Mood Disorder Following DBS of the Left Amygdaloid Region in a Dystonia Patient with a Dislodged Electrode

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Abstract: **Continuous high-frequency stimulation of the globus pallidum internum (GPi) is an accepted treatment for patients with primary dystonia. In a series of 18 consecutive dystonia cases that were successfully treated by bilateral GPi stimulation, 1 patient had an adverse event involving the downward migration of the electrodes. He developed remarkable behavioral complications and was found to have dislodgement of the left electrode to a position close to the left amygdala. The patient developed behavioral changes consisting of depression, psychotic symptoms, and heightened pain perception. This syndrome reverted when the left electrode was removed and a new one inserted in the correct position. We describe in detail the clinical features associated with left amygdala dysregulation induced by high-frequency stimulation through the displaced electrode.** © 2007 Movement Disorder Society

Key words: amygdala; deep brain stimulation; globus pallidum; dystonia; depression.

Dystonia is a clinical syndrome characterized by sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures; the movement disorder may remain stable or progress to a variable severity. Deep brain stimulation (DBS) of the globus pallidum internum (GPi) has emerged as an effective new therapeutic strategy for dystonia, particularly for generalized or cervical dystonia.[1] It has been reported that behavior and mood remain stable in these patients after bilateral GPi implants.[2]

We describe here a patient with cervical dystonia who developed marked behavioral symptoms following migration of the left electrode into the left amigdaloid region.

CASE REPORT

A right-handed man developed neck pain and involuntary neck movements at age 19 and was referred to us in 2001 at age 26. He had non-DYT1 primary generalized dystonia with unremarkable family history for movement disorders or other neurological or psychiatric diseases. The patient was initially treated with botulinum toxin and oral medications without benefit.

In 2005, he was readmitted for electrode implantation in the globus pallidum internum (GPi): the dystonia had become more severe with major trunk involvement and lumbar lordosis, which was a source of intense pain. There were head postures and continuous dystonic movements of the trunk, head, and upper limbs. The motor condition was rated with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Fahn-Marsden Dystonia Rating Scale (FMDRS)[3] (Table 1). Neuropsychological evaluation before implant was unremarkable. The Structured Clinical Interviews for DSM-IV Axis I and II disorders (SCID)[4] ruled out psychosis, substance abuse, mood, anxiety, or personality disorders. The patient had no premorbid psychiatric features, including depression.

After informed consent, Medtronic 3389 electrodes were implanted bilaterally in the GPi under stereotactic condition.[5] The electrodes were connected to a single subclavicular pulse generator (Kinetra, Medtronic). Postoperative CT brain imaging and skull X-ray confirmed a bilateral placement in the GPi (Fig. 1a). Amplitude and pulse width were increased gradually. The final settings were as follows: right side 2.4 V, 150 μs, 180 Hz, contact 2 monopolar cathode; left side 2.7 V, 180 μs, 180 Hz, contact 5 monopolar cathode.

Four months after implant, the TWSTRS and FMDRS scores were markedly reduced (Table 1). Dystonia had improved in all body regions and pain had almost completely disappeared. The patient reported that regression of symptoms had improved his quality of life; he was socially involved with family and friends, looked for work, and made plans for the future.

The patient was scheduled for a re-evaluation 6 months after implant, but did not show up. He presented, instead, 9 months after implant accompanied by his brother, who reported that 5 months after implant there had been a recurrence of dystonia, particularly in the neck, which progressed slowly and was accompanied by pain.

Mood had deteriorated and the patient appeared depressed, overtly irritable, with abrupt onset of short-

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TABLE 1. *Motor and neuropsychological profile of the patient at different times of observation*

	Before implant	4 months after implant	9 months after implant	After reimplant
Motor tests				
FMDRS	35.5	5.5	19	6
TWSTRS				
Severity	25	10	15	8
Disability	23	5	16	3
Pain	9.5	2.5	12.5	2
Neuropsychological tests (normal scores)				
Mini-mental state examination (≥24)	26		28	
Memory				
Visuo-spatial span (≥3.75)	4		4	
Supraspan visuospatial learning (≥5.75)	27.54		26.68	
Attention and executive functions				
Raven's coloured progressive matrices (≥18)	25		28	
Attentional matrices (≥31)	54		54	
Modified card sorting test	Normal		Normal	
Language and praxis				
Token test (≥26.5)	32		31	
Buccofacial praxis (≥18)	20		20	
Upper limb praxis (≥17)	20		20	

Abbreviations: FMDRS, Fahn-Marsden Dystonia Rating Scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

lasting rage against his relatives. He had frequent outbursts of anxiety (increased lability), particularly during social interactions. His brother further reported that he had expressed feelings of hopelessness and helplessness, talked about committing suicide, progressively lost appetite (weight loss of 7 kg), and was only sleeping about 1 hour at night, but had begun sleeping during the day. Most recently he was spending nearly all the day in his bed. He had not taken antidepressants or other analgesic drugs and had not requested medical assistance. His brother had difficulty persuading the patient to return to us.

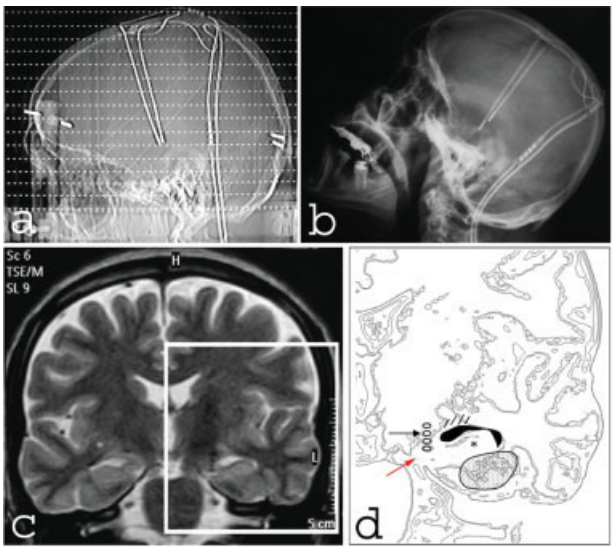

FIG. 1. (**a**) X-ray image showing localization of the electrodes after the first DBS implant; (**b**) X-ray image showing displacement of the left electrode; (**c**) MRI image of the displaced left electrode tip showing contacts located in the left amygdaloid region; (**d**) anatomical drawing showing detail of the box in panel c. Symbols: *: Hippocampal formation; →: Active contact; ■: Temporal horn of lateral ventricle; ///: Area of stria terminalis; ▨: Area of posterior amygdala; ⬭: Contacts; ➞: Fimbria.

On examination, 9 months after implant, with stimulation turned on, there was overt dystonia, with severe painful involuntary movements in the trunk and neck. Pain was reported as more intense than before implant, but axial dystonia had not recurred to preimplant severity. Neuropsychological evaluation was unchanged (Table 1). The neuropsychiatric inventory (NPI),[6] filled in by the brother, indicated severe apathy and depression, moderate anxiety, mild agitation, irritability, and delusions with megalomanic content. SCID showed severe depressive mood with incongruent delusions. The patient demanded that people follow his orders and ask his permission before they take any action; he also reported having had paranormal abilities and experiences in the past, and claimed to be able to heal people.

Electrode migration was confirmed by MRI, CT, and skull X-ray: the left electrode tip was no longer in the GPi, but had moved to the region of the amygdala (Fig. 1b,c). Reconstruction of MRI images suggested that contact 0 was in the fimbria, whereas active contact 2 was in the stria terminalis (Fig. 1d). The right electrode had remained in the correct position. The left electrode was then turned off and the patient was addressed to surgery for its immediate removal. This was successfully per-

formed and a new electrode was placed in the left GPi under stereotactic guidance. Post-reimplant CT confirmed the correct positioning, and the following stimulation parameters were set: right side 2.1 V, 210 μs, 130 Hz, contact 2 monopolar cathode; left side 2.3 V, 180 μs, 130 Hz, contact 5 monopolar cathode. The patient's dystonia improved soon after reimplant. Fast dystonic movements of the neck and trunk disappeared and postural dystonia, particularly retrocollis, improved. Behavioral and mood abnormalities also improved gradually. A month later, the SCID was unremarkable and the NPI (filled in by the brother) suggested only mild anxiety.

Five months after reimplant the TWSTRS and FMDRS scores were improved (Table 1). The SCID ruled out psychosis or other psychiatric disorders. The patient had difficulty remembering episodes in the period immediately preceding reimplant, he particularly had no memory of his recurrent thoughts of death, but did remember having delusions.

DISCUSSION

Migration of DBS electrodes is not a rare occurrence, particularly in cervical dystonia patients, whose forceful head and neck contractions are the primary cause of displacement.[7] This case is unique because of the site of migration (left amygdaloid region) and of the ensuing syndrome that reversed following replacement of the displaced electrode. The resulting clinical syndrome was dramatic, and progressive, and consisted in depression, psychotic symptoms, and heightened pain perception. The observed behavioral features are different from mood changes reported after GPi DBS and can be specifically related to the involvement of the left amygdala.

In dystonia patients with GPi implants, transient mood changes, mainly consisting in improvement of depression, have been reported.[2,8] They are most likely because of the marked alleviation of disabling dystonia and improvement of functional abilities. It is remarkable that in this case no mood changes were reported immediately after surgery, i.e., before lead migration presumably occurred.

The incidence of electrode migration is 0 to 6.3% in Parkinson's disease patients and 3 to 7.9% in dystonia patients.[7] This is usually detected some time after its occurrence, on average between 12 and 36 months postoperatively.[7,9] In our patient, electrode displacement occurred after the evaluation at 4 months that showed a significant postoperative improvement and no side-effects.

The left amygdaloid syndrome observed in this case encompassed affective disturbance (depression and apathy), psychotic symptoms (delusions with megalomanic content), and heightened pain perception. This picture fulfilled DSM-IV criteria for major depressive episode with mood-incongruent psychotic features. Notably, this patient had not suffered from depressed mood during the 11 years of dystonia prior to implant, nor was he depressed during the 4 or 5 months of bilateral GPi stimulation following implant. We presume the electrode became displaced at around this time, in coincidence with the development of mood and behavioral changes.

Dramatic behavioral changes with sedation have been reported following unilateral or bilateral ablative lesions of the amygdala.[10] High-frequency stimulation is thought to inactivate cell bodies in the stimulated area, and to stimulate nerve fibers of passage; the electrical field generated using therapeutic stimulation settings is capable of directly affecting tissue up to 4 mm from the electrode.[11] The location of the displaced electrode in our case is compatible with the stimulation of both the amygdalofugal pathways and the hippocampal efferents traveling in the fimbria. The amygdaloid output might be activated through the stimulation of the stria terminalis, located close to the inferior horn of the lateral ventricle, medial to the tail of the caudate nucleus (shaded area in Fig. 1). As an alternative, the observed mood disorder could be explained by the stimulation of the hippocampal fimbria (arrow in Fig. 1). In laboratory animals, the development of learned helplessness, one of the most widely studied models of depression, is completely blocked by fimbria-fornix transection.[12] Moreover, the same model is characterized by a reduction of GABA activity in the hippocampus,[13] suggesting that a hyperactivity of the hippocampal output facilitates helpless behavior.

There are no human reports of left amygdaloid syndromes. Preclinical studies indicate that the left amygdaloid body is involved in the perception of fear with a different time course compared to the right amygdala.[14] The left amygdala is particularly involved in depression and in the modulation of associated behavioral and emotional responses.[15] Interestingly, transient depression has also been described following high-frequency stimulation of the left substantia nigra[16]; in that case, in fact, the midbrain stimulation may have produced its effects by influencing the left amygdala, which has direct projections to the substantia nigra pars compacta and in turn receives dopaminergic projections from the midbrain.

The occurrence of delusions may also be related to stimulation of the left amygdala.[17] In keeping with this, it has been observed that the size of the left amygdala inversely correlates with the severity of thought disorder, and that its metabolic activity correlates with positive symptoms in schizophrenic subjects.[18] Finally, heightened pain perception reported by our patient may be

related to a dysfunction of the central nucleus, the so-called nociceptive amygdala.[19] It is well accepted that the amygdala is involved in pain processing.[20]

It is remarkable that such complex behavioral changes can be evoked by electrical stimulation of a minute region of the brain in a person with no history of depression or other altered behavior. In our patient the observed behavioral alterations were all plausibly attributable to activation of the left amygdala and it is noteworthy that they all regressed when the source of activation was removed. The observed adverse event confirms and broadens, with a direct observation in man, the role of the amygdaloid complex previously depicted by animal studies.

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