例の報告もあり[15]，長期予後も良好と考えられる．

2．Meige症候群

Meige症候群は両側性の顔面攣縮を主体とするジストニアと考えられている[16]．1例報告が主であるが，6例のMeige症候群に対してGPi-DBSが少なくとも6カ月間にわたり70％以上の症状改善をもたらしたという報告もある[17]．われわれの経験では，最長10年にわたり十分な効果が持続している症例もあり[18]，Meige症候群もボツリヌス毒素注射などの保存的加療に抵抗性の場合は両側GPi-DBSのよい適応と考えている．

3．痙性斜頸

痙性斜頸は頻度の高い一次性局所性ジストニアの一つであり，14％もの患者がボツリヌス毒素治療抵抗性を呈する[19]．Kraussらは，6カ月間の経過観察でGPi-DBSが3例の痙性斜頸に対してModified Toronto Western Spasmodic Torticollis Rating Scale（TWSTRS）の50％前後の改善をもたらしたことを報告した[20]．その後，相次いで同様の症状改善を示した報告がなされたが，平均31.9カ月にわたりGPi-DBS後の10例の痙性斜頸を経過観察し，50％を超えるTWSTRSの改善を得られたとの結果がHungらにより示され[21]，長期予後に関しても期待されている．しかしながら，痙性斜頸に関しては，異常収縮を呈する胸鎖乳突筋対側の片側GPi-DBSでも有効であるとの報告もあり[22]，片側のみで十分なのか，あるいは両側刺激のほうがより効果的であるのかさらなる検討が必要である．

Focal hand dystonia

FHDは手・前腕の主動筋・拮抗筋群の過剰な共収縮に起因する一次性ジストニアである[23]．文字を書くときのみジストニアが出現する場合はsimple writer's crampと呼ばれ，他の動作時にも症状が出現するようになるとfocal dystonic writer's cramp，症状が持続性となるとfocal arm dystonia，頸部，体幹，顔面など，ほかの部位も巻き込まれればsegmental dystoniaと進行度に応じて名称が変化していく[23]．

FHDのうち，simple writer's cramp, dystonic writer's crampに対してはVo-complexの視床破壊術が有効であると報告されている[24]．また，Vo-complexとVimの両方の刺激が5例のwriter's crampに対して有効性を示したとの報告もある[25]．われわれの施設では，さらに進行したfocal arm dystoniaにVo-complexとGPiのDBSのいずれもが効果的であった症例も経験しており[26]，今後それぞれのターゲットの刺激術のみならず破壊術のいずれがどの段階のFHDに対してより有効であるかさらに検討していく必要がある．

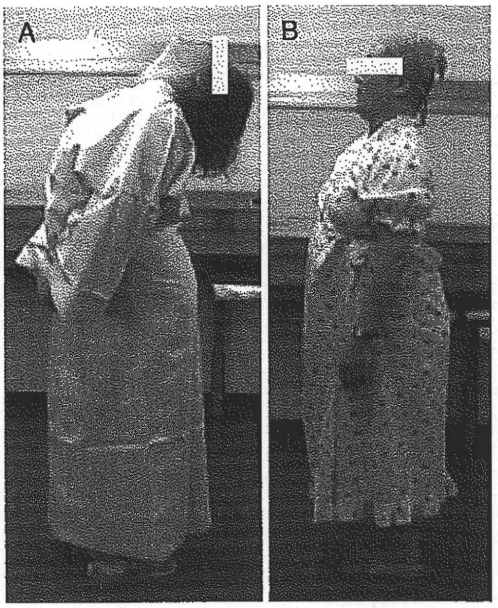

図3　遅発性ジストニアに対するDBSの効果
術前には体幹の高度の後屈を示していたが(A)，両側GPi-DBSにより上記の症状は改善した(B)．

二次性ジストニア

明確な発症要因が存在する二次性ジストニアはDBSに抵抗性であることが多い[27]．難治性である二次性ジストニアの中でも，ジストニア-舞踏アテトーゼ型脳性麻痺[28]，NBIA[29]などにはGPi-DBSが若干の効果を示すが，とくに抗精神病薬の副作用により生ずる遅発性ジストニアはGPi-DBSによく反応し，その改善率は80％を超える（図3）[30]．また，線条体における病理が明確な遺伝性ジストニアであるDYT3に対してもGPi-DBSが行われており，良好な結果が得られている[31]．その他にも1例報告のレベルでは種々の二次性ジストニアに対してDBSが有効であったという論文が多数存在するが，今後どういった型の二次性ジス

トニアがよりよい手術適応となるか，また，いずれの核がターゲットとなりうるか，さらなる報告の蓄積・検証が必要である．

おわりに

ジストニアに対する脳深部刺激(DBS)術を中心に論じてきた．ジストニアは生活の質を大きく左右する疾患の一つであるが，その病態生理の大部分は依然として闇に包まれており，根治的治療法も未だに存在しない．

そのような中でDBSはボツリヌス毒素治療と並ぶジストニアに対する有用な治療法であるが，それによる十分な治療効果が得られている症例はまだ一部である．より多くの患者がDBSの恩恵に与れるよう今後新たな刺激ターゲットの探索，DBSの作用機序の解明を含めさらなる基礎・臨床研究が望まれる．この総説がジストニアとジストニアに対するDBSに関する理解の一助となれば幸いである．

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Pre-operative Inclusion and Exclusion Criteria for Deep Brain Stimulation in Dystonia

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ABSTRACT

When considering a patient with dystonia for deep brain stimulation (DBS) surgery several factors need to be considered. However, to date the selection criteria for DBS - specifically in terms of patient features (severity and nature of symptoms, age, time of evolution, or any other demographic or disease aspects) - have not been assessed in a systematic fashion. In general, dystonia patients are not considered for DBS unless medical therapies have been previously and extensively tested, including different groups of drugs, botulinum toxin injections, and physiotherapy. The vast majority of reported patients have had DBS surgery when the disease was provoking important disability, with loss of independence and impaired quality of life. Current evidence suggests that subjects with primary generalized dystonia (PGD) should undergo DBS at an early age and sooner rather than later after disease onset to gain the optimal benefit from DBS. There does not appear to be an upper age limit nor a minimum age limit, although there are no published data regarding the outcome of globus pallidus internus (GPi) DBS for dystonia in children younger than seven years of age. All motor features and associated pain in primary dystonia are potentially responsive to GPi DBS, although response of speech has been less consistent. While dystonic features may improve, spasticity and other neurological deficits in secondary dystonias do not respond to DBS. Previous ablative procedures, such as thalamotomy, pallidotomy, and peripheral denervation, should not prevent consideration of DBS.

INTRODUCTION

Dystonia is a movement disorder characterized by involuntary, sustained muscle contractions causing twisting and repetitive movements.[1] Dystonia may affect only certain regions of the body or may be generalized, and can be primary, heredodegenerative or secondary.[1-2] Drug treatment for generalized dystonia is often unsatisfactory or is limited by adverse effects.[3] Surgical treatments for dystonia, such as thalamotomy, pallidotomy, and deep brain stimulation (DBS), have improved in their efficacy to safety ratio through a combination of technological advances and better understanding of the role of the basal ganglia in dystonia.[3-4]

In this chapter the evidence is reviewed regarding the factors that influence the selection of patients with various types of dystonia for treatment with DBS. Included in five sections are the following factors: patients characteristics (appropriate time for DBS with respect to age and duration of disease, co-morbidities that may present risks for adverse events during or after DBS or may predict a poor outcome); clinical features of dystonia (degree of severity and disability, type and nature of the dystonia, predictive factors of outcome, relationship with the surgical target, features that might not respond to DBS); previous medical treatment; predicted outcome if previous surgical procedures for the dystonia were attempted; and genetic factors.

METHODS

Search Strategy

The literature search was performed using PubMed, CINAHL and the Cochrane Collaborative databases initially from 1980 to January 2008 using the terms: dystonia AND deep brain stimulation; pallidal stimulation AND dystonia; subthalamic stimulation AND dystonia; thalamic stimulation AND dystonia; secondary dystonia AND DBS; neurodegenerative diseases AND DBS. The search was combined with the one used for neuropsychology, neuropsychiatry, microelectrode recording, neuroimaging, electrophysiology, surgical techniques, complications and targeting. Only English-language publications involving human subjects' were considered. A total of 235 papers were retrieved. To facilitate the committees' work, the articles were divided in 3 groups, which often overlapped: pre-operative, intra-operative and post-operative. A PDF file was created for each paper obtained from the search and put in a CD that was mailed to the members. During the writing phase additional 71 articles were added to update the search, covering the period from January 2008 to September 2009.

Process of Generating Clinical Recommendations

The Consensus Committee members of the Task Force included neurologists, neurosurgeons, neurophysiologists, psychiatrists, neuropsychologists, nurses and mid-level practitioners with expertise and experience in DBS. The experts were also chosen from different countries in Asia, Europe, North and South America, to provide a more comprehensive contribution to the Task Force. The authors of each chapter were selected taking into account their specific expertise in the field. The steering committee prepared a list of questions related to pre-operative, intra-operative and post-operative issues and established two chairs responsible for each of these 3 areas (subcommittees). These chairs then assigned a few questions to be addressed by each member of the subcommittees. The answers to the questions had to be formulated after reviewing the available literature (provided on CD) and combining their expertise. Since the level of evidence for most of the DBS studies was low, the responses were organized following the template previously used for the Special Supplement on DBS for Parkinson's disease (PD): 1) available data, 2) conclusions, 3) pragmatic

recommendations, and 4) points to be addressed.[5] A first document was prepared from this initial work and was reviewed and discussed by the entire Task Force group during a one-day meeting. During this meeting the Task Force members provided further feedback and agreed on additional refinements of the whole document adding the comments and remarks collected during the meeting. Special attention was paid to formulate pragmatic recommendations in absence of available studies. A second version of the project was sent to the entire working committee for final approval. The Executive Committee then met again to refine the Special Issue document before submission.

SECTION 1

Patients' characteristics

a. Age

What is the best age for surgery? Is there any age limit for surgery (a "critical" age)?

Available Data

The influence of age on the selection of patients for DBS varies for different forms of dystonia. Therefore these will be reviewed separately.

Primary generalized dystonia

Several studies have assessed the factor of age as a variable regarding the outcome of DBS in primary generalized dystonia (PGD) and enough data is provided in other papers to make a statement on outcome versus age.[6-8] Age considerations include age of dystonia onset or the age at the time of surgery. Most studies have looked at the age at the time of surgery; however this variable is linked to the duration of symptoms.
Some studies have found an association between outcome and age at the time of surgery. Alterman et al.[8] reported a retrospective study of 15 patients with PGD who underwent bilateral globus pallidus internus (GPi) DBS. They found a significant correlation with outcome based on the age at time of surgery (r^2= 0.63, $p<0.001$). Subjects who were <21-year-old (n=8) experienced a median improvement in the Burke Fahn Marsden Dystonia Rating Scale – Motor score (BFMDRS-M) of 97% (range 84-100%) at one year. Subjects >21-year-old (n=7) experienced a 69% (range 40-89%) improvement in BFMDRS-M at one year after DBS. The significant difference between the groups was maintained even when the three DYT-1 mutation negative subjects (all older than 21) were excluded from the analysis. The youngest age at operation was 10 years. There was also a negative correlation with outcome based on the durations of symptoms (r^2=0.63, p=0.011), with the older group having had a longer duration of symptoms (mean of 20.7 years versus 5.1 years in the younger group). The same authors had previously found predictive value of post surgical benefit of age of onset in a larger group of 39 patients (children and adults) with primary dystonia.[9] Patients > 21 years at surgery (n. 17) improved 15% less ($p<0.001$) than those <21 years (n. 15) at 12 months after surgery.

Coubes et al.[10] reported the outcome of seven patients with DYT-1 mutation. Six were children (age 14 or less) and one was an adult (age 27). The youngest at operation was 8 years of age. No duration of disease was given. The six children walked again after surgery, but the adult did not, due to "secondary skeletal deformities of the spine and lower limb." Coubes et al.[11] also reported the 2-year outcome from 31 patients with PGD who underwent bilateral GPi DBS. The group comprised 12 adults (17 years of age or older) and 19 children. Children showed significantly better improvement in motor scores (BFMDRS-M) than adults

(p=0.04), but there was no significant difference between children and adults in level of improvement in disability scores (BFMDRS-D) (p=0.95). This age-related finding was not a function of being positive or negative for the DYT-1 mutation. There was no specification of the exact ages of the children, but a comment in the paper mentioned a subject who was 6 years of age. This appears to be the youngest patient operated on in the literature of PGD.

Halbig et al.[12] reported the 3-12 months outcome of 13 patients with PGD. The youngest subject was 13 year-old at the time of operation (disease duration of 5 years, improvement in BFMDRS-M of 65%). The oldest subject, 68 at surgery, had the least improvement (disease duration of 18 years, improvement in BFMDRS-M of 25%). Five other PGD patients were above 50 and had a 43-67% improvement.

Other studies have found that a longer duration of symptoms was associated with a worse outcome. For instance, Cersosimo et al.[13] reported the outcomes of 10 patients with PGD (9 of 10 tested positive for the DYT1 gene mutation). They did not report outcome by age, but 9 of 10 patients were under 20 and the other was 28. Unlike the study from Alterman et al.,[8] the 28-year-old patient had a short duration of symptoms (4 years) and showed the fastest time of the whole group to achieve maximal benefit (24 hours). The outcome of the 28-year-old was better than that of the youngest subject (9 years old) (69.7% improvement in BFMDRS-M after 3 years versus 53.3% after 2 years). Both were DYT-1 mutation positive.

A correlation with disease duration was found by Isaias et al.[9] analyzing predictors of surgical outcomes in a population of 39 primary dystonia patients with GPi DBS. Thirty-five of these patients tested positive for the DYT-1 gene defect. Disease duration negatively correlated with clinical outcome and with disability scores at 1 year after surgery ($p<0.05$). Patients with disease >15 years (n.12) improved 13% less than patients with shorter duration (n. 20). These authors stated that the fact that age at the time of surgery has been found to be significantly correlated with outcome in other studies may be largely due to the fact that younger subjects would have had the disease for a shorter period of time. Seven patients with fixed skeletal deformities had a significant poorer outcome at 12 months after surgery.

Eltahawy et al.[14] compared the outcomes of pallidal lesions (four subjects) versus pallidal DBS (two subjects) in PGD patients. The authors found a tendency for better outcome scores in patients who were younger and had an early onset of dystonia and shorter duration of disease before surgery.

In contrast, Valldeoriola et al.[15] found a positive association (p=0.001) between motor improvement with DBS and patients' age at the moment of surgery in a group 24 PGD patients with bilateral GPi DBS, but not with disease duration or age at onset of dystonic symptoms.

In a meta-analysis of DBS for all types of dystonia Holloway et al.[16] found a significant correlation between duration of symptoms and outcome (p=0.003). Age at onset and age at the time of surgery did not influence the outcome. However, a multiple regression analysis performed using nucleus stimulated, aetiology of dystonia, and duration of symptoms was highly significant for nucleus stimulated and aetiology, but not duration of symptoms (p=0.117).

Cervical dystonia

The age at the time of operation for cervical dystonia (CD) tends to be older than for PGD due to the nature of the disease, which usually presents in adulthood. Two independent studies with 10 patients at 1 year[17] and at 3 years[18] after bilateral GPi DBS did not find correlation between age and duration at time of surgery with outcome or adverse effects of

GPi DBS, but these findings might be related to the small sample of patients. From small case series regarding the outcome of GPi DBS for CD there is not enough data to make any statement about age at the time of surgery as a predictive factor of outcome, except that the surgery appeared to be safe in elderly subjects (the oldest subject was 78 year-old at the time of surgery).[17-20] Of note, however, is the association of the duration of CD and the risk of the development of cervical myelopathy, which may suggest that DBS for CD should be considered before this occurs. Tonomura et al.[21] reported a case of a 53-year-old patient with CD since childhood who developed atlantoaxial rotatory subluxation. GPi DBS was performed first, followed by atlantoaxial transarticular screw fixation and fusion. GPi DBS improved the CD so that the spinal fusion could be done. The authors warn that subjects with severe CD can develop unstable necks with severe morbidity.

Other focal dystonias

DBS surgery has been performed for other focal dystonias, many of which occur in adulthood and no formal recommendation concerning age as a predictive factor has been reported.[20,22-26] However, the same recommendations concerning increasing age and duration of symptoms as well as risks for medical co-morbidity and fixed skeletal deformities can apply. So DBS, if indicated, should be performed before these occur.

Pantothenate Kinase Associated Neurodegeneration

This group is included since it can benefit from bilateral GPi DBS. The age of onset of pantothenate kinase associated neurodegeneration (PKAN) is variable but usually starts in childhood. Castelnau et al.[27] reported the outcomes of GPi DBS in six subjects with genetically confirmed PKAN whose ages at the time of surgery were 10-39 years. The 10-year-old had symptom onset at age 1 year (the youngest age of onset) and had the least improvement (46% in BFMDRS-M, compared to mean of group of 74.6%) despite not having the longest duration of symptoms. This was the only subject who could not return to walking, unlike three other wheelchair bound subjects who resumed independent walking with DBS. The oldest subject at the time of surgery (39-year-old) had an 82% improvement, disease duration 22 years, and had spasticity.

Secondary dystonia

No study has systematically determined age to be a factor in patient selection in secondary dystonias, including tardive dystonia, hemidystonia, and post-anoxic dystonia.

Conclusions

Primary generalized dystonia (PGD)

From the studies available, mostly class IV, there appears to be evidence that subjects with PGD should undergo GPi DBS at an earlier age or sooner rather than later after disease onset to gain the optimal benefit from DBS for PGD. There is still controversy in the literature regarding whether symptom duration is an independent factor associated with outcome but there is agreement that DBS should be performed before the development of fixed skeletal deformities, which may occur after a long duration of PGD. One recent study found that duration of symptoms rather than age at the time of surgery was inversely correlated with outcome even after the patients with fixed skeletal deformities had been removed from the analysis,[9] although another found that age at the time of surgery and not symptom duration was predictive of outcome.[15]

Cervical and other segmental and focal dystonias

Subjects with CD tend to be older than those with PGD. No statement can be made regarding age as a predictive factor for DBS, from the few case series published. However, DBS appeared to be safe in the older subjects (65-78 years). For focal dystonias a longer duration of symptoms appears to pose a risk of subsequent fixed skeletal deformities, such as cervical myelopathy or spine instability in CD and limb contractures for other focal dystonias. DBS should be considered before these complications are irreversible.

Pantothenate kinase associated neurodegeneration (PKAN) and secondary dystonias

There is no available data to predict whether age or symptom duration are predictive of outcome of DBS.

Minimum and maximum ages for DBS for dystonia

Currently there are no data regarding the outcome of DBS for dystonia in children younger than seven years of age. From experience and comments in the surgical literature, implanting neurostimulators (even in the abdominal region) in very small children, especially those emaciated from disease such as PKAN, may lead to skin erosion. However, the procedure is well tolerated in young children and the extension connecting the DBS lead to the neurostimulator appears to allow for growth. As far as an upper age limit is concerned, there have been no reports of increased risk of intracranial haemorrhage in older patients with dystonia. However, patients with dystonia are usually younger than patients with PD at time of surgery.

Pragmatic Recommendations

Age itself should not be used as an inclusion or exclusion criterion for GPi DBS: children as well adults can benefit from the procedure. No data are available on children under 7 years of age. A practical approach is that any subject with dystonia should undergo surgery before developing fixed skeletal deformities or cervical myelopathy.

Points To Be Addressed

Future studies should tease out the relative contribution of age and symptom duration on surgical outcomes.

b. Co-morbidities

Are there patients who are not eligible for surgery due to co-morbidities? Are there absolute and relative co-morbidity contraindications?

Available Data

Brain imaging

Brain imaging is mandatory in order to determine the aetiology of dystonia and should be done before considering a patient for DBS.[28] No major structural abnormalities are detected with conventional brain CT or MRI studies in subjects with primary dystonia, although certain basal ganglia and cerebellar abnormalities, such as changes in volume and grey matter density have been found.[28-30] Secondary and neurodegenerative dystonias may show structural abnormalities such as stroke, demyelination, tumor, brain atrophy, etc. There are no studies specifically addressing the impact of these abnormalities on the surgical outcomes, although abnormal brain MRI was associated with less post-surgical improvement (after pallidotomy and pallidal DBS) in a small series of 15 patients with primary and secondary

dystonia.[14] As DBS is considered to be more effective for primary dystonias than secondary dystonias,[14] the main purpose of conventional brain MRI in surgical candidates is to support or refute the diagnosis of a primary dystonia and to rule out other incidental findings.

Psychiatric issues

Most published studies have used exclusion criteria for patients with severe depression or "major psychiatric disorders". No study has examined the rate of suicide in subjects with dystonia post-DBS. There are few anecdotal reports of suicide after DBS for dystonia. Burkhardt et al.[31] reported the suicide of one patient with post-anoxic dystonia and a prior history of depression, suicide ideation and attempt, aggressive behavior and drug dependency. Foncke et al.[32] reported suicide in two dystonia patients with GPi DBS with a previous history of depression.

These three cases of suicides in the DBS dystonia represent an exception to the general experience reported in published series. Furthemore, GPi DBS has been used safely in tardive dystonia patients with history of depression and psychosis.[33-34] There is also one report of remarkable mood improvement in a patient with severe depression who underwent bilateral GPi stimulation for tardive dyskinesia.[35]

A specific paper in Section II of this Supplement will further address psychiatric issues in patients with dystonia and DBS.[36]

Dementia

Certain studies of PGD used exclusion criteria similar to those used for PD and included a cut-off on the Mattis Dementia Rating Scale (<120/144).[37] Other studies of PGD did not screen subjects for dementia due to their young age. There are no available studies focusing on patients with dystonia and dementia who have had DBS surgery. However, some studies have reported on patients with secondary dystonias and pre-operatively impaired neuropsychological evaluation. No major differences in cognitive performances were observed after surgery.[38-39] A specific paper in Section II will further address this issue.[36]

Fixed skeletal deformities

Several studies have reported that patients with PGD who have fixed skeletal deformities do not improve as much from GPi or subthalamic nucleus (STN) DBS as those who do not.[9,40]

Conclusions

Minor structural abnormalities in the basal ganglia in primary dystonia do not seem to be a contraindication for GPi DBS surgery. Brain MRI is considered mandatory in the pre-operative selection process for subjects with dystonia, who are considering DBS in order to support the diagnosis of primary or secondary dystonia. From the studies available, the incidence of suicide after DBS is very low and occurred in patients with pre-operative psychiatric disease. Pre-operative evaluation of any fixed deformities is required, as the latter may limit the benefit from DBS. In secondary dystonia patients the degree of spasticity and possible other neurological deficits need to be carefully assessed in order to provide a realist prediction of outcome.

Pragmatic Recommendations

Screening for psychiatric co-morbidities, including depression and suicide attempts, is recommended. If the premorbid psychiatric symptoms are deemed severe this may be a contra-indication to surgery. For older patients, co-morbidities such as hypertension and cognitive impairment should be taken into account in the risk/benefit analysis. Careful assessment of other neurological deficits should be included in the pre-operative evaluation, especially in cases of secondary dystonia. Prediction of functional outcome should be carefully assessed and discussed with the patient and care givers.

Points To Be Addressed

Issues regarding psychiatric co-morbidities and vulnerabilities suggest that this area needs more study.

c. When to operate on patients, taking into account possible remission of dystonia over the years?

Available Data

The relationship between dystonia duration, severity or disability and outcomes of DBS is not well known. As previously discussed, and based on small series, the symptoms' duration and age at time of surgery[15] may be inversely correlated with the surgical outcome.[8-9,16]

In general, spontaneous remission of dystonia can occur, possibly in up to 15% of patients. For instance, 10-20% of patients with CD may have spontaneous remissions.[41] However, most of these patients have recurrent dystonia within 5 years with no further remissions. There is a report of an individual with spontaneous resolution of hemidystonia 4 years after onset and another whose hemidystonia resolved after 3 months of medical treatment.[42] Chuang et al.[43] examined 33 cases of hemidystonia after stroke, trauma, perinatal injury, infection, congenital lesion and tumor. Using follow-up telephone interviews they found that 11 patients were unchanged or improved while none had resolution of dystonia. Of note, this was at very different times after the onset of hemidystonia, as the range of dystonia duration was 1-58 years. In their review of the literature the authors found that most cases of acquired hemidystonia progress and then stabilize but do not resolve spontaneously.[43]

Conclusions

There is not enough evidence of spontaneous persistent resolution of dystonia. Even in patients who experience symptomatic remission within the first 5 years from the onset, dystonia usually relapses and become permanent. Conversely, there is some evidence supporting DBS surgery earlier rather then later during the course of the disease. Thus, DBS surgery should not be delayed if it is otherwise indicated. However, it is prudent to wait until the symptoms have stabilized, especially in relatively acute new onset of dystonia.

Pragmatic Recommendations

DBS for dystonia should be considered as a treatment option once it has become clear that medical therapy provides insufficient symptom control.

Points To Be Addressed

None.

SECTION 2

Clinical features of dystonia

a. What are the specific indications for surgery (mobility and activities of daily living scores, pain score, degree of disability)?

Available Data

There are no studies that directly assess, in a prospective fashion, which characteristics of dystonia are ideal for surgery. In most of the original case series concerning DBS for dystonia, inclusion criteria for DBS were: disabling motor symptoms, impairment in activities of daily living (ADL), severe pain, and progression of symptoms, in the context of unsatisfactory response to medical treatment.[37,44] From these studies it remains unknown which specific characteristics would respond better to DBS. [12,44-49]

Conclusions

The question of which patient features define a good candidate remains unanswered, as this issue has not been systematically examined. Severity of motor impairment, pain, limitations in quality of life and ADLs are currently the most frequent indications for DBS.

Pragmatic Recommendations

At the present time DBS can be recommended for dystonia patients with limitations of functions (caused by motor impairment, pain and disability). There is no recommendation about the severity of dystonia or any cut off scores for the same. Both the patient and the treating physician should agree on the impairment of ADL (especially motor function), reduced quality of life and severity of pain.

Points To Be Addressed

Future studies need to assess which clinical features are predictive of response to DBS in a more rigorous fashion. Outcomes should include disability, QoL and non-motor symptoms.

b. Are there specific types of dystonia (primary, secondary, neurodegenerative, etc.) which better support the indication of surgery and why?

Available Data

Primary segmental and generalized dystonia generally have good surgical outcome. The most rigorous studies using blinded assessment and larger number of patients were done in patients with primary dystonia (generalized or cervical, positive and negative for the DYT-1 gene).[17,37,44,48-49] The post-operative improvement of patients with primary dystonia who receive GPi DBS or ablative treatment is within a range of 40–90% using standard dystonia rating scales.[6,8,10,13,15,16-18,37,44-45] In a French multicenter study of bilateral GPi DBS in PGD, blinded video-ratings revealed 54% improvement of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) severity score, along with 44% improvement on the BFM disability score.[44] Adults with primary dystonia (DYT-1 positive and negative) and children with DYT-1 positive dystonia can achieve similarly good outcomes from GPi DBS.[8,10,44] Cervical dystonia and Meige's syndrome[23-26,50] have also shown a good response to bilateral GPi DBS.

There is a single study comparing retrospectively the surgical results in patients with primary vs. secondary dystonia and concluding that the outcome is better in patients with primary dystonia.[14]

Other types of dystonia, such as pantothenate kinase associated neurodegeneration (PKAN),[27,51-53] tardive dystonia,[33-35,54-58] Lubag[59-60] and myoclonus-dystonia[61-63] may respond to DBS favourably in a consistent fashion, especially the mobile dystonic features.

In contrast, there are a number of case reports and small series of patients with secondary dystonia who obtained little or no benefit from DBS.[14,64-65] However, a recent prospective study of 13 adults with dystonia-choreoathetosis from cerebral palsy without cognitive impairment, reported a mean improvement of 24.4% at one year with significant improvement in disability, pain, and mental health-related QoL.[66] There was no worsening of cognition or mood. Accurate placement of the DBS lead in the posteroventral segment of the GPi was important for outcome. Another recent study reported improvement of 41.4% in the motor and 29.5% in the disability scores of the BFMDRS in 8 subjects with different types of secondary dystonia.[67] Secondary dystonias associated with a previous encephalitis or structural brain lesion probably respond less favourably.[14,68]

Conclusions

Patients with primary dystonia experience the most benefit from DBS, whether it is generalized, segmental and focal. Other types of dystonia (secondary, neurodegenerative, dystonia-plus) may have more variable outcome. Patients with hyperkinetic cerebral palsy without cognitive impairment may have modest but significant functional improvement in their QoL from GPi DBS such that it might be considered.

Pragmatic Recommendations

GPi DBS should be considered for patients with PGD who do not respond adequately to medical therapy and who are limited in their ADL. GPi DBS can be considered for primary CD associated with pain or severe retrocollis or laterocollis and without adequate response to botulinum toxin. There is evidence that GPi DBS may be considered for drug resistant TD. In other dystonic syndromes, especially those secondary to other causes, DBS can be considered in cases of severe disability, although the response is generally less favourable than primary dystonia.

Points To Be Addressed

Well designed trials (prospective, randomized, controlled, blinded evaluation, large series) are needed in secondary dystonia syndromes to address the question of the efficacy of DBS.

c. Is there any predictor of response to surgery (mobile dystonia versus fixed dystonic postures, etc.)?

Available Data

In most of the studies of DBS in primary or secondary dystonia, phasic hyperkinetic movements respond more rapidly and better than tonic or fixed postures; patients who had little improvement tended to have severe tonic posturing.[9,20,37,44,48,69-70] In some of these subjects fixed skeletal deformities may have contributed to the worse outcome with tonic dystonic posturing.[8]

Primary dystonia patients respond well to DBS regardless of the presence of the DYT-1 mutation.[44]

Recent studies have suggested that a pattern of electromyographic activity with repeated bursts could indicate better or earlier response to GPi DBS.[71-72] Age at time of surgery and

duration of dystonia seem to predict postsurgical outcomes, at least at one year follow-up.[9] Secondary dystonia seems to respond less favourably to DBS surgery.[14]

Conclusions and Pragmatic Recommendations

Primary dystonia predicts better outcome. Phasic hyperkinetic movements generally respond faster and better than tonic postures.

Points To Be Addressed

Different clinical features of dystonia may not be adequately captured by current clinical rating scales (such as tremor, type of dystonic movement). In addition, especially in secondary dystonia, primary outcomes may need different scales or other evaluation instruments.

d. Are there specific types of dystonia or indications that encourage preferential choice of one target over another (thalamus, GPi, STN)?

Available Data

No prospective randomized study has compared one target to another for primary dystonia. The choice of GPi as the target of choice in primary dystonia emerged from the successful treatment of dystonia in PD with pallidotomy, followed by the early studies showing dramatic improvement in DYT-1 positive PGD patients with GPi DBS.[10,14] The GPi and ventrolateral thalamus have been considered suitable targets for secondary dystonia,[3-4,73-74] although in one study **stimulation of GPi was associated with better outcomes compared to thalamic stimulation.**[64] The STN has also been considered for primary and secondary dystonia in small case series with controversial outcomes.[40,75-76] Thalamic DBS has also been used to treat writer's cramp and musician's dystonia with success.[77]

Conclusions

There is Level B evidence that confirms the efficacy of GPi DBS in the treatment of primary (generalized and segmental) dystonia. There is level C evidence that GPi DBS is a good therapeutic option for patients with medically refractory CD and TD. Due to the paucity of data, no conclusions can be made at this time on the preferred target for the treatment of dystonia. There are no comparative studies for the other targets and for secondary dystonia.

Pragmatic Recommendations

GPi DBS can be recommended for dystonia patients who are candidates for DBS surgery. Further studies of DBS performed at other targets, including STN and thalamus, are warranted.

Points To Be Addressed

Randomized, controlled studies are now mandatory to better assess the target for DBS in the treatment of severe dystonia. Future studies of DBS in secondary dystonia need to specifically define the aetiology and features of the dystonia for each patient, rather than collectively grouping these disparate conditions together.

e. Are there motor and non-motor features that reliably do not respond to surgery? When should these be sufficiently important to contraindicate surgery?

Available Data

A study of 40 patients with primary generalized and segmental dystonia showed statistically significant motor improvement of all body regions (face, speech/swallowing, neck/trunk, arms/legs), as well as improvement in pain.[37] Depression/anxiety/psychiatric scores were generally low at baseline and did not significantly change after 3 months. The physical component of the QoL scale improved but the mental one did not. An open-label evaluation after 6 months revealed improvement in depression and both the physical and mental components of the quality of life scale. In the report of Diamond et al.[69] of generalized dystonia (presumably most of primary type), significant improvement occurred in neck, trunk, arm, and leg regions, but not in face or speech. In another study with 22-patients at 3-year follow-up of primary generalized dystonia treated with bilateral GPi DBS, axial, limb, and face scores significantly improved from baseline, although speech did not (though baseline scores were quite low to start).[44,49] The study of 10 patients with cervical dystonia by Kiss et al.[17] showed improvement in cervical dystonia and related pain. Numerous other studies referenced in earlier sections of this paper support the efficacy of GPi DBS for the reduction of motor signs and pain in various types of dystonia.

Conclusions

All motor features of primary dystonia are potentially responsive to GPi DBS, although response of speech is less consistent or robust. Non-motor features, other than pain, of dystonia are not well studied or reported in the literature, although there is evidence that mild depression and anxiety scores (which may reflect improvement in the somatic items) may be improved following DBS. There are no specific motor or non-motor features such that when present would contraindicate treatment with DBS.

Pragmatic Recommendations

At the present time, each patient's clinical situation needs to be assessed on a case-by-case basis to determine the extent and severity of motor features and associated dysfunction or disability when making a risk/benefit calculation and recommendation to the patient regarding DBS.

Points To Be Addressed

Further study of the non-motor features of dystonia and associated response to DBS is desirable.

More objective and quantitative assessment of speech and swallowing dysfunction and its response to DBS is needed.

SECTION 3

Previous medical therapy for dystonia

What medical treatment should be mandatory prior to considering surgery? How many drug trials and how long should have been attempted?

Available Data

Virtually all the reports of DBS for dystonia referenced in earlier sections indicate that patients have failed "appropriate" or "optimal" pharmacological therapy, but the details are often not defined. Similarly, in series focused on focal or segmental dystonia, an entry

criterion is typically failure of adequate or continued response to chemodenervation treatment with botulinum toxin.

Conclusions

Evidence-based data do not currently inform the answer to this question, largely because pharmacological treatment tends to be individualized to each patient's needs and tolerability of treatment.

Pragmatic Recommendations

Medical management using appropriate pharmacological therapy needs to be tailored to the patient before considering surgery. It is not mandatory to try all the available medications for primary dystonia. Clinical practice generally suggests that patients with dystonia should undergo trials of maximally tolerated doses of appropriate medications, including one or more of the following classes of drugs: dopaminergic, anti-cholinergic, and benzodiazepine. In children high doses of anticholinergic drugs may be very beneficial. This therapy has to be weighed with the evidence that performing GPi DBS in primary generalized dystonia should be done sooner rather than later in the duration of disease and especially before the formation of fixed skeletal deformities. High dose anticholinergic therapy may not be tolerated in adults due to adverse cognitive side effects. Affected muscle regions that can be effectively targeted with botulinum toxin(s) should be so treated in a manner that optimizes localization and dose.

Points To Be Addressed

Rigorous study of the efficacy of pharmacotherapy on various types of dystonia is needed, with the goal of developing probabilistic models of response to inform appropriate timing of surgical intervention.

SECTION 4

Previous surgery for dystonia

Does previous functional surgery (thalamothomy, pallidotomy, peripheral denervation, myectomy, etc.) influence the outcome from DBS and if so should this influence whether or not to offer DBS?

Available Data

There are few data available on DBS in patients who had previous surgery (lesions or previous DBS) for dystonia. In fact, previous surgery, such as thalamotomy, pallidotomy, and peripheral denervation, is rarely stated as exclusion criterion for DBS.

Katayama et al.[78] studied five cases of PGD treated with bilateral GPi DBS. Two of the patients had been treated previously with bilateral thalamotomy or unilateral pallidotomy. They found a marked effect of GPi DBS even in patients who had previously undergone ablative procedures. Vercueil et al.[64] performed thalamic (VLp) DBS in 12 patients, three of whom later underwent a second operation with GPi DBS lead implantation because of lack of efficacy. Two of these patients had secondary dystonia. After the second DBS surgery, the benefit was reported as moderate in two and marked in one out of three patients.

On the other hand, some have pointed out that a history of multiple thalamotomies is a negative outcome predictor for GPi DBS in patients with dystonia.[8] These authors studied 31 **patients with medically refractory primary dystonia (20 DYT-1 positive) who underwent GPi**

DBS. Three patients had undergone multiple thalamotomies before DBS. An average improvement in all the patients was 69.4% at 12 months. They found that previous thalamotomy was the major factor showing a significant negative correlation with clinical outcome at 1 year ($p<0.01$).

As for combination of pallidal or thalamic DBS and contralateral lesioning, Cersosimo et al.[13] reported the long-term follow-up data of pallidal DBS in 10 patients with PGD: five of them had unilateral pallidotomy and contralateral GPi DBS. The authors conclude that combined DBS with pallidotomy may be more effective than bilateral pallidal DBS.

There are no data on previous peripheral surgeries such as denervation or myotomy regarding their influence on the outcome of DBS.

Conclusion and Pragmatic Recommendations

Previous surgical treatments (i.e., thalamotomy, pallidotomy, peripheral denervation) should not prevent consideration of DBS. There are only a few reports on the effect of previous surgical treatment. Patients who have undergone peripheral denervation for cervical dystonia with unsatisfactory results and/or with symptoms that have extended to other parts of the body may be considered as candidates for GPi DBS.

Points To Be Addressed

None.

SECTION 5

Genetic causes of dystonia

Should patients with DYT-1 dystonia or other genetic causes of dystonia be treated any differently with respect to the issues listed above?

Available Data

There are no prospective studies specifically addressing the question whether patients with genetic dystonia have different postoperative outcomes after DBS surgery. Genetic testing is usually done to specify diagnosis,[2] for counselling and research purposes. It is not routinely performed in every patient with dystonia considered for DBS, although the DYT-1 mutation was tested in PGD patients in many studies reporting outcomes after DBS surgery.

DYT-1

Initial reports suggested that DYT-1 mutation positive patients would have better outcomes compared to DYT-1 negative patients. In 2000 Coubes et al.[10] reported the 1 year outcomes after bilateral GPI DBS in 7 PGD patients (6 children and 1 adult) with DYT-1 mutation. The motor benefit was on average 90.3% (range 60-100). Krauss et al.[65] subsequently reported 2 non-DYT-1 PGD patients who improved by 74% at 2-year follow-up. Similarly, several other studies reported somewhat lower results in non-DYT1 patients.[19,73,79]

However, other subsequent series, including a follow-up report by Coubes et al.,[11] have not identified significant differences between DYT-1 patients and other PDG cases.[37,44] In 2004 Coubes et al.[11] reported the 2-year follow-up of 31 PGD patients with GPi DBS and found no difference in the motor outcome (79% improvement) in the DYT-1 positive subjects compared to the DYT-1 negative subjects. In a prospective controlled multicenter study with GPi DBS in PGD, there was no difference (50% improvement) in the benefit at 1 year and 3 years in the 7 DYT-1 positive patients compared to the 17 DYT-1 negative patients.[44,49]

Recently, DYT-1 mutation status has again been implicated as a predictor of better DBS outcome in children and adolescents. Borggraefe et al.[6] described 6 PDG pediatric patients having GPi DBS and also reviewed the literature finding 44 reported PDG cases with surgery occurring before age 21 years, known DYT-1 status, and post-surgical evaluations at 4 weeks o more. The authors found DYT-1 positive patients (29/50) improved significantly more than mutation negative patients.

DYT-11

There is a small number of reports of DYT-11 (myoclonus-dystonia) patients undergoing thalamic or GPi DBS. Thalamic DBS was reported effective in one patient with myoclonus dystonia,[62] as well as bilateral GPi DBS in another two patients.[61,63]

Other genetic dystonias

Several case reports about GPi DBS in secondary dystonias due to inherited disorders have been published. Bilateral GPi DBS in Huntington's disease,[80-82]neuroacanthocytosis,[83] Lubag (X-linked dystonia-parkinsonism, DYT-3),[59-60] Lesh-Nyhan syndrome,[84] PKAN,[51-53] type 3 gangliosidosis[85] has been performed so far. The surgical outcomes have been heterogeneous, but no worsening of pre-operative conditions has been reported.

Conclusions

Most studies have not found that DYT-1 mutation positive PDG patients differ in their clinical benefits from GPi DBS compared to mutation negative PGD patients, although one recent meta-analysis of children and adolescents undergoing GPi DBS suggests DYT-1 positive patients have better outcome. The role of DYT-1 genetic testing and determination of gene status in PDG as a predictor of surgical outcome, therefore, remains to be determined and may differ in paediatric and adult populations. There are few data available for other genetic dystonias. Secondary dystonias due to genetic disorders have differing outcomes.

Pragmatic Recommendations

Testing for DYT-1 dystonia or myoclonus dystonia (DYT-11) is helpful to confirm the diagnosis and for counseling the patient regarding outcomes of treatment.

Points To Be Addressed

Other genetic PGD (e.g. DYT-6) might have a different response to DBS surgery. Further studies that systematically test PDG patients for both DYT-1 and DYT-6 should clarify whether surgical outcomes are associated with mutation status.

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