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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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2．患者はなぜ怖がる？　医師はなぜ嫌がる？

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◎患者は強迫性を持っていることがあり，必要以上に怖がる可能性がある．
◎ボツリヌス毒素療法の手順は，注射日前後でとても面倒である．
◎うつ病や統合失調症の患者もおり，対応には注意を要する．
◎左右間違いをしたら大問題だ．

Key Words　強迫性，面倒な手順，うつ病，統合失調症，左右間違い

□ 患者はなぜ怖がる？

注射自体はそれほど怖いわけではないのだが，痙性斜頸患者は潜在的に強迫性[1,2]を持っていることがあり，必要以上に怖がる可能性がある．また自己否定的でストレスを溜め込みやすい[3]．眼瞼けいれん患者でもそのような傾向がある．

やはり前項で述べた「副作用について」や「その他の注意点」の記載が心配の元になっていると思う．この部分は前項で述べたので割愛する．

眼瞼けいれん患者と同じように顔面のけいれんを持ち，ボツリヌス毒素療法の適応がある片側顔面けいれんの患者は，あまり怖がることはない．なぜなら片側顔面けいれんは血管圧迫症候群であり，高血圧症や糖尿病，高コレステロール血症のような成人病が原因であることが多い[4]．

眼の周りや首の筋肉に注射を打つのだから，当然痛いとは思う．特に眼の周りは敏感なので，注射を打つ際に看護師に手を握ってもらわないと打てない女性患者も複数いる（男性ではいないが）．少しでも痛みを軽減するため，当院では眼内注射用の30Gの注射針を用いて眼周囲や顔面には注射している．

□ 医師はなぜ嫌がる？

ボツリヌス毒素療法を行っている医師でも，「顔面は打つが，首には打たない」という医師もいる．眼科医が行っているからという理由もあるかもしれないが，以下のことも重要だと考える．

1．注射自体はそれほど難しいものではないが，手順が面倒である

【注射前の診察時】には①同意書をもらう，②登録票に記載する，③注射をオーダーする，③登録票を薬剤部に持って行く，④GSK社にFAXする，

【注射日の注射時】には①医師自身が薬剤部にボトルを貰いに行く，②生理食塩水で溶解する，③注射する，④注射部位をカルテに記載する，⑤注射の実施登録をする，⑥次回の予約をする，

【注射日の注射後】には①失活する，②ボトルを薬剤部に返しに行く，といった手順が必要である．

【注射後の診察時】だとしても，①カルテに状態を記載する，②注射をオーダーする，③登録票を薬剤部に持って行く，④GSK社にFAXする，等の手順が必要であり，どの手順も省くことはできない．

ボツリヌス毒素の溶解や失活は，講習が終了した医師が施行しなければならず，看護師等が代行できないことも要因だと考える．

2．ボツリヌス毒素注射は，筋電図やMRIなどの設備の整った大学病院や，比較的規模の大きな病院で行われていることが多い

大学の医局に限らず大病院でも，「科の方針，病院の方針」が存在する．「ジストニア，ボツリヌス毒素治療」が科の方針，病院の方針である場

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合はほとんどないと考えてよいと思う．神経内科でいえば，脳卒中などに比べ，圧倒的に患者の数が少なく，多くの利益を生まないことが1つの理由である．大学病院であっても，ボツリヌス毒素療法を行っていない場合が多い．また，大学病院では異動も多く，「注射を打てる医師がいなくなった」という理由で当院に紹介するケースも多い．

3．医師自身の性格もあると考える

前述のように，ボツリヌス毒素治療をする医師は，医局に1人か2人居れば良く，「一匹オオカミ」のようになってしまう可能性がある．外科のようにチーム医療が好きな人や，神経内科で言えばチームで行う血管治療が好きな人は向かないだろう．スポーツで言えば，ラグビーやサッカー，野球をしていた人は向かないかもしれず，テニスや卓球，ゴルフなど，技巧を要する個人スポーツをしていた人が向くかもしれない．

（筆者はテニス部出身で，全医体にも出場した．中学時代に一時野球部に所属したが，合わないのでテニスに戻った．バントが嫌いだった．）

4．薬剤性ジストニア患者は本物のうつ病患者，統合失調症患者である

薬剤性ジストニアの数ははっきりしないが[5]，ドーパミン受容体遮断作用があり，薬剤性ジストニアを起こしやすくする三環系抗うつ薬を服用しているような患者は重症である．前項に記載したように，実際に自殺してしまうこともある．また，1回自殺企図をすると抗精神病薬を処方されることもあり，こちらもドーパミン受容体遮断作用がある．また，統合失調症患者でも重症な患者ほど，ドーパミン受容体遮断作用が強い定型群が処方されているケースが多く，高率でジストニアを発症する．

当院に紹介される薬剤性ジストニア患者のうち，精神病院に入院中の場合もあるし，精神症状のため仕事に就けない患者も多い．そのような患者は，医師の都合も考えず，どうでもよいような質問や症状についての質問を電話で相談してきたり，外来で延々と話したりする．精神科の患者を診たことのない医師は，この時点で参ってしまうこともある．

5．薬剤性ジストニアの場合は，薬物の減量や，錐体外路系の副作用が比較的少ない薬剤に変更するのが基本である

うつ病ならSSRI（selective serotonin reuptake inhibitors），SNRI（serotonin noradrenalin reuptake inhibitors），統合失調症ならSDA（serotonin-dopamine antagonist），MARTA（multi-acting receptor targeted antipsychotics），DSS（dopamine system stabilizer）のような非定型群が該当する．

しかし精神科のコントロールが不良な状態で紹介されることもあり，このような場合はまずは精神科の治療を優先してもらうこととしている．外来で泣き出したりする患者や，「俺は東大と慶應の医学博士号を持っている」などと妄想の強い患者（実際は某私立大学経済学部中退）が紹介されることもある．内科の場合は精神科と違い，1人の患者に多くの時間を割くシステムになっていない．医師をはじめ看護師等のスタッフも当惑してしまう．

6．片側顔面けいれん患者や痙性斜頸患者の注射に際して「左右間違い」をしたら大問題になるし，針を使用するので危険と隣合わせである

チームで行っていないので，責任はすべて自分が負わなければならない．病院のシステム上，ハイリスクであってもハイリターンにならないことが多く，医師は疲弊してしまう．経験の浅い医師が，特に痙性斜頸患者に注射する際に注射すべき側と反対側に打ってむしろ症状を悪化させてしまい，当院に紹介されるケースもある．

いろいろな原因があり，ボツリヌス毒素注射，ジストニア治療を専門に行おうとする医師が増えない現状がある．

では筆者なりに，**ボツリヌス毒素療法のよい点**を挙げてみたいと思う．

1．ドラマチックによくなることもあり，自分の技術で治したという外科医のような達成感がある．神経内科は治らない病気も多いが，やり方によっては治すこともできるという喜びがある．
2．まれなケースが多く経験でき，論文を書きやすい．
3．専門医が少ない分，逆にネットワークが築きやすい．
4．紹介されることが多いが，人に頼られるのも悪い気はしない．（人に頼らなければならないよりはずっとよい）
5．新しい技を身につける喜びがある（眉間の皺とり，手足の拘縮など）．

デメリット（嫌がる点）に比べてメリット（よい点）のほうが圧倒的に少ない気もするが，ボツリヌス毒素療法を行っている医師が増えていくことを願ってやまない．

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Syndrome Handbook

症候群ハンドブック

◉総編集◉
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■解説　AIDS 認知症症候群は HIV 感染により引き起こされる認知運動障害であり，主に AIDS 発症時期に著明となり亜急性に進行するが，緩徐進行性の経過を示す例もある．この病態の中心は，脳内血管周囲に存在する HIV-1 感染マクロファージとミクログリアである．HAART 中でも軽症認知障害患者が相当数いること，抗ウイルス療法が成功しても認知障害が発症する場合のあることが指摘されており，HAART 導入後も AIDS 認知症症候群に注意が必要である．

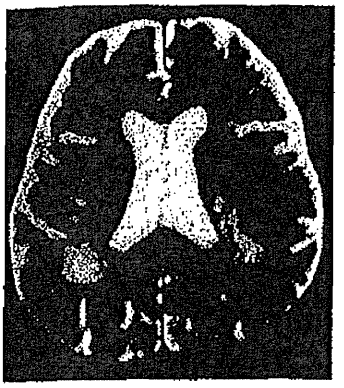

図 1　AIDS 認知症候群における脳萎縮画像

HIV 感染を知らない，あるいは治療を自己中断して AIDS 認知症症候群を発症する患者の割合が増加している．

■所見　初期：複雑記憶，注意，遂行機能の障害．頭部 MRI では明らかな脳萎縮はなく；軽度の白質病変のみ．
脳血流 SPECT：前頭葉の血流低下．
進行例：高度の認知機能低下，頭部 MRI 上の白質病変・脳萎縮（**図 1**）．

（中川正法，近藤正樹）

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トゥレット症候群　Tourette syndrome

■疫学　本症は必ずしも診断がなされていないことが多く，疫学調査は難しい．しかし，限られた地域，集団を対象としたものがいくつか行われており，有病率は 10,000 人に 5～10 人とされている．また，学童における一過性のチックは 5～24%という報告もある．

男女比は 3:1～4:1 と男児に多い．人種差はない．

■病因と発症に関わる遺伝子　本症は小児期に発症し，男児に多く，家族例が多いことから，素因に基づいた性差のある神経系の発達に関する要素の重要性が指摘されてきている．病因遺伝子の解明に関しての研究は，本症に対するドパミン神経系を調節する薬剤の効果から，その関連の遺伝子に加え，多くの候補遺伝子の解明の研究．近年では genome wide association study（GWAS）も行われてきているが，いまだ解決に至っていない．

■診断　本症はチック症のなかに区分される．すなわち，チック症につき，運動チックと音声チックの出現が，どの程度の期間経過しているかに基づき，1 年以上を慢性とし，4 群に分けられた．それらは，単純な一過性の小児期チック症，慢性運動チック症，慢性音声チック症，音声チックを伴う多発性運動チックが 1 年以上の慢性の経過をとるもの，の 4 群であり，最後の“音声チックを伴う慢性多発性運動チックが 1 年以上続くもの”が Tourette 症候群と定義された．

■治療　1962 年，本症に対するハロペリドールの効果が注目され，以後ハロペリドールが最も多く使われているが，その効果は必ずしも期待できず，かつ副作用には注意を要する点である．その後，多くの治療法の提唱がなされてきているが，病態に鑑みた有効なものはない．筆者らは本症の病態の解析に基づき，10 歳以下の小児ではハロペリドールは

禁忌であると考えている．筆者らはごく少量のレボドパが，病態と考えられる発達過程に生じたドパミン受容体の過感受性の軽快に必要であると考えている．本症のコントロールには環境要因（特に睡眠覚醒リズムの形成，ロコモーションに関する神経系と関連する神経系）の適切な調整が重要である．

■関連語・同義語　チック症，音声チックを伴った多発性運動チック症が慢性の経過をとるもの．併発症状として注意欠陥多動性障害（attention deficit hyperactivity disorder; ADHD），強迫性障害（obsessive-compulsive disorder; OCD）がしばしばみられる．

■ EBM・診療ガイドライン　多くの臨床研究に基づいた診療に関するガイドラインがある．わが国では，平成22年度厚生労働科学研究費補助金（難治性疾患克服研究事業）「トゥレット症候群の診断，治療，予防に関する臨床的研究」があり，その報告書が発表されることとなっている（平成23年4月）．

■大規模臨床研究　多くの臨床研究が世界各地，地域にて行われてきている．

■関連団体・学会　世界各地で患者の会がつくられ，活発な活動がなされてきている．わが国では，「日本トゥレット協会」がある．国際学会も多くなされてきている．

■解説　本症は1885年Gilles de la Tourette により記載された．近年の研究は，1960年代Shapiro らにより本症をチック症の一型としてとらえるという考えから始まる．臨床的に素因と性差をもった発達に関するという点，その病態に関してドパミンを主体とし，他のモノアミン神経系の関与が示唆されている．

■所見　運動チック，音声チックが増悪・寛解を繰り返し経過することを特徴とする．チックの種類はそれぞれ単純と複雑に分類され，単純運動チックは瞬き，顔しかめ，首ふりなどで，複雑運動チックは上下肢を動かす，ジャンプする，スキップするなど主として四肢，体幹を動かすなどである．単純音声チックは咳払い，発声など，複雑音声チックは文節，文章を言うなどであり，汚言（coprolalia）も複雑音声チックの一種と考えられるが，必発ではない．チックは当初は寛解の時期があるが，年齢とともに，特に10歳代以降には消失することがなくなる傾向である．

併発症のADHD は年少にて，OCD は10歳代に目立ってくることが多い．他に攻撃性などが併発することもある．10歳代になり，睡眠覚醒リズムの障害が出現してくることもあり，これらの併発症の病態と関連することが少なくない．片頭痛，うつ症状を伴うこともある．

（野村芳子）

Letter to the Editor

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Reduced Serum Ceruloplasmin Levels in Cervical Dystonia

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Dear Sir,

We read with interest the article by Ling and Bhidayasiri [1] demonstrating the decrease of serum ceruloplasmin (Cp) level in neurodegenerative movement disorders, especially in Parkinson's disease. In their analysis, the Cp level was normal in 7 patients with idiopathic focal dystonia.

They did not refer to our article [2] published in 2000, where the serum Cp and copper levels were significantly lower in 51 patients with cervical dystonia than those in 39 disease controls. Previous studies have repeatedly demonstrated disturbances of copper metabolism in primary dystonia by transcranial ultrasound [3–5], leukocyte analysis [6], and neurochemical analysis of trace metals and proteins in the brain tissue [7, 8]. The findings were also reproduced in post-surgical secondary dystonia [9], implying the presence of subjects susceptible to dystonia, although the copper gene might be irrelevant by itself to the pathogenesis of dystonia [10].

We agree with the authors' inference that Cp might be associated with the cascade of neurotoxicity in neurodegenerative movement disorders, and current evidence strongly indicates that this is also the case in dystonia.

Disclosure Statement

Dr. Mezaki has worked as a consultant of GlaxoSmithKline K.K. Dr. Kaji has nothing to disclose and has no conflicts of interest.

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1．患者にどう説明するか

堀内　正浩*
ほりうち　まさひろ

- 3ヵ月で元に戻ることが多いということを説明する．
- 65点で合格，と説明する．
- 向精神薬の減量は慎重に行う．
- 副作用については，顔面とそれ以外の領域をわけて説明する．
- 治療費についてきちんと説明する．

Key Words　3ヵ月間，65点，向精神薬，副作用，治療費

ボツリヌス毒素は患者にとって垣根の高い存在と思われる．3ヵ月で効果がなくなることから，「美容院に行くようなものと考えてください．たとえ気に入らなくても，約3ヵ月間で元に戻ることが多いです」と説明している．

患者は100%を希望することも多いが，「65点で合格とさせてください」と説明している．ジストニアは大脳基底核や大脳皮質の異常により惹起される．たとえ内服加療や対症療法としてのボツリヌス毒素注射を行ったとしても，100%の満足度は得られない．痙性斜頸患者は潜在的に強迫性[1,2]を持っていることがあり，必要以上に怖がる可能性がある．また自己否定的でストレスを溜め込みやすい[3]．このことを念頭に入れ，やんわりと説明するのはよいと考える．

向精神薬（抗精神病薬，抗うつ薬）の副作用で二次性（薬剤性）ジストニアの患者には，「精神症状を優先して治療していきましょう」，「病気と共存していきましょう」と話すようにしている．

確かに向精神薬を減量していくとジストニア自体は改善してくるが，精神症状が悪化する．著者は400人以上のジストニア患者を診てきたが，以下に自殺企図をした例を紹介する．

□ 症例1

うつ病に眼瞼けいれんを合併している患者が，治療経過中にカッターで頸部を切って自殺企図をしたとのことで当院に搬送された．私も救命病棟に呼ばれ，来院時の写真を見て驚いた．まったくためらい傷がなく，ひと思いに切られていたのだが，幸いにも手元がずれて見事な気管切開の状態になっていた．意識を失った状態で倒れているところを，帰宅した家人に発見され119番通報されたのだが，気管を切っただけなので出血量が少なく，呼吸状態も保たれていた．私が患者の回復後に理由を聞いたところ，「とにかく辛かった」とのことであった．精神科の治療を優先させ，現在も精神科に通院されている．

□ 症例2

東北某県からの体軸ジストニア患者で，うつ病を合併していた．当院でボツリヌス毒素療法を含めた治療を受けて症状が改善し，地元の病院に帰っていった．1年程後に母親が訪ねてきた．1ヵ月程前に裏山で首を吊っているところを発見されたとのことであった．病気に関して地元で理解を得られず，苦しんでいたそうである．なぜ担当医がわかったかというと，退院する際に記念に撮った写真に私も写っていたからだそうだ．精神科は通院していなかったようであった．母親は我々の治療に感謝して御帰宅された．

眼瞼けいれんや軸性ジストニアで命を落とすことはないが，うつ病の治療をおろそかにすると，思わぬ結果を招くこともある．特にうつ病患者の

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