ような様々な条件を考慮した上で，個々の症例でDBSか凝固術を選択するのが妥当である．

V 髄腔内baclofen投与治療（intrathecal baclofen；ITB）

ITB療法は本来痙縮の治療として導入されたが，様々なジストニアに対しても行われてきた[16)17)]．DBSの効果が大きく期待できない脳性麻痺などによる二次性のジストニアが主な対象である[18)]が，近年ではDBSと併用してより効果が期待できるというような報告もある．手術自体は単純ではあるが，長期にわたり問題なく効果を持続するには細やかな配慮が必要である[17)]．治療に非常に難渋する複雑局所疼痛症候群やfixed dystoniaに対する効果も期待されている[19)]．

以上に概説したように，ジストニアと言ってもその症状，原因は極めて多様であり，それぞれに対応するには様々な治療方法に精通しておかなければならない．この意味で機能的脳神経外科が現在ややもすると脳深部刺激術一辺倒になっている状況が危惧されるところである．Parkinson病では様々な新しい薬物治療が展開され，今後再び外科的治療が低迷する可能性も考えておく必要がある．しかし，ジストニアではこのような画期的薬物治療の出現が期待できないと考えられ，外科的治療の役割は大きい．少なくともある程度の保存治療で効果のないジストニアに関しては，外科的治療を積極的に考慮するべき時代になっているものと考える．しかし，一方でこれらの治療がまだ十分に医療者の間でも知られていないこと，外科的治療が究極の危険な方法であるという誤解，短絡的な思考ではその作用機序が説明がつかないため治療自体が理解が得られなくいことなどの理由で，本来は社会復帰できるようなジストニア患者が多く放置されているのではないかと危惧している．

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Update on Multimodal Neurosurgical Management of Dystonias

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The neurosurgical treatment of dystonia has progressed markedly since the introduction of deep brain stimulation of the globus pallidum interna. However, dystonia is not a single disorder but comprises various types and causes, and it is true that deep brain stimulation cannot cover the complex nature of dystonia. Depending on the distribution of symptoms and causes, we have to consider other surgical managements such as thalamotomy, peripheral denervation, and intrathecal baclofen. Such a multi-modal strategy has enabled us to treat and even cure many patients with dystonias. No treatment other than various neurosurgical approaches yields better results in the management of dystonias. In this sense, we are now at a stage where we should regard dystonia as a neurosurgical disorder in terms of treatment.

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SUPPLEMENT

Pre-operative Evaluations for DBS in Dystonia

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ABSTRACT:
Background: The preoperative evaluation in dystonia aims at characterizing the severity and topography of motor symptoms in patients, who have previously been selected for deep brain stimulation (DBS). **Methods:** The literature search was performed using PubMed, CINAHL, and the Cochrane Collaborative databases. **Results:** Commonly used scales for clinical assessment are the Burke-Fahn-Marsden dystonia rating scale for generalized dystonia and the Toronto Western Spasmodic Torticollis Scale for cervical dystonia. Motor assessment is completed by quality of life and functional scales, such as the Short-Form Health Survey (SF-36) or the Parkinson's Disease Questionnaire 39. Validated rating scales for cranial or upper limb dystonia are lacking. **Discussion:** In common clinical practice, these outcome measures can be administered in an open-label fashion because double blind assessment is only required for ascertaining new treatment indications or research purposes. The same measures are to be used postoperatively to revaluate outcome after DBS. Brain MRI is required to confirm diagnosis and assess structural abnormalities. Other imaging techniques, particularly functional imaging, are used for research purposes. © 2011 *Movement* Disorder Society

Key Words: DBS; dystonia

Introduction

Preoperative evaluation is a crucial step in the management of patients with dystonia who are candidate for deep brain stimulation (DBS). Issues related to inclusion and exclusion criteria for DBS surgery have been detailed in a previous article[1] of this supplement. Before entering preoperative workup, each patient should be classified along with the three axes of aetiology, age of onset, and spread of dystonia;[2] this will allow identifying the most appropriate tools for assessment. Preoperative evaluation aims at characterizing the severity and topography of motor symptoms and their impact on activities of daily living (ADLs) and social activities and provides a baseline reference for mid- and long-term postoperative evaluations. The quality and accuracy of the preoperative assessment and the choice of assessment tools is crucial as will affect all subsequent postoperative comparisons. The preoperative phase also includes a number of steps related to the assessment of the surgical risk and the determination of the surgical trajectory. This article will review the evidence on the application and evaluation of clinical scales to be used for preoperative and postoperative evaluation of patients undergoing DBS for dystonia.

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 DBS; pallidal stimulation and dystonia; subthalamic stimulation and dystonia; thalamic stimulation and dystonia; secondary dystonia and DBS;

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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 articles were retrieved. To facilitate the committees' work, the articles were divided in three groups, which often overlapped: preoperative, intraoperative, and postoperative. A PDF file was created for each article 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 article were selected taking into account their specific expertise in the field. The steering committee prepared a list of questions related to preoperative, intraoperative, and postoperative issues and established two chairs responsible for each of these three 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. As 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.[3] 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.

Methods of Assessments

Descriptions and Interest of the Different Scales for Dystonia

Motor Scales. Motor scales for dystonia have been the object of a number of publications, encompassing descriptions of rating instruments and validation studies.[4–11] However, none of the scales fulfils all the recommended criteria for health measurement rating scales defined by the Scientific Advisory Group of the Medical Outcomes Trust (SAC).[12] These criteria include: conceptual and measurement model; reliability; validity; responsiveness; interpretability; respondent and administrative burden; alternate forms; cultural and language adaptations. In particular, none of the scales that will be described below has been specifically designed to assess responsiveness to a treatment.[13] Nevertheless, several controlled studies have demonstrated that these scales are able to detect significant improvement in dystonic patients undergoing different treatments. This is the case, for example, for botulinum toxin type A in cervical dystonia (CD), whose efficacy was demonstrated using specific scales in numerous class I studies[14] (using the classification proposed by the American Academy of Neurology).[15] In addition, the efficacy of DBS in dystonia could also be assessed in one class I study[16] and in five class III studies.[17–21] These trials provide a clear demonstration that dystonia can be assessed using objective measures.

Generalized/Segmental Dystonia. The Burke–Fahn–Marsden dystonia rating scale (BFMDRS)[4] was introduced to assess generalized dystonia patients. It is composed of a motor part assessing dystonia and a part assessing the resulting disability. The motor subscale evaluates two clinical features of dystonia (severity and provoking factors) in eight body regions (eyes, mouth, neck, and the four limbs) and one functional area (speech and swallowing). Severity ranges from 0 (no dystonia) to 4 (severe dystonia). The provoking factors assess the situation under which dystonia occurs and range from 0 (no dystonia) to 4 (dystonia at rest). These two features, severity and provoking factors, are multiplied and then scores are summed, except for the eyes mouth and neck which are halved before summing as they are considered regions of "lower weight." The resulting maximum total score on the BFM severity is 120.[4] The BFMDRS was clearly designed to assess patients with severe generalized dystonia and has limitations when applied to milder or nongeneralized cases. These include the fact that arms and legs are given one rating each, without distinguishing proximal and distal components, the combination of functional features (such as speech and swallowing) with the inspection of dystonia in other body regions, and the arbitrary reduction of the weight in the cranial/cervical region.

The BMFDRS clinimetric properties were assessed in a study of 10 patients with dystonia rated by four different examiners: the overall reliability, inter-rater agreement, and concurrent validity were demonstrated

for the BMFDRS total score but not analyzed for each different body regions and area of function.[4] After the first encouraging effort, the BFMDRS was not further systematically developed and tested as a multicenter instrument.

The BFMDRS section on disability assesses the effects of dystonia on ADL (speech, handwriting, feeding, eating/swallowing, hygiene, dressing, and walking), and the total maximum score is 30.

The unified dystonia rating scale (UDRS) was designed to overcome limitations of the BFMDRS. It includes a more detailed assessment of separate body areas with specific ratings for proximal and distal limbs, and does not mix bodily inspection with functional variables, such as speech and swallowing.[9] In addition, the UDRS rates duration similarly to the duration factor previously validated for the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[9] Furthermore, the UDRS weights the different body regions equally. Fourteen body areas are evaluated: eyes and upper face, lower face, jaw and tongue, larynx, neck, trunk, shoulder/proximal arm (right and left), distal arm/hand (right and left), proximal leg (right and left), and distal leg/foot (right and left). For each of these, the UDRS requires rating the severity and duration. Severity rating is specific for each body region and varies from 0 (no dystonia) to 4 (extreme dystonia); duration also ranges from 0 to 4 and assesses whether dystonia occurs at rest or with action, and whether it is predominantly of maximal or sub maximal intensity. The total UDRS score is the sum of the severity and duration factors, with a maximum total of 112. The severity score is expressed as a percentage of the maximum amplitude of the physiological movement, which indicates that this, as all other dystonia scales, is more appropriate to rate mobile dystonia versus fixed posturing.

The global dystonia rating scale (GDS) evaluates the severity of dystonia in the same 14 body areas as the UDRS.[9] The GDS is a Likert-type scale with ratings of 0–10 (from 0, no dystonia, to 10, severe dystonia). There are no modifying factors in the GDS, and the total score is the sum of all the body area scores with a maximum of 140. The GDS is a very simple scale that allows a quick rating of dystonia but does not give precise indications about its clinical aspects (mobile vs. fixed; disability...). On the other hand each body part has a similar weight, which has the advantage not to minimize any features of dystonia. The other advantage of this scale is its ease of use.

A comparison of the internal consistency and reliability of the BFMDRS, UDRS, and GDS was performed by 25 dystonia experts using a standardized videotape protocol.[9] All three scales showed excellent internal consistency and good correlation among raters. The inter-rater agreement was excellent being lowest for eyes, jaw, face, and larynx. There was higher inter-rater consistency for motor severity than for the ratings of modifying factors (duration in the UDRS and provoking factors in the BFM). Seventy-four percent of the raters found the GDS the easiest to apply against 38% for the BFM and only 5% for the UDRS.[9] A recent study showed that the UDRS and BFM scales provide similar accuracy and reliability to assess the consequences of DBS in dystonia.[22]

The global outcome scale (GOS) scores the global improvement of the dystonia after a therapeutic intervention. The improvement is rated from 4 (marked) to 0 (no effect).[23] The GOS is a very simple but imprecise scale that does not differentiate the improvement of each body part. Because of these limitations the scale is rarely used.[23]

For tardive dyskinesia, which encompasses dystonia and other movement disorders (particularly chorea, myoclonus, and tremor), composite scales are more appropriate, such as the abnormal involuntary movement scale (AIMS) or the extrapyramidal symptoms rating scale (ESRS).[5–6] The ESRS is divided into four subscales and four clinical global impression severity subscales. These consist in a questionnaire of drug-induced extrapyramidal symptoms, an examination of parkinsonism and akathisia, an examination of dystonia, an examination of dyskinesia, and a clinical global impression severity scales for tardive dyskinesia, parkinsonism, dystonia, and akathisia.[6] The AIMS contains seven items assessing the severity of abnormal movements in different body locations. This scale also includes a global judgment of the severity, consequences, and patient's awareness of abnormal movements. It has been observed that the ESRS and the AIMS have a high degree of concordance.[10]

Cervical Dystonia. The Tsui Torticollis Rating Scale was the first rating scale specifically designed for CD.[7] It contains six items and is designed for video assessment. This scale evaluates the amplitude and duration of neck involuntary movements in the neck, elevation of shoulder, and head tremor.

The TWSTRS[9] was developed to provide clinical investigators with a better instrument to assess the severity and disability of CD, which is the most common form of focal or segmental dystonia. The TWSTRS was developed in 1990 and consists of 22 items. The total TWSTRS is comprised of three separate subscales: motor severity, disability, and pain due to CD. The motor severity scale consists of 10 items assessing the severity of head posture in several axes of movement (turning, tilting, anterocollis, retrocollis, and shoulder elevation), the effect of sensory tricks, range of motion, and duration of dystonia. The score for motor severity subscale ranges from 0 (no symptoms) to 35 (severe CD). The TWSTRS subsection for

motor severity has been validated for inter-rater reliability and validity and a teaching tape has been developed to ensure consistency across raters for multicenter trials.[8,24] The disability subscale consists of seven items assessing the effect of CD on work performance, ADLs, driving, reading, watching television, conducting activities outside home, and social embarrassment. The maximal score for the disability subscale is 32. The pain subscale consists of five items to assess CD related pain at its maximal, minimal and usual level, and to indicate the duration of pain during a day, and disability due to pain. The maximum score for the pain subscale is 20. The total TWSTRS is the sum of the three subscale scores, with a maximum value of 87. The total TWSTRS has been used extensively as an outcome variable in clinical trials of pharmacological and surgical interventions.[25–32]

It has been shown that there is a good correlation between the scores obtained with the TWSTRS and the Tsui scale.[33] The metric properties of the total TWSTRS and of severity subscales were investigated. Factor analysis showed that 18 of the 22 items of the total TWSTRS fall into three clinically distinct and relevant factors: (1) motor severity, (2) disability, and (3) pain.[8] These domains correspond to the three subscales of the total TWSTRS, and each measures a separate aspect of CD. The item for social embarrassment did fall in any factor as well as three additional items (sensory trick, lateral and sagittal shift).[8] There are two possible explanations for this inconsistency. First, the range of scores available for these items is limited to absence/presence (lateral and sagittal shift) or to 0–2 (sensory tricks). Second, it has been observed that the observation of sensory tricks is a clinical feature relevant to the diagnosis rather than to clinical signs. Furthermore, the TWSTRS does not clearly assess dystonic tremor, as well as complex combination of phasic and tonic dystonic features.

Focal Dystonias. The clinical evaluation of focal dystonias is often difficult.

A scale of 0 (normal) to 4 (worst) has been proposed to rate the severity of blepharospasm and oromandibular dystonia, but the inter-rater reproducibility was poor.[34,35] In a recent study, the metric properties of the Jankovic Rating Scale (JRS) and a self-rating patient response outcome scale (the Blepharospasm Disability Index, BSDI) have been compared in blepharospasm patients.[36] The internal consistency and retest reliability of the BSDI were good and the scores obtained using both scales were well correlated. Therefore, these authors suggest that JRS and BSDI can both be used to reliably assess blepharospasm in treatment trials.

For task-specific dystonias, the writer's cramp rating scale (WCRS) was developed for patients with writer's cramp.[37] The WCRS is divided into three subscales, respectively studying the dystonic posture, the latency for dystonia to occur, and the presence of writing tremor.[26] Although this scale is easy to implement and has sufficient inter-rater reliability it remains largely unused.

The main characteristics of the above mentioned scales have been summarized in Table 1.

Quality of Life Scales. The assessment of quality of life (QoL) is crucial to determine the impact of the surgery on ADL. Most studies assessing this outcome measure have used the Short-Form Health Survey (SF-36) or the PD Questionnaire 39 (PDQ-39).[38–41] The SF-36 scale assesses the general and mental health, the physical and social functioning, the physical and emotional roles, and the pain and vitality.[42] The scores on each subscale are comprised between 0 (worst) to 100 (best). The PDQ-39 scale was originally designed for PD[43] but has also been used for dystonia. It is divided into seven sections: mobility, ADL, emotional well-being, stigma, cognition, communication, and bodily discomfort.

The CD Impact Profile (CDIP-58) has been developed for CD. It measures the health impact of the disease from patient's perceptions.[44] This scale is divided into eight sections (head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning). This composite scale is more sensitive in measuring the functional outcome of a treatment, such as botulinum toxin, than the SF-36 or TWSTRS.[45] However, its use has not gained wide diffusion.

Conclusions

For generalized and CD, the two most accepted and used rating scales are the BFMDRS and TWSTRS, respectively. For other focal dystonias, there are no generally agreed upon scales. The currently available rating scales have several limitations. The BFMDRS scale uses weighting factors that can minimize the real impact of eyes, mouth, and neck dystonia. In addition, other associated movement disorders, such as tremor or myoclonus, are not considered in most of the available dystonia scales. Moreover, the available current scales do not sufficiently discriminate mobile (phasic) dystonic movements from fixed (tonic) dystonic postures.

Pragmatic Recommendations

The features of dystonia should be monitored before DBS using the most appropriate among the available dystonia scales. The choice of which scale to use should depend upon the type of dystonia, according to topography rather than aetiology. For generalized dystonia, it is recommended to use the total BFMDRS,

TABLE 1. Description and metric properties of the different dystonia scales

Scales	Indication	Composition	Score	Intrarater reliability	Interrater reliability	Cross scale correlation
BFM	Generalized dystonia	Motor part Disability part	/150	High for motor part: Spearman's coef: 0.98–0.99	High for motor part: Spearman's coef: 0.85–0.96	High between BFM and UDRS Pearson's coef: 0.98
UDRS	Generalized dystonia	Severity Duration	/112	Unknown	High Intraclass correlation coef: 0.994–0.997	High between BFM and UDRS Pearson's coef: 0.98
GDS	Generalized dystonia	Severity	/140	Unknown	Unknown	High between BFM and GDS Pearson's coef: 0.98
AIMS	Tardive dystonia	Severity Global judgement	/40	Unknown	High Intraclass correlation coef: 0.79–0.93	AIMS and ESRS: 96% agreement
ESRS	Tardive dystonia	Eight sections	/198	Unknown	High Spearman's coef: 0.80–0.97	AIMS and ESRS: 96% agreement
Tsui	Cervical dystonia	Four parts	/25	Unknown	High Spearman's coef: 0.86	Good between Tsui and TWSTRS Pearson's coef: 0.57
TWSTRS	Cervival dystonia	Severity, disability, pain	/87	Unknown	High Kendall coef: 0.76-0.98	
JRS	Blepharospam	Severity, frequency	/8	Unknown	Unknown	
BSDT	Blepharospam	Situations in which dystonia occurs	/24	Good Spearman's coef: 0.453–0.595	Unknown	Good between JRS and BSDI Pearson's coef: 0.73
WCRS	Writer cramp	Writing movement and speed	/30	Unknown	Moderate to substantial	

BFM, Burke Fahn Marsden Scale; UDRS, Unified Dystonia Rating Scale; GDS, Global Dystonia Scale; AIMS, Abnormal Involuntary Movement Scale; ESRS, Extrapyramidal Symptoms Rating Scale; TWSTRS, Toronto Western Spasmodic Torticollis Scale; JRS, Jankovic Rating Scale; BSDI, Blepharospasm Dsability Index; WCRS, Writer's Cramp Rating Scale.

which may not always be appropriate for focal dystonias. As an alternative, the GDS provides a rapid assessment and is easily applied, although it has been used less frequently than the BFMDRS. The UDRS may also be used, although its implementation is more difficult. For CD, the TWSTRS, including subscales for severity, disability, and pain, is recommended. These scales have been designed to assess patients with primary dystonia and do not always capture complex dystonia phenotypes, such as those observed in dystonia-plus or in secondary dystonias.

Given these limitations, it is recommended that a limited number of expert evaluators be charged to rate patients with dystonia and that standardized videos are performed during each assessment.[4]

The impact of surgery on QoL is a crucial issue that may provide outcome results divergent from the motor assessment.

Points to Be Addressed

New more comprehensive scales for dystonia should be developed: they should also accurately measure tonic postures and phasic movements. Finally, there is a need for uniform training for the BFMDRS and UDRS. Uniform training is available for the TWSTRS, although it has not been shown whether such training improves inter-rater reliability. For other focal dystonias, although several scales exist, their internal consistency and reliability have been poorly studied and their use remains incidental. Thus, there is a clear need for specific scales that objectively quantify the effect of DBS in focal dystonia.

Clinical Use of the Scales for Dystonia

Should Standardized Evaluation Be Performed Preoperatively and Postoperatively? How? When?

Motor Assessment. Postoperative objective and subjective assessments have been compared with the preoperative condition in a number of publications, encompassing clinical series, case control studies, cohort studies, and single case reports.[16–20,32,38,41,46–82] There are only six controlled trials that evaluate the effects of GPi DBS in a blinded fashion (one class I level study[16] and five class III studies[17–21]). These trials provide a clear demonstration of the benefit of DBS for the primary generalized and tardive dystonias and also for CD.[16–20] Favorable outcome has also been reported for PKAN.[46] In these studies a videotaped assessments scored by independent blinded raters

allowed controlled evaluations of the effects of the surgery.[16–20] It is notable that data on the benefit of DBS in dystonia reported by open studies are in keeping with the findings reported by controlled studies.

A number of practical issues have been addressed by the available studies. Preoperatively the assessment is most often performed between the last month and the last week preceding surgery.[16–20,32,38,41,46–82] The time interval between surgery and the first postoperative evaluation is usually between 3 and 12 months.[16–20,32,38,46–82] Patient management of the does not require more frequent controls and the first preoperative evaluation is aimed at assessing the acute effects of stimulation on dystonia and the thresholds for stimulation-induced side effects. Most of the studies have clearly shown that the improvement starts within the first hours or days after beginning the stimulation, and then progresses. Most of the benefit is usually obtained after 3–6 months.[16–20,32,38,46–82] The improvement first affects phasic dystonic movements and later tonic postures.[16] Some additional improvement can occur later but, usually, to a less extent and slower. Some studies, however, have shown an additional 10–30% improvement of the dystonia between 1 and 1.5 years.[48,80–81] The postoperative outcomes will be discussed in detail in another article on this same issue.[83]

Quality of Life Assessment. The QoL assessment is usually performed when the patients have the preoperative motor assessment, that is, from 1 month to 1 week before surgery.[16–19,38–39,41] The interval between surgery and the postoperative evaluation of QoL is generally between 3 and 18 months.[16–19,38–39,41] QoL usually improves significantly after GPi DBS in generalized and segmental dystonia and CD.[16–19,38–39,41]

Conclusions

Validated motor and disability scales are widely used to assess patients before surgery in all the published studies. Most of the time evaluations have been done in open label fashion.

Pragmatic Recommendations

Validated scales (see previous section) should be used to assess patients with dystonia within few weeks before surgery. The benefit should be evaluated at 3–6 months after surgery and further evaluations should be scheduled at yearly intervals. Videotaped assessments are recommended.

Points to Be Addressed

The ideal time-frame to assess the efficacy of DBS in different forms of dystonia needs to be better defined. It remains also to be specified if this should differ for primary generalized or focal forms or for secondary dystonias.

Should Evaluation in the OFF Stimulation Condition Be Performed in Routine or Research Protocol? How Long and When?

Evaluations are rarely performed in OFF stimulation condition. OFF stimulation condition has only been assessed in three class III and in five class IV studies.[17–18,20,56,58,66,71,82] However, assessments without stimulation may provide important information on the immediate effect of stimulation, the delay of reoccurrence of the clinical signs and possibly further worsening of preoperative motor conditions. OFF stimulation studies thus allow better comparison with the preoperative motor condition and may show evidence of underlying disease progression.

The duration of the stimulation wash-out period preceding assessment may be variable. This has been specifically studied by Grips et al.,[58] who showed that most of the phasic motor symptoms in patients with segmental dystonia reoccurred within 4 hours after switching off bilateral GPi DBS, while the tonic signs may take much longer to worsen. In the study of Vidailhet et al.[17] on generalized dystonia, the maximum tolerated duration of the OFF stimulation period was 7 hours. In a single case study in Lesch–Nyhan dystonia, the stimulator could be switched off for 1 months.[71] By contrast, tardive dystonia and CD may worsen very quickly after the stimulator is switched off.[20,82] This indicates that the effects observed after switching off stimulation may depend on the etiology of dystonia. Furthermore, it has to be taken into account that severe worsening of dystonia may be life threatening in severe generalized cases; this can be prevented by careful observation of patients during this period.

Conclusions

Evaluations in the OFF stimulation condition have been performed in few studies, which provide interesting data concerning the posteffect duration of DBS in dystonia.

Pragmatic Recommendations

A reasonable duration of the OFF period may be of around 3–4 hr although this does not lead to the worst off condition. In routine clinical setting, OFF stimulation evaluation is not acceptable because of the risk of reoccurrence of severe dystonia manifestations.

Points to Be Addressed

It is unclear whether the time course of motor signs reoccurrence after DBS switch-off depends on the etiology of dystonia. This needs to be addressed by specific studies.

Role of Imaging

Is There Any Role for Preoperative Imaging (Brain MRI, PET)?

Morphological Imaging: Conventional MR Imaging. Brain imaging is mandatory to determine the aetiology of dystonia and should be performed before considering any patient for surgical treatment.[1] In primary dystonia, there are no major structural abnormalities, as seen with brain CT or MRI. However, some detailed MRI studies indicate changes of gray mater density in the motor circuit or changes of basal ganglia volume.[2,84–86] One study with conventional MRI showed T2 bilateral abnormalities in the lentiform nucleus in primary CD.[87] However, the abnormalities were only detected on calculated T2 values; no obvious signal changes could be recognized on visual inspection of T2-weighted images.[87] Recently, structural abnormalities were shown in the cerebellum and sensorimotor circuit in writer's cramp.[88] Using voxel-based morphometry, gray matter density decrease was found in the hand area of the left primary sensorimotor cortex, bilateral thalamus, and cerebellum.[88] However, other studies rather found grey-matter increase in motor and prefrontal cortex and basal ganglia.[89–90] Differences in the genetic status of these patients may explain these discrepancies.[91] However, such changes were not visualized on conventional images. The main aim of conventional structural MRI brain images in surgical candidates is to determine the feasibility of surgical implantation and the technical approach independently of the search for the cause of the dystonia. Surgeons will use this brain MRI to rule out major surgical contraindications such as brain tumors, severe vascular changes, or malformations and to visualize the target structures. Some secondary dystonias such as PKAN, poststroke dystonia, neuroacanthocytosis, or inborn errors of metabolism are associated with severe basal ganglia damage that can have an impact on the choice of the target of implantation and on the expected results.[92–95] In most of the published series, the brain MRI sequences are not described.

Nonconventional MR Imaging. Brain MR spectroscopy revealed no abnormal *N*-acetylaspartate/creatine (NAA/Cr) and lactate/creatine ratios in patients with focal hand dystonia, whereas it has been shown that NAA/Cho and NAA/Cr were significantly lower in patients with spasmodic torticollis.[96–97]

There are some reports on diffusion tensor images (DTI) indicating abnormal fractional anisotropy and mean diffusivity in CD and idiopathic dystonia.[98,99]

Conclusions

Brain MRI is required for the aetiological diagnosis of dystonia. At the preoperative evaluation stage brain MRI is used to ensure that no focal lesions may interfere with the implant. Other imaging modalities such as fMRI, MR spectroscopy, and DTI are used only for research purpose and, thus, not useful for routine preoperative evaluation.

Pragmatic Recommendations

Brain MRI should be performed in every patient considered for DBS to ascertain if there are structural lesions that may be causative of dystonia or interfere with the surgical procedure. Functional MRI, MR spectroscopy, and DTI are not necessary in general clinical practice of DBS and do not influence surgical procedure or outcome. Therefore, they should be done in specialized centers for research on movement disorders.

Points to Be Addressed

Morphological brain MRI is required before DBS in dystonia for every patient. However, the sequences to be used may differ from a center to another. It would be useful to define a common protocol that could be applied in every center aiming at implanting patients with dystonia. The contribution of new MRI sequences also needs to be clarified.

Functional Imaging

The pathophysiology of dystonia is complex and not fully understood. Electrophysiological and functional imaging studies have shown an excess of brain activation, a loss of cortico-cortical inhibition, and a lack of the selectivity of brain activation.[100] More precisely, functional imaging studies have shown overactivity of the dorsolateral prefrontal cortex, premotor and anterior cingulate cortex, cerebellum, and putamen in patients with primary and secondary dystonia.[100–103] In primary dystonia (generalized or focal) a decrease of rCBF is usually seen in the primary motor cortex.[101–105] On the other hand, in secondary dystonia rCBF is often increased in the primary motor cortex.[106] fMRI studies performed in writer's cramp and Meige's syndrome have demonstrated an altered somatotopic representation, which contributes to the loss of functional selectivity of muscle activity.[107] In tardive dystonia, an increase in regional cerebral blood flow has been found in the prefrontal cortex (areas 8 and 11), the anterior cingulated, and the lateral premotor cortex.[108] Other PET or SPECT studies in tardive dystonia patients have looked at the modifications of the postsynaptic dopaminergic system. In patients studied after long-term neuroleptic treatment withdrawal, an upregulation of dopaminergic D2 receptors has been observed using PET and [11C]-Raclopride, a D2 receptor ligand.[109] Notably, these studies concerned patients with severe tardive dystonia, and they are in agreement with the suspected role of dopamine

receptor trafficking in the occurrence of this pathology.[109] In contrast, other studies showed normal dopamine D2 receptor density and/or affinity in TD.[110]

Conclusions

PET functional imaging has clearly demonstrated that the abnormal movements and postures in dystonia are related to a widespread excess of brain activation, whatever the cause of dystonia.

Pragmatic Recommendations

Despite their potential applicability to elucidate the pathophysiology of dystonia, functional imaging studies have no clear role at present in routine clinical practice.

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SUPPLEMENT

Inclusion and Exclusion Criteria for DBS 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. Level B evidence has shown that all motor features and associated pain in primary generalized and segmental dystonia are potentially responsive to globus pallidus internus (GPi) DBS. However, improvements in clinical series of ≥90% may reflect methods that need improvement, and larger prospective studies are needed to address these factors. Nevertheless, 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. 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. There does not appear to be an upper age limit or a minimum age limit, although there are no published data regarding the outcome of GPi DBS for dystonia in children younger than 7 years of age. There is currently no enough evidence to prove that subjects with primary-generalized dystonia who undergo DBS at an early age and sooner rather than later after disease onset may gain more benefit from DBS than those undergoing DBS after the development of fixed skeletal deformities. There is no enough evidence to refuse or support consideration of DBS in patients with previous ablative procedures. ©2011 *Movement* Disorder Society

Key Words: DBS; dystonia; pallidal stimulation; surgery; thalamic stimulation

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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, comorbidities 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 DBS; 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 articles were retrieved. To facilitate the committees' work, the articles were divided in three groups, which often overlapped: preoperative, intraoperative, and postoperative. A PDF file was created for each article 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 preoperative, intraoperative, and postoperative issues and established two chairs responsible for each of these three 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. As 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 1-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.

Patients' Characteristics

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 class IV 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 articles 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 1 year. Subjects >21-year-old (n = 7) experienced a 69% (range 40–89%) improvement in BFMDRS-M at 1 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] Of note the same patients may have contributed to both studies. 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 ages of the children, but a comment in the article 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 class IV studies have found that a longer duration of symptoms was associated with a worse outcome. 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 vs. 53.3% after 2 years). Both were DYT-1 mutation positive.

A correlation with disease duration was found by Isaias et al.[9] Disease duration negatively correlated with clinical outcome and with disability scores at 1 year after surgery ($P < 0.05$). 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, the prospective class III study reported by 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 class IV 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 comorbidity and fixed skeletal deformities can apply. So DBS, if indicated, should be performed before these occur.

Pantothenate Kinase-Associated Neurodegeneration. This group is included because 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 with mean of group of 74.6%) despite not having the longest duration of symptoms. This was the only subject who could not return to walk, 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 postanoxic dystonia.

Conclusions

Primary-Generalized Dystonia. From the studies available, mostly class IV, there is no enough evidence to prove that subjects with PGD who undergo GPi DBS at an earlier age may gain more benefit from DBS for PGD than those operated at a later age. There is also controversy in the literature regarding whether symptom duration is an independent factor associated with outcome One class IV 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 a class III study found that age at the time of surgery and not symptom duration was predictive of outcome.[15] From these mostly retrospective studies it is suggested that DBS should be considered before the development of fixed skeletal deformities, the presence of which was associated with a poorer outcome. As there is not enough evidence to support this suggestion, larger prospective studies are needed to further address this issue.

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 class IV 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 and Secondary Dystonias. There is no available data to predict whether age or symptom duration is 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 7 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 a progressive generalized or CD should consider surgery before developing fixed skeletal deformities or cervical myelopathy.

Points to Be Addressed

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

Comorbidities

Are There Patients Who Are Not Eligible for Surgery due to Comorbidities? Are There Absolute and Relative Comorbidity Contraindications?

Available Data

Brain Imagin. From a systematic review of the diagnosis and treatment of dystonia by a European Task Force,[28] it is suggested that brain imaging should be mandatory in order to determine the aetiology of dystonia and should be done before considering a patient for DBS. 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, and so forth. There are no studies specifically addressing the impact of these abnormalities on the surgical outcomes, although abnormal brain MRI was associated with less postsurgical improvement (after pallidotomy and pallidal DBS) in a small class IV series of 15 patients with primary and secondary dystonia.[14] As DBS is largely 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 postanoxic 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 after DBS for dystonia may 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 case report of remarkable mood improvement in a patient with severe depression who underwent bilateral GPi stimulation for tardive dyskinesia.[35]

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

Dementia. Certain class IV 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 preoperatively impaired neuropsychological evaluation. No major differences in cognitive performances were observed after surgery.[38,39] A specific article 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 as addressed above.[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 preoperative selection process for subjects with dystonia, who are considering DBS in order to support the diagnosis of primary or secondary dystonia. From the class IV studies available, the incidence of suicide after DBS is very low and occurred in patients with preoperative psychiatric disease. Preoperative evaluation of any fixed skeletal 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 to provide a realistic prediction of outcome.

Pragmatic Recommendations

Screening for psychiatric comorbidities, including depression and suicide attempts, is recommended. If the premorbid psychiatric symptoms are deemed severe this may be a contraindication to surgery. For older patients, comorbidities 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 preoperative 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 comorbidities and vulnerabilities suggest that this area needs more study.

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 class IV 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, whereas 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

Currently, there is not enough evidence of spontaneous persistent resolution of dystonia to delay DBS surgery if it is otherwise indicated. Even in patients who experience symptomatic remission within the first 5 years from the onset, dystonia usually relapses and become permanent. 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.

Clinical Features of Dystonia

What Are the Specific Indications for Surgery (Mobility and Activities of Daily Living Scores, Pain Score, and 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 class IV 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, quality of life (QoL), and nonmotor symptoms.

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. One class I study[37] and several class III studies using blinded assessment and larger numbers of patients were done in patients with primary dystonia (generalized or cervical, positive, and negative for the DYT-1 gene).[17,44,48–50] The postoperative 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] 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] Meige's syndrome[23–26,51] has also shown a good response to bilateral GPi DBS from class IV series.

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

Other types of dystonia, such as PKAN,[27,52–54] tardive dystonia,[33–35,55–59] Lubag,[60,61] and myoclonus-dystonia[62–64] may respond to DBS favorably 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.[14,65,66] However, a class III, prospective study of 13 adults with dystonia-choreoathetosis from cerebral palsy without cognitive impairment, reported a mean improvement of 24.4% at 1 year with significant improvement in disability, pain, and mental health-related QoL.[67]

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. A small class IV 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.[68] Secondary dystonias associated with a previous encephalitis or structural brain lesion may respond less favorably.[14,69]

Conclusions

Level B evidence suggests that patients with primary dystonia experience benefit from DBS, whether it is generalized or segmental. Level C evidence of benefit is provided for CD and GPi DBS. Other types of dystonia (secondary, neurodegenerative, and dystonia-plus) may have more variable outcome. This latter evidence is from open label retrospective case series. However, one prospective series has shown that patients with hyperkinetic cerebral palsy without cognitive impairment may have modest but significant functional improvement in their QoL from GPi DBS.[67]

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. In other dystonic syndromes, especially those secondary to other causes, DBS might be considered in cases of tardive dystonia, hyperkinetic cerebral palsy, and/or cases with severe disability, although more large prospective trials are needed to support evidence of benefit. Secondary dystonia from encephalitis and/or structural lesions may not respond well to DBS.

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.

Is There Any Predictor of Response to Surgery (Mobile Dystonia vs. 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.[9,20,37,44,48,70,71] 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]

One center has suggested that a pattern of electromyographic activity with repeated bursts could indicate better or earlier response to GPi DBS.[72,73] As stated above age at time of surgery and duration of dystonia may predict postsurgical outcomes, at least at 1 year follow-up.[9] Secondary dystonia may respond less favourably to DBS surgery but this issue needs further study before a recommendation can be made.[14]

Conclusions and Pragmatic Recommendations

Primary dystonia predicts a good outcome. Level B evidence suggests that 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.

Are There Specific Types of Dystonia or Indications that Encourage Preferential Choice of One Target Over Another (Thalamus, GPi, and 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 case series 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,[3,4,74,75] although in one class IV study stimulation of GPi was associated with better outcomes compared with thalamic stimulation.[65] The STN has also been considered for primary and secondary dystonia in small case series with controversial outcomes.[40,76,77] Thalamic DBS has also been used to treat writer's cramp and musician's dystonia with success.[78]

Conclusions

There is Level B evidence that confirms the efficacy of GPi DBS in the treatment of primary (generalized and segmental) dystonia and level C evidence for GPi DBS in treating medically refractory CD. Because of the paucity of data with thalamic or STN DBS, 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.

Are There Motor and Nonmotor Features that Reliably Do Not Respond to Surgery? When Should These Be Sufficiently Important to Contraindicate Surgery?

Available Data

A class I 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.[45] 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. A class IV study of generalized dystonia reported significant motor improvement in neck, trunk, arm, and leg regions but not in face or speech.[70] In another study with 22 patients at 3-year follow-up of PGD 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 CD by Kiss et al.[17] showed improvement in CD and related pain. Numerous other studies referenced in earlier sections of this article support the efficacy of GPi DBS for the reduction of motor signs and pain in various types of dystonia.

Conclusions

Level B evidence has shown that all motor features of primary dystonia are potentially responsive to GPi DBS, although response of speech is less consistent or robust. Pain also showed improvement. Other nonmotor features of dystonia are not well studied or reported in the literature. Thus, there is no evidence that specific motor or nonmotor 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 nonmotor 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.

Previous Medical Therapy for Dystonia

What Medical Treatment Should Be Mandatory Before 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 PGD should be considered sooner rather than later in the duration of disease and 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.

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

The only data available on DBS in patients who had previous surgery (lesions or previous DBS) for dystonia is from small observational case series. In fact, previous surgery, such as thalamotomy, pallidotomy, and peripheral denervation, is rarely stated as exclusion criterion for DBS.

Katayama et al.[79] 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.[65] 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, a level IV study 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

There is no enough evidence to prove that previous surgical treatments (i.e., thalamotomy, pallidotomy, and peripheral denervation) should prevent consideration of DBS. There are only a few retrospective case series on the effect of previous surgical treatment. Patients who have undergone peripheral denervation for CD with unsatisfactory results and/or with symptoms that have extended to other parts of the body may be considered as candidates for GPi DBS.

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 counseling 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 class IV studies 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.[66] 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 PGD 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 with the DYT-1 negative subjects. In a level III, 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