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Update on neurosurgical treatment for obsessive compulsive disorder

Atualização sobre o tratamento neurocirúrgico do transtorno obsessivo-compulsivo

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Abstract Responses to pharmacotherapy and psychotherapy in obsessive-compulsive disorder (OCD) range from 60 to 80% of cases. However, a subset of OCD patients do not respond to adequately conducted treatment trials, leading to severe psychosocial impairment. Stereotactic surgery can be indicated then as the last resource. Five surgical techniques are available, with the following rates of global post-operative improvement: anterior capsulotomy (38-100%); anterior cingulotomy (27-57%); subcaudate tractotomy (33-67%); limbic leucotomy (61-69%), and central lateral thalamotomy/anterior medial pallidotomy (62.5%). The first technique can be conducted as a standard neurosurgery, as radiosurgery or as deep brain stimulation. In the standard neurosurgery neural circuits are interrupted by radiofrequency. In radiosurgery, an actinic lesion is provoked without opening the brain. Deep brain stimulation consists on implanting electrodes which are activated by stimulators. Literature reports a relatively low prevalence of adverse events and complications. Neuropsychological and personality changes are rarely reported. However, there is a lack of randomized controlled trials to prove efficacy and adverse events/complication issues among these surgical procedures. Concluding, there is a recent development in the neurosurgeries for severe psychiatric disorders in the direction of making them more efficacious and safer. These surgeries, when correctly indicated, can profoundly alleviate the suffering of severe OCD patients.

Keywords Obsessive-compulsive disorder. Psychosurgery. Neurosurgery. Surgery. Review.

Resumo O transtorno obsessivo-compulsivo (TOC) responde aos tratamentos habituais (fármacos e psicoterapia) em cerca de 60 a 80% dos casos. Existe, assim, uma parcela de pacientes resistente aos tratamentos usuais, mesmo que adequadamente conduzidos, com grave prejuízo psicossocial. Nestas situações, a neurocirurgia pode ser indicada. Existem cinco técnicas cirúrgicas disponíveis, com as seguintes taxas de melhora global pós-operatória: capsulotomia anterior (38 a 100%); cingulotomia anterior (27 a 57%); tractotomia subcaudado (33 a 67%); leucotomia límbica (61 a 69%) e talamotomia central lateral com palidotomia anteromedial (62,5%). A capsulotomia anterior pode ser realizada através de diferentes técnicas: neurocirurgia padrão, radiocirurgia ou estimulação cerebral profunda. Na neurocirurgia padrão, circuitos neurais são interrompidos por radiofreqüência via trepanação no crânio. Na radiocirurgia, uma lesão actínica é induzida sem a necessidade de abertura do crânio. A estimulação cerebral profunda consiste na implantação de eletrodos ativados a partir de estimuladores. A literatura indica taxas relativamente baixas de eventos adversos e complicações, sendo raramente descritas alterações neuropsicológicas e de personalidade. Cumpre ressaltar, no entanto, a falta de ensaios clínicos randomizados que comprovem a eficácia e investiguem os eventos adversos ou complicações dos procedimentos cirúrgicos acima mencionados. Concluindo, há um recente aprimoramento das neurocirurgias dos transtornos psiquiátricos graves no sentido de torná-las cada vez mais eficazes e seguras. Estas cirurgias, quando adequadamente indicadas, podem trazer alívio substancial ao sofrimento de pacientes com TOC grave.

Descritores Transtorno obsessivo-compulsivo. Psicocirurgia. Neurocirurgia. Cirurgia. Revisão.

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Introduction

Obsessive-compulsive disorder (OCD), particularly in its severest forms, course with a high degree of psychical suffering and psychosocial impairment, sometimes comparable to that of schizophrenia.[1,2]

The therapeutical response to the usual treatments is still limited. Currently, 60% to 70% of patients respond to pharmachotherapy with serotonin reuptake inhibitors (SRI), while 60% to 80% of them improve with behavioral therapy.[3-4] Therefore, nearly 40% of OCD patients do not respond well to adequate therapeutic measures. Different treatment approaches are proposed for resistant cases, such as the association of medications, aiming to their augmentation. Neurosurgeries are a therapeutical alternative when all conventional approaches failed.

History of neurosurgery in psychiatric disorders and in OCD

The first neurosurgeries for the treatment of psychiatric disorders were the cases described by Egas Moniz.[5] The inexistence of therapeutical alternatives promoted the rapid proliferation of this treatment in the '40s and the '50s, sometimes indiscriminately. Pre-frontal leucotomy was the main technique in the different neurosurgical centers at that time. Personality alterations and frontal lobe dysfunctions were, however, the rule among operated patients. The ensuing advent of effective medications and the pressures from the public opinion regarding the negative effects of the surgery have culminated in the progressive decline in the utilization of psychosurgery.

In 1947 the first stereotactic neurosurgeries were developed, reducing considerably many post-operative adverse effects and complications.[6] Since then, different centers have started to employ several stereotactic techniques, such as anterior cingulotomy (US),[7] capsulotomy (Sweden),[8] subcaudate tractotomy[9] and limbic leucotomy[10] (England and Australia). Afterwards, Leksell simulated capsulotomy lesions focusing gamma rays beams emitted by Cobalt-60 radioactive isotope on the internal capsule.[11] Currently a new technique starts to be investigated (lateral central thalamotomy with anteromedial pallidotomy).[17]

The last two decades witnessed the rebirth of neurosurgeries in the treatment of mental disorders, particularly OCD. This occurs due to the great number of patients non-responsive to the several therapeutical alternatives and to the fact that the stereotactic techniques induce a much lower profile of adverse events and complications, with promising therapeutical responses. Recent technical refinements, such as Gamma-Knife radiosurgery, prevent the need of opening the skull or, when this is needed, such as in deep brain stimulation, allow the reversibility of the procedure.

Criteria for the indication of neurosurgery in OCD

The most recent studies generally include the following criteria: OCD as the main nosological entity, with duration of at least 5 years, and:

- Previous utilization of at least 3 SRI (clomipramine, mandatorily), and 2 augmenting agents (e.g., other antidepressants, neuroleptics, and clonazepam) in the maximum prescribed/tolerated doses, for at least 12 weeks.
- Minimum of 20 hours of behavioral therapy;
- Symptomatic improvement lower than 25% in the Yale-Brown (Y-BOCS) scale.

Exclusion criteria are not uniform among the studies; sometimes, neurological diseases, mental retardation and, occasionally, some personality disorders (e.g., paranoid personality disorder) are excluded.

Neuroanatomic substrates, neurocircuits and neurosurgical techniques

The theoretical grounds of surgical interventions are supported in the findings of functional neuroimaging on OCD.[12] Several studies with PET and SPECT suggest that OCD patients in rest state have an increase in their metabolic activity in the orbitofrontal cortex, in the cingulate and in the caudate nucleus, differently from normal controls. Symptom-provoking studies have also revealed activation in those same areas. Besides, it is observed normalization of the metabolic activity in those regions after drug or behavioral therapy among responsive subjects.[13]

From these findings, it is suggested that neurocircuits interconnecting cortical areas (orbitofrontal cortex, cingulate), basal ganglia (mainly the caudate nucleus) and medial dorsal thalamus are important in the pathophysiology of OCD.[13] The theoretical basis supporting neurosurgery for OCD is related to the selective section of one or more points of the pathways which interconnect these structures.

For example, in anterior cingulotomy electrodes are bilaterally introduced, through stereotaxy, in the anterior portion of the cingulate, producing termical lesions by radiofrequency in the neuronal tissue.

Anterior capsulotomy, in turn, consists in the bilateral stereotactic lesion of portions of the anterior arm of the internal capsule. In this case, the fibers, which interconnect the middle-dorsal thalamus to the orbitofrontal cortex and the subgenual anterior cingulate, are sectioned.[13] The internal capsule undergoes lesions through three technical modalities: conventional neurosurgery with termolesion by radiofrequency, stereotactic radiosurgery by gamma rays (Gamma-Knife), or neurosurgery with deep brain stimulation.

In Gamma-Knife capsulotomy, 201 gamma beams emitted by a Cobalto-60 camera are focused in the anterior arm of the internal capsule. Individually, the beams emit a low radiation dose, although, the confluence of 201 beams at one point, for several hours, allows the exposure of that anatomic site to doses equal to or higher than 160 Gy, with the consequent lesion in the desired site with great precision and low adjacent radiation. The higher advantage of this technique is that there is no need to open the skull.

In deep brain stimulation, electrodes are introduced in the anterior arm of the internal capsule, without the need of a termolesion in the adjacent tissue. The electrodes are afterwards connected to a pace-maker, capable of emitting high-frequency stimulations in the neuronal site. It is an invasive procedure,

although potentially reversible, due to the possibility of turning the neuro-stimulation off at any time.[14,15]

In subcaudate tractotomy, neurosurgical lesions are promoted in the *substantia inominata*, an area ventral to the caudate nucleus, containing neuronal cell bodies with similar connections to those of the ventral portions of the striatum and of the *globus palidus*. The fibers which interconnect the thalamus to the orbito-frontal cortex and to the cingulated are submitted to lesions. Limbic leucotomy, in turn, consists in a subcaudate tractotomy associated with several lesions in the cingulate.

Finally, in lateral central thalamotomy with anteromedial pallidotomy, the anterior and medial portions of the *globus palidus* undergo lesions, as well as the posterior part of the lateral central nucleus of the thalamus. The objective of this procedure is to normalize the thalamocortical activation. There is only one published study about this technique, composed by 8 patients having OCD associated with other psychiatric comorbidities.[16]

Efficacy

Lopes[18] has assessed the treatment efficacy and the profile of the adverse events in the different stereotactic techniques, categorizing the studies according to the their methodological design.[17] Prevalences of post-operative global improvement after cingulotomy, capsulotomy, subcaudate tractotomy, limbic leucotomy and thalamotoy/pallidotomy were respectively 27% to 57%, 56% to 100%, 33% to 67% and 61% to 69%, and 62.5%.[17-18] Statistically, it was not possible to establish if one procedure was superior to the other in terms of its clinical efficacy. No description of worsening of symptoms with capsulotomy was informed, but the reported rates with cingulotomy, subcaudate tractotomy and limbic leucotomy ranged from 7% to 30%, 0% to 5% and 6% to 13 %.[18]

Adverse events and complications

Contrarily to what was observed in the old open neurosurgeries (lobotomy, pre-frontal leucotomy), the current stereotactic techniques induce a profile of less severe adverse events and complications (Table 1).[18,19] Among the most frequent neurological alterations, there are reports of post-operative convulsions. They were mainly isolated convulsions, which did not demand the continuous use of anticonvulsants. There were descriptions of occasional cases of intrabrain hemorrhage in cingulotomy and incapsulotomy (with traditional neurosurgery). 'Minor' neurological manifestations included post-operative delirium and headache. There were also isolated cases of hipomania/mania in the post-operative follow-up.[18,19]

Most common clinical problems were transient alterations in the control of sphincters (cingulotomy), weight gain and fatigue. The severest complications, such as air emboli (one case submitted to cingulotomy) and bronchopneumonia associated with a dislocation of the radioactive rod (one case with subcaudate tractotomy) were scarcely frequent.[18,19]

Regarding radiosurgery (capsulotomy), the most common complication was edema, whose clinical complication was headache, with good response to treatment with dexametasone; there is also report of asymptomatic caudate nucleus infarct. As there is no need of opening the skull, the possible complications related to 'in-the-open' techniques (such as intrabrain hemorrhage, infections) are prevented.

The study related to thalamotomy/pallidotomy does not mention if there were or not post-operative adverse events or complications.[17]

Suicide rates range from 1.1 (capsulotomy) to 3.2% (limbic leucotomy) of operated cases. We may also remind that many patients submitted to surgery to treat refractory OCD had already had previous histories of suicide ideation and attempts.

Table 1 - Occurrence of the main post-operative adverse events and complications for the treatment of obsessive-compulsive disorder, in several studies.

Adverse event or complication	Surgical technique			
	Anterior cingulotomy (n = 297)	Anterior capsulotomy* (n = 91)	Subcaudate tractotomy (n = 382)	Limbic leuucotomy (n = 219)
Convulsive crises	11	3 (in the immediate post-operative)	20	6
Intrabrain hemorrhage	2	1	0	0
Infection in the CNS	0	0	0	1
Delirium	1 (for few days)	8 (duration from 1 day to 3 weeks)	5	> 4
Headache	3	4	0	?
Dizziness	8 (transient)	0	0	0
Insomnia	5	0	0	?
Depressive symptoms	0	0	0	?
Mania/hipomania	2	0	1	1 (transient)
Psychosis	0	0	0	1
Visual hallucinations	1	0	0	0
Bronchopneumonia + dislocation of radioactive implant	0	0	1	0
Air emboli	1	0	0	0
Lack of control of sphincters	1 (transient)	0	0	? (few days)
Urinary retention	8 (1 day to several weeks)	0	0	
Weight gain	4	0	13	1
Fatigue	0	5	25	0
Suicide attempt	0	0	20	6
Suicide	7	1	5	7
Death not related to surgery	1	0	16	1
Death related to surgery	0	0	1	0

** Including capsulotomy by radiofrequency, gammacapsulotomy and deep brain stimulation.*
Source: Lopes, 2001; Kim et al., 2003.

Table 2 - Occurrence of the main post-operative neuropsychological and personality alterations of stereotactic treatment of obsessive-compulsive disorder, in different studies.

Neuropsychological or personality alteration	Surgical technique			
	Anterior cingulotomy (n = 297)	Anterior capsulotomy* (n = 91)	Subcaudate tractotomy (n = 382)	Limbic leucotomy (n = 219)
Memory deficit	1	0	1	2
Concentration deficit	0	0	1	0
Decrease in the logical performance	0	4 (only specific tests)	0	0
Visual-spatial deficits	0	0	0	4
Perseveration	0	0	0	> 1
Mental slowness	0	0	0	10
Impulsivity	0	1	?	1
Aggressiveness	0	1	0	4
Irritability	0	0	12	0
Apathy	0	9	1	5
Lack of inhibition	0	3	1	1

** Including capsulotomy by radiofrequency, gammacapsulotomy and deep brain stimulation.*
Source: Lopes, 2001; Kim et al., 2003.

Of 382 cases, one submitted to subcaudate tractotomy died due to neurosurgical complications.[18]

Cognitive aspects and personality alterations

Published studies indicate that only in few cases stereotactic techniques induce relatively small memory or concentration deficits or decrease in the logical performance (Table 2). Generally, the observed deficits are specific for certain neuropsychological tests, and do not promote intense cognitive impairment. Some of these alterations are not maintained in long-term follow-up.

Personality alterations, when present, consist mainly in the so-called frontalization symptoms. Most frequent manifestations were apathy (0.3 to 9.9% of cases, in capsulotomy, subcaudate tractotomy and limbic leucotomy), mental slowness (4.6% of cases, in limbic leucotomy), irritability (3.1% of cases in subcaudate tractotomy), aggressive behaviors (incidence of 1.8%, in limbic leucotomy, mainly), and behavioral lack of inhibition (0.3 to 3.3% of patients).[18,19]

Up to now, deficits in neuropsychological or personality tests related to radiosurgery (capsulotomy) have not been described.

Limitations of the studies

Up to the current date, there are 36 studies of surgery on OCD, except for isolated case reports. Among these, only two are random clinical trials, but with a very reduced number of patients, preventing any unbiased conclusion about clinical outcomes.[18] Therefore, there is a lack of studies employing random, placebo-controlled clinical trials and with an adequate number of patients.

Moreover, several studies have methodological problems regarding the design outline, besides biases in the selection of samples, in the execution, attrition and detection. There is also a lack of prospective studies with a sufficient number of patients and adequate clinical investigation to allow the identification of factors predictive of response.

On the other hand, in better delineated studies, it is surprising the rate of clinical improvement among patients who were previously non-responsive to the conventional interventions.

Conclusions

Despite the advances in pharmacotherapy and behavioral therapy for the treatment of OCD, there is still a subset of patients for whom no conventional treatment is satisfactory. For these, neurosurgery may be indicated. Other ethical aspects should be taken into account before the accomplishment of this procedure. In the present issue of the Official Journal of the Brazilian Psychiatric Association there are three editorial articles which deeply discuss the subject.

The interest in the utilization of functional neurosurgery for the treatment of OCD has been renewed since the ‘90s.[15-17,19] Besides the traditional techniques in which lesions are provoked by radiofrequency, other less invasive ones, such as radiosurgery, or potentially reversible, such as deep brain stimulation are being developed and tend to minimize the risk of these procedures. In the near future, with the higher knowledge about the neurobiological substrates involved in the etiopathogenesis of OCD and the improvement of these techniques it may be expected the discovery of more and more precise targets, with lower profile of side-effects. Reciprocally, the result of the treatment with these techniques will generate new information for the knowledge of the pathogenesis of OCD.[13]

Concomitantly, new prospective and better delineated studies are under development. In this sense, in collaboration with Brown University, we are beginning the first random, placebo-controlled clinical trial of Gamma-Knife radiosurgery for the treatment of OCD.

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