrocytoma	120 µs, 50Hz, 3.5V	66.4	44.8	32	20	75	28	60	24
9	Thalamic stroke	120 µs, 30Hz, 2.8V	75	28.4	62	60	80	44	76	24
10	Post-Traumatic putamenal stroke (bilat.)	150 µs, 30Hz, 4V	84	66	22.3	40	40	56	60	120
11	Thalamic stroke	150 µs, 40Hz, 4V	80	74	7.5	40	40	50	64	4

the different subcircuits of the cortico-striato-pallido-thalamo-cortical loops are likely at work. Maladaptive cerebral plasticity may subtend secondary FD. In one of our patients, FD developed after surgery for a right bulbopontine cavernous hemangioma; the role of brainstem lesions in the pathophysiology of dystonia has not been elucidated, but several reports point to a role of dysfunction of ascending and descending pontomesencephalic pathways such as the central tegmental tract and the dentatothalamic fascicle, as well as the pedunculopontine nucleus and the nucleus interstitialis of Cajal (Loher and Krauss 2009). The problem of CS-refractory patients can be explained by maladaptive plasticity extending beyond the targeted areas, perhaps even bilaterally, and this must be explored in future studies.

In sum, surgical CS is a new alternative for the management of FD.

Table 11.3:

Pt nr.	Origin	Stimulation Parameters	BFM (global) at baseline	BFM at 3 months (Stim OFF)	BFM at 3 months (Stim ON)	VAS at baseline	VAS at 3 months (Stim OFF)	VAS at 3 months (Stim ON)
1	Right subthalamical and cerebral peduncle stroke	60 μ s, 40Hz, 3.8V	22	20	17	8.2	3.72	6.38
2	Right globus pallidus stroke	60 μ s, 40Hz, 3.8V	14	18.5	20	6.2	7.98	0
3	Right striatum stroke	60 μ s, 40Hz, 3.8V	20	20	24	6.1	5.67	7.55
4	Right striatum and frontotemporo-parietal cortex stroke	60 μ s, 40Hz, 3.8V	22	15	15	7.1	3.62	4.15
5	Right striatum and right parietal cortex stroke	60 μ s, 40Hz, 3.8V	28	24	32.5	7.1	4.95	9.25

References

- Canavero S, Bonicalzi V, Paolotti R, et al. Therapeutic extradural cortical stimulation for movement disorders: a review. *Neurol Res* 2003;25:118-22.
- Franzini A, Ferroli P, Servello D, et al. Reversal of thalamic hand syndrome by long-term motor cortex stimulation. *J Neurosurg*. 2000;93:873-875
- Franzini A, Ferroli P, Dones I, et al. Chronic motor cortex stimulation for movement disorders: a promising perspective. *Neurol Res*. 2003;25:123-126.

- Franzini A, Messina G, Marras C, et al. Poststroke fixed dystonia of the foot relieved by chronic stimulation of the posterior limb of the internal capsule. *J Neurosurg.* 2009;111:1216-1219.
- Huang YZ, Edwards MJ, Bhatia KP, et al. One-Hz repetitive transcranial magnetic stimulation of the premotor cortex alters reciprocal inhibition in DYT1 dystonia. *Mov Disord.* 2004 ;19:54-9
- Ibrahim NM, Martino D, van de Warrenburg BP, et al. The prognosis of fixed dystonia: a follow-up study. *Parkinsonism Relat Disord.* 2009;15:592-7
- Katayama Y, Oshima H, Fukaya C, et al. Control of post-stroke movement disorders using chronic motor cortex stimulation. *Acta Neurochir Suppl.* 2002;79:89-92.
- Khedr EM. Noninvasive stimulation for treatment of movement disorders. In: Canavero S (ed) *Textbook of therapeutic cortical stimulation.* New York: Nova Science, 2009, pp 183-200
- Lalli S, Piacentini S, Franzini A, et al. Epidural premotor cortical stimulation in primary focal dystonia: clinical and 18F-fluoro deoxyglucose positron eMission tomography open study. *Mov Disord.* 2012;27:533-8
- Loher TJ, Krauss JK. Dystonia associated with pontomesencephalic lesions. *Mov Disord.* 2009;24:157-67
- Messina G, Cordella R, Dones I, et al. Improvement of secondary fixed dystonia of the upper limb after chronic extradural motor cortex stimulation in 10 patients: first reported series. *Neurosurgery.* 2012;70:1169-75
- Murase N, Rothwell JC, Kaji R, et al. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain.* 2005 ;128(Pt 1):104-15.
- Nuti C, Vassal F, Mertens P, et al. Improved dexterity after chronic electrical stimulation of the motor cortex for central pain: a special relevance for thalamic syndrome. *Stereotact Funct Neurosurg* 2012;90:370-8.
- Opavsky R, Hlustik P, Kanovsky P. Cortical plasticity and its implications for focal hand dystonia. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2006;150:223-226
- Rieu I, Aya Kombo M, Thobois S, et al. Motor cortex stimulation does not improve dystonia secondary to a focal basal ganglia lesion. *Neurology.* 2014 ; 82:156-62
- Romito LM, Franzini A, Perani D, et al. Fixed dystonia unresponsive to pallidal stimulation improved by motor cortex stimulation. *Neurology.* 2007;68: 875-876.
- Schrag A, Trimble M, Quinn N, et al. The syndrome of fixed dystonia: an evaluation of 103 patients. *Brain.* 2004;127(Pt 10):2360-72.
- Trompetto C, Avanzino L, Marinelli L, et al. Corticospinal excitability in patients with secondary distonia due to focal lesions of the basal ganglia and thalamus. *Clin Neurophysiol.* 2012;123:808-14
- Yamamoto T, Katayama Y, Watanabe M, et al. Changes in motor function induced by chronic motor cortex stimulation in post-stroke pain patients. *Stereotact Funct Neurosurg.* 2011;89:381-9.