RESEARCH PAPER

Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders

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ABSTRACT

Background For patients with psychiatric illnesses remaining refractory to 'standard' therapies, neurosurgical procedures may be considered. Guidelines for safe and ethical conduct of such procedures have previously and independently been proposed by various local and regional expert groups.

Methods To expand on these earlier documents, representative members of continental and international psychiatric and neurosurgical societies, joined efforts to further elaborate and adopt a pragmatic worldwide set of guidelines. These are intended to address a broad range of neuropsychiatric disorders, brain targets and neurosurgical techniques, taking into account cultural and social heterogeneities of healthcare environments.

Findings The proposed consensus document highlights that, while stereotactic ablative procedures such as cingulotomy and capsulotomy for depression and obsessive-compulsive disorder are considered 'established' in some countries, they still lack level I evidence. Further, it is noted that deep brain stimulation in any brain target hitherto tried, and for any psychiatric or behavioural disorder, still remains at an investigational stage. Researchers are encouraged to design randomised controlled trials, based on scientific and data-driven rationales for disease and brain target selection. Experienced multidisciplinary teams are a mandatory requirement for the safe and ethical conduct of any psychiatric neurosurgery, ensuring documented refractoriness of patients, proper consent procedures that respect patient's capacity and autonomy, multifaceted preoperative as well as postoperative long-term follow-up evaluation, and reporting of effects and side effects for all patients.

Interpretation This consensus document on ethical and scientific conduct of psychiatric surgery worldwide is designed to enhance patient safety.

BACKGROUND

The majority of patients affected by psychiatric disorders can be managed effectively by means of pharmacological therapies, psychotherapy and in some cases, more technical interventions such as electroconvulsive therapy. These evidence-based treatments may be used either alone or in combination. However, a substantial minority of patients either does not respond, fails to sustain response or experiences unacceptable adverse effects. It is for these patients, who are even more at risk with non-treatment, that the use of neurosurgical procedures such as stereotactic focal ablative surgery or deep brain stimulation (DBS) may be considered.[1 2] Case reports, case series and small-scale clinical trials of neurosurgical interventions have been reported in patients with obsessive-compulsive disorder (OCD), major depressive disorder (MDD), substance abuse/addiction and anorexia nervosa, among others.

The published experience of DBS for these conditions would appear to have intuitive appeal since DBS is both adjustable and in most cases reversible in contrast to stereotactic ablative techniques. DBS nonetheless requires an invasive implantation of a permanent device in the brain, with the inherent risks of the surgical procedure and the burden of managing, maintaining and replacing the device. Until scientifically proven otherwise, DBS is not superior to ablative surgery for psychiatric disorders. Clinical studies in this field may provide an unprecedented opportunity for fundamental work with regard to examining disease pathophysiology and the mechanisms of action of these therapies.[3]

METHODS

The Committee for Neurosurgery for Psychiatric Disorders, as part of the World Society for Stereotactic and Functional Neurosurgery (WSSFN) and the European Society for Stereotactic and Functional Neurosurgery (ESSFN), partnering with the Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application', along with the Psychiatric Neurosurgery Committee of the American Society for Stereotactic and Functional Neurosurgery (ASSFN), the Latin American Society for Stereotactic and Functional Neurosurgery (SLANFE), the

Asian-Australasian Society for Stereotactic and Functional Neurosurgery (AASSFN) and the World Psychiatric Association (WPA), propose an expanded set of guidelines to articulate a consensus summary of clinical research standards that are applicable to testing of DBS and ablative neurosurgery in addition to other emerging neurosurgical interventions for neuropsychiatric disorders.

The need for such consensus of guidelines was first identified by the Committee for Neurosurgery for Psychiatric Disorders (WSSFN) in early 2011. Then the first text was drafted and revised by HW and BN, respectively, based on literature review. MH provided an important part of the references. This text was presented by BN to the Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application' for further in-depth discussion, leading to a very extensively modified version of the previous text. Afterwards, it was distributed internally by BN among representatives of different international societies (WSSFN, ESSFN, ASSFN, SLANFE, AASSFN and WPA), from whom remarks were received, leading to an optimised consensus text, which was finally approved and endorsed by the representatives of the different societies in late 2011/early 2012.

The guidelines for neurosurgery for psychiatric disorders presented in this document recognise the Declaration of Helsinki, issued by the World Medical Association in 1964, amended several times, as the fundamental document in the field of ethics in biomedical research.

The following guidelines are built directly upon the core elements of previously published guidelines, reviews, correspondences and legislation from expert neurosurgical, neurological, psychiatric and neuroethics groups, and health administrations around the world with an interest in the practice of neurosurgery for psychiatric disorders. We have adopted a pragmatic view in defining a set of guidelines that attempt to serve the range of neuropsychiatric disorders and, crucially, the cultural and religious diversity and heterogeneity of healthcare environments of the international collaborative partners engaged in these endeavours. The guidelines represent a shared attempt to articulate these norms at this time. We appreciate that views can and will evolve over time; therefore, we encourage and welcome the start of an iterative process. The consensus group wishes to emphasise the potential importance of neurosurgical interventions in the future management of psychiatric disorders. These guidelines are not meant to inhibit, but rather to guide ethical and effective research in order to facilitate proper development of promising therapies. They represent an international multidisciplinary consensus on best ethical practices, norms and professional behaviours both in clinical and research settings.

The scope of neurosurgical interventions for psychiatric disorders

Neurosurgical therapies for psychiatric disorders range from those that have been in routine use in specialist centres for several decades (eg, anterior cingulotomy for MDD, anterior capsulotomy for OCD), to those that remain highly experimental and have only been tested in very small number of patients (eg, DBS for anorexia nervosa). However, despite the lengthy history and the weight of publications, associated with lesion procedures in particular, the accumulated evidence supporting the application of all neurosurgical treatments for psychiatric disorders requires to be strengthened. While certain procedures are considered to represent 'established' practice for severe, treatment-refractory psychiatric disorders in some countries (eg, radiofrequency anterior capsulotomy for severe, treatment-refractory OCD in Belgium, thermal anterior cingulotomy for MDD and OCD in the USA, Scotland, South Korea and elsewhere), the nature of these and many other procedures in neurosurgery, including DBS for psychiatric disorders, remains at a 'proof-of-principle' investigational stage of development.[4]

Current practised stereotactic ablative procedures do not have level I evidence with randomised controlled trials, but their safety and efficacy are supported by level II evidence in treatment-refractory MDD and OCD. However, this degree of evidence is not yet available for 'new' lesioning methods such as gamma knife and stereotactic-focused ultrasound.

In this delicate field of neurosurgery for psychiatric disorders, it seems reasonable to state the following requirement before the surgical intervention can be stated as 'approved therapy'. At least two blinded (if possible) randomised controlled clinical trials from two different groups of researchers need to be published, both showing an acceptable risk–benefit ratio, at least comparable with other existing therapies.

Furthermore, there is a resurgence of ablative procedures in resource-poor contexts, where access to medication, psychotherapy and more expensive neurosurgical interventions like DBS is limited. Ablative surgery also becomes an alternative in cases where a DBS procedure has failed to control the patient's symptoms or where DBS or other neuromodulatory strategies are inappropriate or impractical.

We encourage researchers to design independent, randomised and blinded (where possible) controlled trials, with the least possible conflict of interest and bias, to strive towards the generation of level I (U.S. Preventive Services Task Force) or level A (U.K. National Institute of Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN)) clinical evidence with regard to neurosurgical procedures for psychiatric disorders. Unfortunately, different organisations use different systems to grade evidence and recommendations. Therefore, a new system—called GRADE—is gaining more acceptance internationally to establish the quality of evidence and the strength of recommendation.[5] Robust, data-driven, evidence-based rationales for disease and brain target selection are required. They will provide further protection of patients' safety, improve clinical choice and outcomes, and provide the basis for studies of disease mechanisms.[3] Further, prior to proceeding to selection of a new brain target or disease, consultation with peers in the field is strongly recommended. High-quality pilot studies, honestly reported with details and accuracy, have usually allowed the generation of new discoveries and can pave the way for bigger clinical trials. The point here is not to blame controlled trials, but to underline that sometimes small pilot studies can be used to guide and prepare larger, international clinical trials by providing preliminary data that will avoid fishing expedition (eg, for the choice of targets and parameters of stimulation).

Involvement of ethics committees and institutional review boards

An independent Ethics Committee or Institutional Review Board (IRB) must have ethical and regulatory oversight for all investigational neurosurgery for psychiatric disorders. These committees, in tandem with local and national regulatory agencies, such as the Food and Drug Administration (FDA) in the USA, the European Medicines Agency (EMA) in the European Union and their counterparts worldwide, must review and oversee all aspects of the investigational protocol. Special attention must be paid to the process of informed consent, avoidance of therapeutic misconception, proportionality in research, the assessment of investigative teams, as well as independent experts

for the interdisciplinary composition necessary to conduct this work.[6] Particular care is required in cases involving vulnerable populations (eg, children, those in hierarchical relationships such as military members, students and prisoners) and in cases of surrogate decision making when one makes decisions for others.[7 8] Ethical norms that govern these decisions should reflect the patient/subject's prior wishes, if they are known, and be in their best interest. For complex cases, functional neurosurgeons, together with members of the psychiatric team, should seek expert bioethics consultation.

A critical distinction must be made for all psychiatric neurosurgery, be it ablative or DBS, whether the intervention has reached therapeutic status or remains investigational. Regulation of the former should be handled as clinical practice and the latter as research, requiring discrete oversight, including a Data Safety Monitoring Board (DSMB) when indicated. Investigators should be careful not to prematurely designate an investigational intervention as the standard of care, based on historic precedent or on limited data, and should seek the advice and guidance of ethics bodies to avoid idiosyncratic practices.

Preoperative evaluation and patient selection criteria

All candidates for neurosurgery for psychiatric disorders should meet generally accepted clinical criteria for severity, chronicity, disability and treatment refractoriness.[9] A comprehensive preoperative assessment by independent experts in the management of psychiatric disorders ensures that all candidates meet rigorous inclusion and exclusion criteria.[10] Although asking advice from independent experts is not common practice in medicine and is difficult to install as a mandatory process worldwide, it has proven to be of value.[11] Evaluations should use standardised rating scales,[10] including scales rating disability and quality of life. The definition of treatment refractoriness will vary by disorder.[4] The suicide risk should be taken into account in all individuals participating in neurosurgery for psychiatric disorders before surgery.[4] All patients should complete a preoperative neuropsychological assessment that includes an evaluation of the patient's current cognitive abilities, psychiatric status, personality and interpersonal functioning, goals and expectations of surgery, treatment adherence and level of family or other psychosocial support.[12]

There should be documentation of failure (eg, due to disabling side effects or lack of efficacy) or limited response to trials of available standard therapies with adequate dose and duration (eg, pharmacotherapy, behavioural or cognitive therapy, electroconvulsive therapy).[13 14] There should be no other reasonable, evidence-based and less intrusive alternatives available, taking into account the aggregate risks, benefits and side effects of the proposed intervention.[13] Furthermore, there should be little hope for spontaneous recovery and a potential for meaningful recovery after surgery.[13]

Treating the patient remains the primary aim of clinical research. Indeed, the fact that, for example, DBS is in general reversible and opens windows to the brain should not be used first for answering an exciting physio-pathological question, while using the clinical aim only as a pretext.

Decision-making capacity, autonomy and informed consent

Informed consent must be obtained from competent patients. This requires an explanation of the risks, benefits and alternatives, as well as a context of the individuals' free choice. Risks are not only limited to known surgical risks but can include unknown risks associated with stimulation, ablation or other forms of modulation at novel sites. The risks of treatment must also be placed in a clinical context and balanced against the risks of no treatment. The consent process should include discussion of what is and is not known of the long-term consequences of neurosurgery for psychiatric disorders.[4] It should be explained clearly that neurosurgery for psychiatric disorders is only one aspect of a comprehensive treatment programme that should continue after surgery.[4] The patient should understand that neurosurgery for psychiatric disorders aims for a symptomatic treatment of psychiatric impairments, but may not be able to 'cure' the disease process.[1]

A. An assessment of the patients' decision-making capacity to consent should be carried out for each potential subject in early phase studies of neurosurgery for psychiatric disorders.[4] The methods used should take into account the potential confounds of psychiatric symptoms.[4] Desperation can lead to decisions in a hurry, in favour of surgery.[15] Decisional capacity may change over the course of illness or treatment, like in depression, and therefore should be regularly assessed.[15] For patients to have decisional capacity, they must satisfy the following three criteria:
   - Sufficient comprehension of the importance of the protected personal spheres (physical and mental) into which a neurosurgical intervention intrudes and of the scope and risk of the intervening clinical measures.
   - Sufficient judgement, that is, the ability to assess the consequences of the intervention in light of one's own matters and interests.
   - Sufficient ability to take self-governed decisions, that is, the basic capability to decide and act according to one's own insights and judgements.

B. The provision of 'care' to competent individuals, with the capacity to consent, without informed consent, is a violation of ethical norms and disrespectful of personhood.

C. It is acceptable to obtain surrogate consent when the individual lacks decision-making capacity. Such use of surrogate decision-makers should represent extremely rare cases. It requires special vigilance as surrogates may, on purpose or unknowingly, pursue their own interests at the expense of the patient.[16] Local legislation may govern such clinical situations in different countries.[17 18] In general, patients who cannot give their own free and informed consent should not be considered candidates for psychiatric neurosurgery unless there is a legally authorised representative and specific laws governing such situations.

An example where a surrogate decision-maker may intervene could be a person with extremely low IQ with extreme autoaggression. There are known cases who perform laparotomy on themselves or pull out one eye and the second eye is in danger. If no other therapy would help, one may think of a neurosurgical procedure that decreases the likelihood of extreme autoaggression. But even in this life-threatening case a surrogate decision-maker only comes into play when every effort has been made to obtain a positive consent from the patient.

D. Patient consent should be maintained and monitored throughout the neurosurgery for psychiatric disorders process, and patients must be free to halt their participation voluntarily.[9]

Experienced multidisciplinary team

Neurosurgery for psychiatric disorders should not be decided by, nor performed by, an individual in isolation and acting alone regardless of specialty. These procedures require an expert multidisciplinary team that includes trained stereotactic and functional neurosurgeons, working in a team with psychiatrists,

neurologists and neuropsychologists. The team should be specialised in the various target disorders and be able to provide comprehensive care.[19] Neurosurgeons should use modern, current standard techniques such as MRI and computerised stereotactic planning software. It is a neurosurgeons' important responsibility to check and maintain accuracy and reliability of the stereotactic system. Postoperative imaging is mandatory (eg, for documentation of the electrode position or place and extent of the lesion).

The composition of the team should be adjusted to the disorder and may involve a neuroethicist, depending on the idiosyncratic demands of the work.[6] Ancillary specialists may also be incorporated into these teams to provide expertise in social work, rehabilitation, psychotherapy and vocational training. For best protection of public and profession, members of multidisciplinary neurosurgical groups should monitor their colleagues to ensure that all members adhere to the proposed guidelines.

It is mandatory to reach a complete consensus with regard to patient selection, preoperative evaluation and neurosurgical therapy among neurosurgeons, psychiatrists and other members of the team as a *sine qua non* condition. In case of disagreement, any member of the team should not act alone, and outside expert evaluation should be sought.

Legitimate therapeutic indications

We agree with the landmark 1977 US National Commission Report on Psychosurgery: "The Commission affirms that the use of psychosurgery for any purpose other than to provide treatment to individual patients would be inappropriate and should be prohibited. (Italics in original) Accordingly, the Commission is recommending safeguards that should prevent the performance of psychosurgery for purposes of social or institutional control or other such misuse."[20 21]

Neurosurgery for psychiatric disorders should never be performed for political, law enforcement or social purposes, but with therapeutic intent aimed at the restoration of normal function and amelioration of distress and suffering.[9 13]

These patients may come from a challenging socioeconomic background. However, they should not be deprived of, nor given, a lesser opportunity to participate in cutting-edge research that may have an important impact in the treatment of their condition. This research should be available to all patients irrespective of race, ethnicity, gender, class, religion, sexual orientation or any other potential cause for bias.

Conflicts of interest

The potential for ethical conflicts of interest exists because this work is often reliant upon collaborations between academia, industry and the clinic.[3] Even though device-related or biotherapeutic companies may economically support a clinical study to benefit the interests of patients, it is undeniable that a legitimate commercial interest in making a profit coexists. In consequence, there is a potential risk that this aspect may hamper the transparency of the study.[22]

Patients and/or their legally authorised representatives should be made fully aware of the potential conflicts of interest in all informed consent discussions.[9] Investigators should be transparent with disclosures of financial conflicts of interests, including (but not limited to) corporate relationships, consulting fees, honoraria, research funding and intellectual property rights. This information should be shared with prospective participants or their surrogates, colleagues, institutional officials and regulators as required by local laws and professional norms. Investigators with potential conflicts of interest should not be precluded categorically from doing research if the conflict is properly and impartially managed.[3]

Postoperative evaluation and long-term follow-up

The ethical principle of non-abandonment obliges clinicians to follow all patients/subjects longitudinally or until proper transfer of care to a qualified clinician occurs. This provision of ongoing care is especially important because specialty care is not routinely available in the community.[21 23]

A. All patients initially enrolled in any treatment programme or clinical trial for neurosurgery for psychiatric disorders should complete comprehensive postoperative assessments, including neurological, psychiatric and neuropsychological evaluations, and should be followed up regularly.[10 24 25]
B. Clinical research teams should report on the outcome for all patients, including failed or withdrawn cases, as is mandatory in any scientific report.[24] Patient trust to enrol in such trials requires that all efforts be made to collect as many scientific data as reasonably possible to not only determine safety and clinical efficacy, but to understand the 'therapy' and the reason for the resulting outcomes. This includes the use of multiple clinical ratings and objective scientific measures, such as functional imaging, wherever possible.
C. In addition to disease-specific symptom outcomes, outcomes in domains such as activities of daily living, cognition, quality of life and global improvement (including family and patient perception) should be considered.[4] Social adjustment following neurosurgery may be challenging for many patients.[1]
D. Research and clinical protocols should include support for long-term safety and efficacy studies on neurosurgery for psychiatric disorders for at least 5–10 years of follow-up.[4] Regulatory agencies should require that device manufacturers collect long-term follow-up data on safety and efficacy.[4]
E. It should not be considered inherently problematic that neurosurgical interventions have the potential to cause personality changes. In view of the fact that many psychiatric disorders may bring about undesirable changes of a patient's personality, it can even be the intended outcome of such interventions to modify personality by undoing the pathological changes.[26] However, all psychiatric and non-psychiatric side effects should be documented.[27]
F. An independent registry, at this moment not yet available, should ideally include de-identified data on all individuals undergoing neurosurgery for psychiatric disorders.[4 28]

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Contributors BN initiated the study, contributed to the writing and reviewing of the manuscript. He coordinated the interactions between different international societies and authors, contacted relevant persons, and finalised the manuscript. HW summarised past literature and drafted the manuscript. He also participated in revising the manuscript and together with BN shares the co-first-authorship. HM contributed to concept of paper, writing of early draft and editing of final draft. MH contributed to literature search, study design, data collection and analysis, writing parts of manuscript and discussion of intellectual content. LG participated in discussions and meetings for development of the current guidelines and tested them for support in the psychiatric community. She critically revised the manuscript and commented on it at several stages. TG did extensive editing of the first draft of the article and gave critical comments on the final manuscript. RM contributed substantially in arguments and wording to sections 'Decision-making capacity, autonomy and informed consent' and 'Legitimate therapeutic indications' and edited work on the entire text. CK did modification and significant editing and revision of original draft. OV-F, as the Past-Chairman of the Committee for Neurosurgery for Psychiatric Disorders of the WSSFN, started the process of bringing together neurosurgeons within the WSSFN to talk about ethical aspects of neurosurgery for psychiatric disorders. OV-F helped in the study design, data interpretation and review of this manuscript. KM, TT, AML, AA, MS, RS, JWC, NL, JV, RC and YL reviewed and agreed with the manuscript. GS contributed to writing and literature search. PD helped in conceiving the idea and implementation as a task force member. He has provided inputs about the guideline format and has also reviewed and edited the manuscript. Thus he has been involved in the study design, interpretation of the manuscript and its final writing. GB contributed in literature search and study design. JR did extensive reviewing of the manuscript. BS did literature search and study design and participated in conferences to discuss the guideline. SE discussed and participated in the evaluation and agreed with the layout. He proofread the manuscript and critically reviewed it. MK contributed to writing and editing the manuscript. EE contributed to the content and reviewed the manuscript. AR performed literature search, writing and editing of the manuscript. JKK participated in discussion of contents and review of the manuscript. PH critically revised the manuscript and commented on it. PR is a reviewer of the manuscript. PC contributed as chairman of the Belgian Committee of Neurosurgery for Psychiatric Disorders. TS drafted the manuscript together with the first authors, repeatedly edited as the manuscript progressed and approved the final manuscript.

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精神疾患に対する定位的脳神経外科治療のガイドラインに関するコンセンサス

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要約

背景: 「標準的」な治療に抵抗性を示す精神疾患の患者に対しては、脳神経外科的手法の適応が考慮されることがある。これまでに脳神経外科的治療の安全性と倫理面を規定したガイドラインが様々な地域や領域の専門家らによって独自に提案されてきた。

方法: 国際的な精神科および脳神経外科の学会代表メンバーが協同し、既存の原案をさらに発展させ、より実用的で国際的に通用するガイドラインとして採用されるように念入りに企画し承認を得るための議論を重ねた。このガイドラインは、医療環境が国によって文化的にも社会的にも異なるという事情を考慮しながら、精神神経疾患、脳内の治療標的部位および脳神経外科テクニックなど幅広く対応するよう意図して作成されたものである。

結論: 一部の国ではうつ病に対する前帯状回切裁術 (cingulotomy) や強迫性障害に対する内包前脚切裁術 (capsulotomy) などの定位的アブレーション手術 (*訳注) が「確立した治療」であるとみなされている。しかし、このたびの合意文書では、それらの手術はまだレベル I のエビデンスを満たしていないことを強調している。さらに、今までに試みられてきたあらゆる脳部位を標的とした脳深部刺激術は、精神疾患や行動障害の治療対象の如何にかかわらず、依然として研究段階にとどまっていることが記されている。研究者には対象となる疾患や脳標的部位の選択のために、科学的なデータに基づいたランダム化比較試験をデザインすることが求められている。いかなる精神疾患に対する脳神経外科治療であっても安全と倫理面を配慮し、治療抵抗性を的確に評価し、患者の能力や主体性を尊重する適切なインフォームド･コンセントを実施し、術前および術後の長期に渡って多角的に追跡評価を行い、すべての患者について効果や副作用を報告するためには、経験豊かな多専門分野からなる医療チームを組織することが必須である。

解釈: 精神外科の倫理的並びに科学的行為を規定したこの国際的な合意文書は、患者の安全性を向上させるように図られている。

(*訳注)

定位的アブレーション手術: 定位脳手術において局所の脳組織を破壊する方法であり、現在広く用いられているのは凝固針を使用した高周波による熱凝固である。歴史的には高周波熱凝固の他に、冷却、アルコールブロック、オイルワックス注入、小ループによる機械的破壊などの方法も用いられてきた。また、ガンマナイフによる定位的放射線照射も実用化されている。さらに、近年では新たな定位的アブレーション手術法として、集束超音波定位脳手術が脚光を浴びつつある。

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背景

精神疾患に罹患した患者の多くは、薬物治療、心理療法、また場合によっては電気けいれん療法のようなよりテクニカルな介入的手法を用いることによって、効果的に治療することができる。これらのエビデンスに基づいた治療は、単独または併用して行うこともできる。しかし、少数ではあるが、治療に反応しなかったり、治療効果が持続しなかったり、許容しがたい副作用が出現したりする患者が実在する。このような患者に対して、定位的局所アブレーション手術や脳深部刺激術 (deep brain stimulation, DBS) のような脳神経外科手術の適応が考慮される (文献 1,2)。脳神経外科的治療が行われた症例報告、ケースシリーズや小規模の臨床試験は、とりわけ強迫性障害 (obsessive-compulsive disorder, OCD)、大うつ病性障害 (major depressive disorder, MDD)、薬物乱用/依存症や神経性無食欲症の患者で報告されている。

このような状況下において精神疾患に対する DBS の経験が蓄積されてきたが、定位的アブレーション手術とは対照的に DBS は調整可能であり、ほとんどの場合可逆的であるため、直感的には魅力があるように思われる。しかしながら DBS は、脳内に恒久的な機器を侵襲的に留置する必要があり、外科手術特有の危険性や装置の管理、維持や交換といった負担を伴う。このため科学的に証明されない限り、精神疾患に対して DBS がアブレーション手術に優るとは言えない。この分野の臨床研究が行われることにより、精神疾患の病態生理や脳神経外科治療の作用機序の解明を目指す基礎的研究に対しても前例のない好機が訪れることになるだろう (文献 3)。

方法

国際定位·機能神経外科学会 (World Society for Stereotactic and Functional Neurosurgery, WSSFN) およびヨーロッパ定位・機能神経外科学会 (European Society for Stereotactic and Functional Neurosurgery, ESSFN) の 1 部門として、精神疾患に対する脳神経外科委員会は、作業部会「精神科における脳深部刺激術: 責任ある研究と臨床応用へのガイドライン」と提携しながら、北米定位·機能神経外科学会 (American Society for Stereotactic and Functional Neurosurgery, ASSFN)、ラテンアメリカ定位·機能神経外科学会 (Latin American Society for Stereotactic and Functional Neurosurgery, SLANFN)、アジア·オーストラリア定位·機能神経外科学会 (Asian-Australasian Society for Stereotactic and Functional Neurosurgery, AASSFN) や世界精神医学会 (World Psychiatric Association, WPA) の精神外科委員会とともに、DBS やアブレーション手術に加えて他に新たに登場してきた精神神経疾患に対する脳神経外科的介入手法を検証する上で確保すべき臨床研究水準に関するコンセンサスの概要を明確にするために一連のガイドラインを提案する。

ガイドラインへのコンセンサスの必要性は、2011 年初頭に精神疾患のための脳神経外科委員会 (WSSFN) において最初に認識された。その後、最初の原案が起草され、文献調査に基づいて、Hemmings Wu および Bart Nuttin がそれぞれ修正を加えた。Marwan Hariz は重要な参考文献を提供した。そして、さらに掘り下げた議論を行うため、Bart Nuttin はこの草案を作業部会「精神科における脳深部刺激術: 責任ある研究と臨床応用へのガイドライン」に提示し、その結果、この草案は非常に広範囲にわたって修正されることになった。その後、Bart Nuttin はその草案をそれぞれの国際的組織 (WSSFN, ESSFN, ASSFN, SLANFE, AASSFN, WPA) の代表者に配布して意

見を集め、コンセンサス草案として適切に修正した後、最終的に 2011 年後半から 2012 年初頭にそれぞれの組織の代表者によって承認された。

本論文で提示した精神疾患に対する脳神経外科治療のガイドラインは、生物医学研究における倫理分野の基本的な合意事項として、1964 年に世界医師会が発表し、以降数回にわたって改正されたヘルシンキ宣言に準拠している。

以下のガイドラインは、世界中の精神外科に関心を持つ脳神経外科学、神経内科学、精神医学や脳神経倫理学の専門家グループ並びに保健行政から公表されたガイドライン、レビュー、公開されたやりとりや法令に基づいて作成されている。われわれは様々な精神神経疾患について、文化や宗教や医療環境の地域的な違いの中で国際共同研究によって取り組みがなされている事情を鑑み、実践的な見地からガイドラインを規定した。本ガイドラインは、現時点でのこれらの規範の明確化を共同で試みた結果である。われわれは、時代によってこの様な規範が進歩していくことを理解しており、将来さらなる検討を繰り返すことを期待している。また、将来の精神疾患の治療に脳神経外科的介入が重要になる可能性があることを強調したい。これらのガイドラインは、有望な治療法が適切に発展するよう促すために、倫理的かつ有益な研究を阻害するのではなく、むしろ導くことを意図している。このガイドラインは、臨床および研究の両者において、最良の倫理綱領であるだけでなく、専門家による見解として、多領域からの国際的な同意を得ている。

精神疾患に対する脳神経外科治療の展望

精神疾患における脳神経外科医療は、専門施設において数十年前から日常的に行われているもの (大うつ病性障害に対する前帯状回切裁術や、強迫性障害に対する内包前脚切裁術)から、実験的な要素が強く少数の患者に行われたにだけ留まるもの (神経性無食欲症に対する DBS など) まで多岐に及ぶ。しかしながら、とりわけ局所アブレーション手術に関しては尚更のこと、いかに長い歴史と数多くの論文があったとしても、精神疾患に脳神経外科手術を実施すること対して、エビデンスの積み重ねによる検討が絶えず求められる。いくつかの国においては、ある特定の手術 (ベルギーにおける強迫性障害に対するラジオ波焼灼による内包前脚切裁術、米国・スコットランド・韓国などにおける大うつ病性障害と強迫性障害に対する熱凝固による前帯状回切裁術) が重篤な難治性精神疾患に対してもはや「確立した」治療法であるとさえ考えられているが、これらの脳神経外科手術手技は精神疾患に対する DBS を含めて、いまだにこれから理論を実証する研究的段階に留まっている (文献 4)。

今日実施されている定位的アブレーション手術は、ランダム化比較試験に基づいたレベル I のエビデンスは存在しないが、治療における有効性と安全性は難治性大うつ病性障害および強迫性障害の治療においてレベル II で証明されている。しかしながら、レベル II のエビデンスはガンマナイフや集束超音波定位手術などの「新しい」アブレーション手術に関してはまだ存在していない。

精神疾患に対する脳神経外科治療というデリケートな領域において、外科治療が承認された治療法となるために、以下のような条件を挙げることが妥当と考えられる。少なくとも２つの盲検 (可能であれば) ランダム化比較臨床試験が２つの独立した研究チームから論文化されていなければならず、その両方の試験に

おいてリスク対効果比が容認できること、少なくとも既存治療と同程度であることが示される必要がある。

さらに、薬物療法、精神療法や DBS のようなよりコストのかかる脳神経外科的治療法を採用しにくい環境や地域において、アブレーション手術が見直される機運がある。アブレーション手術はまた、DBS 無効例、あるいは DBS などのニューロモデュレーションが適切でないか、現実的でない場合においても選択肢となる。

精神疾患に対する脳神経外科医療の確立に向けて、独立した盲検 (可能であれば) ランダム比較臨床試験であり、かつ可能な限り最小限の利益相反および最小のバイアスを兼ね備えた臨床試験をデザインし、レベル I (米国予防医療専門委員会: U.S. Preventive Services Task Force) あるいはレベル A (英国国立医療技術評価機構: U.K. National Institute of Clinical Excellence, NICE およびスコットランド大学連合ガイドラインネットワーク: Scottish Intercollegiate Guidelines Network, SIGN) のエビデンスの獲得に向けて努力するよう研究者に奨励する。このようにエビデンス・レベルや推奨レベルは認定組織ごとに異なっているのは残念であるが、GRADE という新しい評価システムがエビデンスの質と推奨度の強さの確立において国際的に受容されている (文献 5)。対象疾患の選択と治療標的部位の選択において、データやエビデンスに基づいた強固な合理性が求められている。それらは、患者の安全性を担保し、臨床上の治療選択とその結果を改善し、病態の解明に向けた研究に役立つ (文献 3)。さらに、新規治療標的部位や対象疾患を選択する場合には、事前に該当領域における第三者の専門家と相談することが強く推奨される。これまでの経験によれば正確で詳細な内容を備えた質の高い先行研究は、新しい発見を可能にし、今後より大規模な臨床研究に道を開くであろう。ここでは比較試験を否定しているのではなく、むしろ時に小規模先行研究は大規模な国際的臨床研究を計画する際の予備的データになると述べたい。これにより有効な治療標的部位や刺激条件を設定する際に無駄な探査的行為を回避することができる。

倫理委員会と制度審査委員会の関わり

精神疾患に対する全ての脳神経外科手術について、独立した倫理委員会または制度審査委員会 (Institutional Review Board, IRB) が倫理的な監督をし、規制の目が行き届くようにする必要がある。これらの委員会は、例えば米国の食品医薬品局 (Food and Drug Administration, FDA) や欧州連合の欧州医薬品庁 (European Medicines Agency, EMA) あるいは各国の類似機関など、国家レベルの規制機関と連携して、研究プロトコールのあらゆる面を検討し、監視する必要がある。インフォームド·コンセントの過程、臨床試験への参加を確立した治療を受けるものと勘違いすることの回避、研究要素の介入度合い、研究チームの評価、さらにこの監視を遂行するための専門家たち各々に至るまで、それぞれ特別な注意を払う必要がある (文献 6)。立場の弱い人々 (例えば子供や権力階級的に弱い立場にいる軍人、学生、囚人など) が対象となる場合や、代諾者によって意志決定がなされる場合には、特に注意が必要である (文献 7, 8)。このような意思決定を支配する倫理的規範は、何よりも被験者である患者の意志を事前に反映したものでなければならない。また患者/被験者の最善の利益を考えたものであることが倫理的に求められる。込み入った症例では、機能的脳外科医は精神科医のチームとともに生命倫理の専門家に相談するべきである。

精神科疾患に対する全ての脳神経外科手術に対して、それがアブレーション手術であろうとDBSであろうと、対象となる外科的処置が確立した治療の域に達したものなのか、それともまだ研究段階なのかは厳しく峻別されねばならない。前者は臨床行為として、後者は研究として、全く別個の監督下におかれる必要があり、適応となる場合にはデータ安全性モニタリング委員会 (Data Safety Monitoring Board, DSMB) 等により規制されるべきである。研究者は、まだ研究段階の外科的処置であるにもかかわらず単に先例が存在することを理由としたり、十分でないデータを根拠としたりして、標準的治療と尚早に呼ぶ事のないように注意すべきで、特異な治療行為を避けるよう倫理機関の助言·指導を求めねばならない。

術前評価と患者選択基準

精神疾患に対する脳神経外科手術の全ての対象者は、疾患の重症度、慢性化度、障害度、既存治療への抵抗性などについて、一般に広く受け入れられている臨床基準を満たしている必要がある (文献 9)。全ての対象者は、精神疾患の管理に精通する独立した専門家によって総合的な術前評価を受け、厳密な選択基準と除外基準を満たしていなければならない (文献 10)。第三者的専門家たちに助言を求めることは通常の医療行為の中では一般的でなく、これを世界中どこであっても必須の過程と位置づけることは難しい。しかし、これは大変有用であると証明されている (文献 11)。個々の評価には、障害の程度と生活の質の評価を含んだ標準化された評価尺度を使用する必要がある (文献 10)。治療抵抗性の定義は、疾患ごとに異なる (文献 4)。精神疾患に対する脳神経外科手術を行う全ての患者に対して、術前に自殺リスクを考慮しておく必要がある (文献 4)。術前に全ての患者に対して、現状での認知機能、精神状態、人格機能、対人関係機能、手術の目標と期待度、治療の継続性、患者家族やその他の心理社会的支援レベルの評価を含んだ神経心理学的評価を総合的に完了する必要がある (文献 12)。

標準的治療 (薬物療法、認知行動療法、電気けいれん療法など) が治療量と治療期間とも適切であったにもかかわらず有効でなかったこと (例えば、障害をもたらす副作用が出現した、または効果がなかった、など)、あるいは効果が限的であったこと、を文書で示しておく必要がある (文献 13, 14)。手術適応を検討する際には、提案されている脳神経外科的処置の他には、リスク·利点·合併症などを考えても、根拠·侵襲度ともこれを上回る処置法があってはならない (文献 13)。さらに、患者には自然治癒がほとんど期待できず、術後に十分意味のある回復が見込まれる可能性がなければならない (文献 13)。

臨床研究は、あくまでも患者の治療につながるものでなくてはならない。例えばDBSは一般的に可逆的であるが、たとえ脳機能解明の機会となるようなことがあったとしても、臨床応用を口実とした生理病理学上の刺激的問題に答えるための手段とすることは断じてならない。

意思決定能力、自主性、インフォームド·コンセント

インフォームド·コンセントは、意思決定能力のある患者から得られなければならない。インフォームド·コンセントでは、危険性や利点、他の治療選択肢を説明する

だけでなく、個人の選択の自由についても言及する必要がある。危険性の説明には、既知の手術の危険性は勿論のこと、刺激術やアブレーション手術、新しい部位への別のニューロモデュレーション手法に関する未知の危険性についての説明が含まれる。治療の危険性については、臨床上の観点で考え、治療を行わない場合と手術を受ける場合のリスクバランスを考慮する必要がある。

インフォームド･コンセントを得る過程で、精神疾患に対する脳神経外科手術の長期成績について何が分かっていて、何が分かっていないかを説明する必要がある (文献 4)。また、精神疾患に対する脳神経外科手術は、術後も継続される包括的治療プログラムの一部分でしかないということを明確に説明しなければならない (文献 4)。精神疾患に対する脳神経外科手術の目指すところは精神障害の対症療法であり、疾患そのものを「治癒」できない可能性がある。このことについて、患者が理解しておく必要がある (文献 1)。

A. 治療対象になり得る患者一人一人に対し、患者に同意を得るための意志決定能力があるかどうか、研究の初期の段階で判断しなければならない (文献 4)。その過程においては、精神症状の混乱が生じる可能性があることを考慮する必要がある (文献 4)。自暴自棄になっている患者は決断を急ぎ、手術を選択することがある (文献 15)。また、うつ病のように、症状の特性や治療の経過によって判断能力が変化することもあるので、定期的に評価することが望ましい (文献 15)。患者に意思決定能力があると判断するためには、以下の 3 つの基準が満たされなければならない。

   ▶十分な理解力、すなわち、脳神経外科的治療を受ける際に本来保護される身体的・精神的な個人領域の重要性と、治療手法の適用範囲とリスクに対する理解力を保持していること。
   ▶十分な判断力、すなわち、自身の状況と利益を照らし合わせて、外科的処置による結果を評価する能力を保持していること。
   ▶十分な自己決断力、すなわち、自分自身の洞察力と判断力に基づいて、決断し、行動する能力を保持していること。

B. 判断能力のある個人に対し、インフォームド･コンセントがないまま「ケア」することは、倫理基準に違反し、人格の尊厳性を軽視する行為である。
C. 患者に意志決定能力が認められない場合には、代諾者より同意を得てもよい。ただし、代諾者が意志決定を行うケースは、極めて稀と考えるべきである。これに関して特に警戒しなければならないのは、代諾者が、故意にであれ、無意識のうちにであれ、患者を犠牲にして自分の利益を得ようとする場合が考えられるからである (文献 16)。国によっては、法律により代諾者の意志決定に関与する行為について定められている場合もある (文献 17, 18)。一般に、自分の自由意志でインフォームド･コンセントが得られない患者に対しては、法律上の権限が与えられた代理人がいるか、またはそのような状況に対して制定された特別な法律がない限り、精神疾患に対する脳神経外科手術の対象としてはならない。

代諾者が介入する例として、患者が極度の自己攻撃性をもち、極端に知能が低い症例が考えられる。例えば、自分で腹を切ったり、自分で片方の目をくり抜き、もう一つの目も危険な状態であったりするような事例である。このような例にお

いて、他の治療法が役に立たない時、脳神経外科手術で極度の自己攻撃性を減弱させられないだろうか、と考えるかもしれない。しかし、このように生命が脅かされるような場合であっても、患者本人から積極的な同意を得られるよう、あらゆる努力がなされた上で、代諾者が意志決定に関与するべきである。

D. 精神疾患に対する脳神経外科治療を行っている期間を通して、患者の同意の意志に変化がないことを監視しなければならない。また同時に、患者には自発的に研究への参加を中止する自由も与えられていなければならない (文献 9)。

経験豊かな多専門分野からなる医療チーム

いかなる専門家であっても、精神疾患に対する脳神経外科手術の適応判断や施術を単独、密室下で行うべきではない。適応判断·施術の過程には多専門分野からなるチームによる連携、すなわち熟練した定位·機能神経外科医と精神科医、神経内科医、神経心理士の共同作業が必要である。この過程を担う多専門分野からなるチームは、包括的な治療を提供するために多種多様な疾患に精通していることが求められる (文献 19)。脳神経外科医は、MRI とコンピュータソフトを用いた手術計画のような現在の標準的な手法を使用するべきである。定位脳手術の正確性と信頼性を確認し維持することは、脳神経外科医の重要な責務である。電極の位置または凝固部位の範囲の確認のため術後の画像検査は必須である。

多専門分野からなるチームは、対象となる疾患に適応するように構成されるべきであり、作業における特殊な要件によっては脳神経倫理学者の参入が必要となる場合もあるであろう (文献 6)。また、ソーシャルワーク、リハビリテーション、精神療法、職業訓練における専門的知識を得るために、補佐的な専門家をチームに組み込むことも必要であろう。透明性と専門性を確実に維持するためには、多専門分野からなる脳神経外科チーム内の全てのメンバーが提唱されたガイドラインを遵守しているか、お互いに監視·確認し合わなければならない。

症例選択、術前評価、脳神経外科的治療を行うにあたり、脳神経外科医、精神科医、その他の多専門分野からなるチームメンバー間で意見が完全に一致していることが必須条件である。意見の一致が得られない場合は、いかなるメンバーも単独で行動することは許されず、外部の専門家に評価を依頼するべきである。

治療適応の正当性

われわれは、1997 年の精神外科に関する米国委員会の精神外科に関しての報告、すなわち、「米国委員会は、患者個人に治療を提供する以外の目的で精神外科治療を行うことは不適切で、禁止すべきであることを宣言する (原文はイタリック)。よって、米国委員会は、精神外科治療が社会的コントロールや施設管理の目的で施術されることや、その他の理由で乱用されることの予防策を講じておくことを推奨する」との指針を支持する (文献 20, 21)。

精神疾患に対する脳神経外科手術は、決して政治的、法的処罰、社会的な目的で行われてはならず、正常な機能を回復させて苦悩や苦痛を軽減させるという治療目的を持って行われるべきである (文献 9, 13)。

治療を希望する患者の社会的·経済的背景が思わしくないこともあるであろう。しかし、こうした患者が、自らの病状の治療に重要な影響をもたらす可能性のある最先端の研究への参加の道を閉ざされたり、機会を減らされたりするべきではない。人種、民族、性別、社会的地位、宗教、性的指向性、その他の考えうるあらゆる偏見要因に関わらず、全ての患者がこの研究に参加可能でなければならない。

利益相反の管理

精神疾患に対する脳神経外科治療の研究は、学術機関、企業や医療機関の密な協力体制に依存した構造になりやすいため、そこに倫理的な利益相反が生じる可能性がある (文献 3)。特に臨床研究などの産学連携活動においては、医療機器や生物学的製剤メーカーによる研究への経済的支援により患者の利益がもたらされることがある一方、利潤を追求する商業的関心に大義を与える側面があることも否定できない。こうした点により、研究の透明性を損なう潜在的危険性がある (文献 22)。

インフォームド·コンセントを得る全ての過程で、患者および法的な代諾者は利益相反の潜在性について十分な説明を受ける必要がある (文献 9)。また、研究者は企業との関係、コンサルタントとしての手数料、謝礼金、研究資金、知的財産権などの利益相反に関して透明性を保持することが求められる。これらの情報は、将来的な臨床研究の対象者またはその代諾者、研究分担者、施設職員、地域の法及び専門的組織による規範で定められた管理者の間で共有されなければならない。潜在的な利益相反がある臨床研究担当者については、それが適切かつ公正に管理されていれば研究への参画を除外されるものではない (文献 3)。

術後評価と長期追跡調査

患者に対する治療を放棄しないという倫理的原則に従って、医師は適切な医師にしかるべきケアを引き継ぐまで、全ての患者/被験者を長期にわたって追跡することが義務付けられる。地域によっては専門的なケアを日常的に受けられるものではないことから、こうしたケアの継続は極めて重要である (文献 21, 23)。

A. 精神障害に対する脳神経外科治療プログラムまたは臨床試験に登録される全ての患者において、神経学的評価や精神医学的評価、神経心理学的評価などの包括的な術後評価を定期的に実施する必要がある (文献 10, 24, 25)。
B. 臨床研究チームは、どの学術分野においても報告が必須であるように、無効例ならびに治療中止例を含めた全症例の転帰を報告する必要がある (文献 24)。このような臨床試験に組み入れられる患者の信頼を得るには、できるだけ多くの科学的データを収集し安全性および臨床効果を明らかにするとともに、治療内容と転帰の因果関係を解明しなくてはならない。評価方法には、複数の臨床的評価尺度とともに機能的脳画像などの客観的測定基準も含まれていることが望ましい。
C. 疾患特異的な症状の転帰のほか、日常生活活動能力、認知機能、日常生活の質および全般的改善度 (患者とその家族の感じ方) などの転帰も考慮する必要

がある (文献 4)。多くの患者にとって術後の社会適応が課題になるであろう (文献 1)。

D. 研究および臨床プロトコールでは、精神障害に対する脳神経外科手術の長期安全性および有効性に関して、少なくとも 5〜10 年間にわたる追跡調査を支援する必要がある (文献 4)。規制機関は医療機器メーカーに対して、安全性および有効性に関する長期追跡データを収集するよう義務付ける必要がある (文献 4)。

E. 脳神経外科的治療によって人格変化を引き起こす可能性があるが、それを本質的な問題と考えるべきではない。多くの精神障害が患者の人格にとって望ましくない変化をもたらす可能性がある事実を踏まえると、病的変化を元に戻して人格を調整することは、脳神経外科治療の意図する結果である (文献 26)。ただし、副作用に関しては精神科領域のものもそうでないものも、全て文書に記録しておく必要がある (文献 27)。

F. 現時点ではまだ独立した登録制度は整備されてないが、精神障害に対する脳神経外科手術を施行した全症例について個人が特定されないよう配慮し、データを登録するのが理想的である (文献 4, 28)。

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