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EFNS TASK FORCE/ CME ARTICLE

A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force

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To review the literature on primary dystonia and dystonia plus and to provide evidence-based recommendations. Primary dystonia and dystonia plus are chronic and often disabling conditions with a widespread spectrum mainly in young people. Computerized MEDLINE and EMBASE literature reviews (1966–1967 February 2005) were conducted. The Cochrane Library was searched for relevant citations. Diagnosis and classification of dystonia are highly relevant for providing appropriate management and prognostic information, and genetic counselling. Expert observation is suggested. DYT-1 gene testing in conjunction with genetic counselling is recommended for patients with primary dystonia with onset before age 30 years and in those with an affected relative with early onset. Positive genetic testing for dystonia (e.g. DYT-1) is not sufficient to make diagnosis of dystonia. Individuals with myoclonus should be tested for the epsilon-sarcoglycan gene (DYT-11). A levodopa trial is warranted in every patient with early onset dystonia without an alternative diagnosis. Brain imaging is not routinely required when there is a confident diagnosis of primary dystonia in adult patients, whereas it is necessary in the paediatric population. Botulinum toxin (BoNT) type A (or type B if there is resistance to type A) can be regarded as first line treatment for primary cranial (excluding oromandibular) or cervical dystonia and can be effective in writing dystonia. Actual evidence is lacking on direct comparison of the clinical efficacy and safety of BoNT-A vs. BoNT-B. Pallidal deep brain stimulation (DBS) is considered a good option, particularly for generalized or cervical dystonia, after medication or BoNT have failed to provide adequate improvement. Selective peripheral denervation is a safe procedure that is indicated exclusively in cervical dystonia. Intrathecal baclofen can be indicated in patients where secondary dystonia is combined with spasticity. The absolute and comparative efficacy and tolerability of drugs in dystonia, including anticholinergic and antidopaminergic drugs, is poorly documented and no evidence-based recommendations can be made to guide prescribing.

Objectives

The objective of the task force was to review the literature on diagnosis and treatment of primary dystonia and dystonia plus to provide evidence-based recommendations for diagnosis and treatment.

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This is a Continuing Medical Education paper and can be found with corresponding questions on the Internet at: http://www.blackwellpublishing.com/products/journals/ene/mcqs. Certificates for correctly answering the questions will be issued by the EFNS.

Background

Dystonia is characterized by sustained muscle contractions, frequently causing repetitive twisting movements or abnormal postures [1,2]. Although it is thought to be rare, it is possibly underdiagnosed or misdiagnosed due to the lack of specific clinical criteria. A recent study evaluated the ability amongst neurologists with different expertise in movement disorders to recognize adult onset

focal dystonia and found relevant disagreement, particularly amongst examiners with lesser expertise [3].

The prevalence of dystonia is difficult to ascertain. On the basis of the best available prevalence estimates, primary dystonia may be 11.1 per 100 000 or early-onset cases in Ashkenazi Jews from New York area, 60 per 100 000 or late-onset cases in Northern England, and 300 per 100 000 for late-onset cases in the Italian population over age 50 [4].

Primary dystonia and dystonia plus are chronic and often disabling conditions with a widespread spectrum mainly in young people. Areas of specific concern include differential diagnosis with other movement disorders, aetiological diagnosis, drug treatment, surgical interventions, and genetic counselling.

Search strategy

Computerized MEDLINE and EMBASE searches (1966 to February 2005) were conducted using a combination of text words and MeSH terms 'dystonia', 'blepharospasm', 'torticollis', 'writer's cramp', 'Meige syndrome', 'dysphonia' and 'sensitivity and specificity' or 'diagnosis', and 'clinical trial' or 'random allocation' or 'therapeutic use' limited to human studies. The Cochrane Library and the reference lists of all known primary and review articles were searched for relevant citations. No language restrictions were applied. Studies of diagnosis, diagnostic test, and various treatments for patients suffering from dystonia were considered and rated as level A to C according to the recommendations for EFNS scientific task forces [5]. Where only class IV evidence was available but consensus could be achieved we have proposed good practice points.

Method for reaching consensus

The results of the literature searches were circulated by e-mail to the task force members for comments. The task force chairman prepared a first draft of the manuscript based on the results of the literature review, data synthesis and comments from the task force members. The draft and the recommendations were discussed during a conference held in Milan on 11–12 February 2005, until consensus was reached within the task force.

Results

Diagnosis

The literature search on the diagnosis of dystonia identified no existing guidelines or systematic reviews. Two consensus agreements [1,6], two reports of workshops or taskforces [7,8], 69 primary studies on clinically based diagnosis and 292 primary studies on the diagnostic accuracy of different laboratory tests were found. Dealing with primary clinical studies, there were six cohort studies, 23 case–control studies, three cross-sectional, and 37 clinical series.

Classification

The classification of dystonia is based on three axes: (a) aetiology, (b) age at onset of symptoms, and (c) distribution of body regions affected (Table 1). The aetiological axis discriminates primary (idiopathic) dystonia, in which dystonia is the only clinical sign without any identifiable exogenous cause or other inherited or degenerative disease, from non-primary forms in which dystonia is usually just one of several clinical signs. Dystonia plus is characterized by dystonia in combination with other movement disorders, for example myoclonus or Parkinsonism. Paroxysmal dystonia is characterized by brief episodes of dystonia with normalcy in between. Primary dystonia and dystonia plus, whether sporadic or familial, are thought to be of genetic origin in most cases.

The clinical features of dystonia encompass a combination of dystonic movements and postures to create a sustained postural twisting (torsion dystonia). Dystonic postures can precede the occurrence of dystonic movements and in rare cases can persist without appearance of dystonic movements (called 'fixed dystonia') [9]. Dystonia has some specific features that can be recognized by clinical examination. Speed of contractions of dystonic movements may be slow or rapid, but at the peak of movement, it is sustained. Contractions almost always have a consistent directional or posture-assuming character. Dystonia is commonly aggravated during voluntary movement and may only be present with specific voluntary actions (called 'task-specific dystonia') [10], or may be temporarily alleviated by specific voluntary tasks, called *gestes antagonistes*, also known as 'sensory tricks' [11,12]. Overflow to other body parts, whilst activating the affected region, is often seen. Dystonia manifesting as tremor may precede clear abnormal posturing.

Two articles have addressed the possibility of identifying clinical features to distinguish between primary and non-primary forms [13,14]. The committee has evaluated that the evidence provided by these studies (both level IV) does not allow the use of their criteria as indicator for aetiological classification.

Recommendations and good practice points

(1) Diagnosis and classification of dystonia are highly relevant for providing appropriate management, prognostic information, genetic counselling and treatment (good practice point).

Table 1 Classification of dystonia based on three axes

By cause (aetiology)
- *Primary* (or idiopathic): dystonia is the only clinical sign and there is no identifiable exogenous cause or other inherited or degenerative disease. Example: DYT-1 dystonia
- *Dystonia plus*: dystonia is a prominent sign, but is associated with another movement disorder. There is no evidence of neurodegeneration. Example: Myoclonus-dystonia (DYT-11)
- *Heredo-degenerative*: dystonia is a prominent sign, amongst other neurological features, of a heredo-degenerative disorders. Example: Wilson's disease
- *Secondary*: dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals. Examples: dystonia due to a brain tumour, off-period dystonia in Parkinson's disease
- *Paroxysmal*: dystonia occurs in brief episodes with normalcy in between. These disorders are classified as idiopathic (often familial although sporadic cases also occur) and symptomatic due to a variety of causes. Three main forms are known depending on the triggering factor. In paroxysmal kinesigenic dyskinesia (PKD; DYT-9) attacks are induced by sudden movement; in paroxysmal exercise induced dystonia (PED) by exercise such as walking or swimming, and in the non-kinesigenic form (PNKD; DYT-8) by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (DYT-10) has also been described

By age at onset
- *Early onset* (variably defined as ≤20–30 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk
- *Late onset*: usually starts in the neck (including the larynx), the cranial muscles or one arm. Tends to remain localized with restricted progression to adjacent muscles

By distribution
- *Focal*: single body region (e.g. writer's cramp, blepharospasm)
- *Segmental*: contiguous body regions (e.g. cranial and cervical, cervical and upper limb)
- *Multifocal*: non-contiguous body regions (e.g. upper and lower limb, cranial and upper limb)
- *Generalized*: both legs and at least one other body region (usually one or both arms)
- *Hemidystonia*: half of the body (usually secondary to a structural lesion in the contralateral basal ganglia)

(2) Based on the lack of specific diagnostic tests, expert observation is recommended. Referral to a movement disorders expert increases the diagnostic accuracy [3] (good practice point).
(3) Neurological examination alone allows the clinical identification of primary dystonia and dystonia plus, but not the distinction amongst different aetiological forms of heredo-degenerative and secondary dystonias (good practice point).

Use of genetic test in diagnosis and counselling

Only one gene (DYT-1) has been identified for primary dystonias [15]. DYT-1 dystonia typically presents in childhood and usually starts in a limb, gradually progressing to a generalized form. However, many exceptions to this typical presentation have been reported. Other described phenotypes of primary dystonia are DYT-2, DYT-4, DYT-6, DYT-7 and DYT-13 [16].

Phenotype–genotype correlations have been assessed in DYT-1 dystonia, where one class II study has been published [17]. DYT-1 testing had a specificity of up to 100% in dystonia patients with positive family history consistently showing twisting or directional movements and postures. This has led to the recommendation that only patients with such features be considered for genetic studies [17,18]; however, this evidence was obtained from American Ashkenazi Jews and does not necessarily apply to the Western European population [19]. In patients with primary torsion dystonia, age at onset below 30 years, site of onset in a limb and a positive family history are the three crucial predictors of the diagnostic accuracy of DYT-1 genetic testing [19–21] (class III evidence). Asymptomatic carriers of DYT-1 genetic mutations have been described; the penetrance of DYT-1 dystonia is considered around 30%.

Four dystonia plus syndromes have been characterized. The most common form of dopa-responsive dystonia is linked to the DYT-5 gene (GCH1; GTP-cyclohydrolase I). This is a treatable and often misdiagnosed disease for which an effort should be made to warrant a correct diagnosis. The classical phenotype comprises childhood-onset dystonia, sometimes with additional Parkinsonism and sustained response to low doses of levodopa, and diurnal fluctuations, with patients being less affected in the morning and more in the evening [22]. However, several atypical presentations and several private mutations have been reported [23] (see the database cured by N. Blau, and B. Thöny: http://www.bh4.org/biomdb1.html). If genetic testing of the GCH1-gene is negative, parkin mutations should be considered, as the two disorders are sometimes difficult to distinguish [24]. There is no evidence for supporting guidelines for genetic testing. It has been proposed to make a diagnostic therapeutic trial with levodopa [25] (class IV) or to perform ancillary diagnostic tests. Phenylalanine loading tests and CSF pterin and dopamine metabolite studies may be a useful

diagnostic complement [26–28], but there is no clear evidence regarding their predictive value. Hence, the recommendation still remains that every patient with early onset dystonia without an alternative diagnosis should have a trial with levodopa.

Myoclonus dystonia is characterized by onset in childhood; the initial symptoms usually consist of lightning jerks and dystonia mostly affecting the neck and the upper limbs, with a prevalent proximal involvement and slow progression [29]. Myoclonus and dystonia are strikingly alleviated by the ingestion of alcohol in many but not all patients [30]. When the phenotype is typical and inheritance is dominant $>50\%$ of patients will have mutations of the epsilon-sarcoglycan gene (DYT-11) [31–34].

The DYT-12 gene (mutated gene: ATP1A3) is affected in rapid-onset dystonia-Parkinsonism, an extremely rare disease with onset in the childhood or early adulthood in which patients develop dystonia, bradykinesia, postural instability, dysarthria and dysphagia over a period ranging from several hours to weeks [35].

A gene for paroxysmal non-kinesigenic (PNKD) form of dystonia (DYT-8) has been identified. This condition is characterized by episodes of choreodystonia lasting many hours and induced by coffee, tea, alcohol and fatigue [36]. Sporadic and more frequently familial cases with an autosomal dominant inheritance have been described [37]. Mutations in the myofibrillogenesis regulator 1 (MR-1) gene have been found to cause PNKD in all families with the typical PNKD phenotype [38–40].

Recommendations and good practice points

(1) Diagnostic DYT-1 testing in conjunction with genetic counselling is recommended for patients with primary dystonia with onset before age 30 years [20] (level B).
(2) Diagnostic DYT-1 testing in patients with onset after age 30 years may also be warranted in those having an affected relative with early onset [20,21] (level B).
(3) Diagnostic DYT-1 testing is not recommended in patients with onset of symptoms after age 30 years who either have focal cranial-cervical dystonia or have no affected relative with early onset dystonia [20,21] (level B).
(4) Diagnostic DYT-1 testing is not recommended in asymptomatic individuals, including those under the age of 18, who are relatives of familial dystonia patients. Positive genetic testing for dystonia (e.g. DYT-1) is not sufficient to make a diagnosis of dystonia unless clinical features show dystonia [20,41] (level B).
(5) A diagnostic levodopa trial is warranted in every patient with early onset dystonia without an alternative diagnosis [25] (good practice point).
(6) Individuals with myoclonus affecting the arms or neck, particularly if positive for autosomal dominant inheritance, should be tested for the DYT-11 gene [31] (good practice point).
(7) Diagnostic testing for the PNKD gene (DYT- 8) is not widely available, but this may become possible in the near future (good practice point).

Use of neurophysiology in the diagnosis and classification of dystonia

Various neurophysiological techniques can document functional abnormalities in patients with dystonia and assist in differential diagnosis, evaluation of the pathophysiology and directing treatment with botulinum toxin (BoNT) injections.

Studies with surface electromyography show co-contraction between muscles with antagonistic functions, overflow of activity to muscles not intended to move, and disordered configuration of the triphasic pattern for ballistic movements [42–46]. Studies of brainstem and spinal reflexes demonstrate an enhanced excitability of brainstem or spinal interneurones that is either limited to the affected area or spreads to adjacent areas in focal dystonia [47–51]. Studies performed with cortical transcranial magnetic stimulation (TMS) have shown depressed intracortical inhibition, decreased duration of the silent period, and abnormally enhanced recruitment of the motor evoked potential with increasing stimulus intensity and degree of muscle contraction [52–54].

Abnormalities of a number of neurophysiological tests of cortical excitability have been reported in symptomatic and non-symptomatic DYT-1 carriers; in contrast, abnormalities of spinal excitability were found only in symptomatic patients. All neurophysiological studies of dystonia are class IV studies, being done in case–control conditions, but not blinded.

Recommendations and good practice points

(1) Neurophysiological tests are not routinely recommended for the diagnosis or classification of dystonia; however, the observation of abnormalities typical of dystonia is an additional diagnostic tool in cases where the clinical features are considered insufficient to the diagnosis [43,46] (good practice point).

Use of brain imaging in the diagnosis of dystonia

Most authors agree that conventional or structural MRI studies in primary dystonia are normal. Indeed, a normal MRI study is usually considered a pre-requisite

to state that a patient's dystonia is primary. Only one conventional MRI class IV study [55] showed T2 bilateral abnormalities in the lentiform nucleus in primary cervical dystonia. However, the abnormalities were only detected on calculated T2 values; no obvious signal changes could be recognized on visual inspection of T2-weighted images. Structural changes in the lentiform nuclei, predominantly in the contralateral pallidum in patients with adult-onset primary focal dystonia, have been suggested by increased echogenicity of these structures on transcranial sonography (class IV) [56].

Interesting prospects to understanding the pathophysiological mechanisms of primary and secondary dystonia are offered by functional MRI studies. Class IV studies conducted in series of patients with blepharospasm [57], writer's cramp [58,59] or other focal dystonia of the arm [60] demonstrated that several deep structures and cortical areas may be activated in primary dystonia, depending on the different modalities of examination. Recent class IV voxel-based morphometry studies demonstrated an increase in grey matter density or volume in various areas, including cerebellum, basal ganglia, and primary somatosensory cortex [61,62]. The increase in grey matter volume might represent plastic changes secondary to overuse, but different interpretations have been considered.

Positron emission tomography studies with different tracers have provided information about areas of abnormal metabolism in different types of dystonia and in different conditions (e.g. during active involuntary movement or during sleep), providing insight on the role of cerebellar and subcortical structures versus cortical areas in the pathophysiology of dystonia (all class IV studies) [63,64]. At present, a practical approach to differentiate patients with dystonia plus syndromes from patients with Parkinsonism and secondary dystonia is to obtain a single photon emission computerized tomography study with ligands for dopamine transporter; this is readily available and less expensive than positron emission tomography. Patients with dopa-responsive dystonia have normal studies, whereas patients with early-onset Parkinson's disease show reduction of striatal ligand uptake (class IV) [65].

Recommendations and good practice points

(1) Structural brain imaging is not routinely required when there is a confident diagnosis of primary dystonia in adult patients, because a normal study is expected in primary dystonia [66] (good practice point).

(2) Structural brain imaging is necessary for screening of secondary forms of dystonia, particularly in the paediatric population due to the more widespread spectrum of dystonia at this age [67] (good practice point).

(3) MRI is preferable to CT, except when brain calcifications are suspected (good practice point).

(4) There is no evidence that more sophisticated imaging techniques (e.g. voxel-based morphometry, diffusion-weighted imaging, fMRI) are currently of any value in either the diagnosis or the classification of dystonia (good practice point).

Treatment

Botulinum toxins

Botulinum toxin treatment was recommended for blepharospasm, adductor spasmodic dysphonia, jaw-closing oromandibular dystonia and cervical dystonia by the National Institutes of Health consensus statement [68].

BoNT treatment for cervical dystonia was analysed in four Cochrane reviews. The first review evaluated BoNT-A therapy and included results from 13 randomized, placebo-controlled trials. They were short-term studies (6–16 weeks) of BoNT-A enrolling 680 patients overall. All trials reported a benefit of a single injection cycle of BoNT-A for cervical dystonia, but did not provide controlled evidence of the long-term effects of repeated BoNT-A injections. Enriched trials (using patients previously treated with BoNT-A), suggested that further injections maintained efficacy in most patients. The most frequently reported treatment-related adverse events were dysphagia, neck weakness, local pain at injection site, and sore throat/dry mouth. Most of the adverse events in patients receiving BoNT-A were mild or moderate; no serious adverse events or laboratory abnormalities were associated with the use of BoNT-A [69].

The second review evaluated BoNT-B and included three short-term (16 weeks) studies enrolling 308 participants. All were multicentre and conducted in the USA. All patients included had previously received BoNT-A. A single injection of BoNT-B improved cervical dystonia [70]. A similar conclusion was reached in a different review, which included the same three trials [71].

The third review compared BoNT-A versus BoNT-B, but no preliminary results were yet available from two ongoing trials [72]. Evidence is currently lacking on direct comparison of the clinical efficacy and safety of BoNT-A versus BoNT-B.

The fourth review analysed BoNT-A versus anticholinergics and found only one randomized trial comparing BoNT-A versus trihexyphenidyl in 66 patients with cervical dystonia. The results favoured BoNT-A [73].

One Cochrane review analysed BoNT-A efficacy in blepharospasm, but the authors concluded that there were no high quality randomized controlled studies to support the use of BoNT-A for blepharospasm [74]. A narrative review of 55 open control studies conducted on 4340 patients in 28 countries reported a success rate of approximately 90% [75].

One Cochrane review analysed BoNT-A for laryngeal dystonia. Only one randomized study was included in this review and no conclusions were drawn about the effectiveness of BoNT for all types of spasmodic dysphonia [76].

The efficacy of BoNT-A treatment for writing dystonia has been reviewed by a recent meta-analysis [77]. Two trials provided class III data suggesting the efficacy of BoNT-A in this condition.

An open randomized class II study compared the costs and effectiveness of a trained outreach nurse practitioner giving injections of BoNT with the standard procedure carried out by medical practitioners within the clinic. The patients had spasmodic torticollis, blepharospasm, or other segmental dystonia, haemidystonia, or generalized dystonia. The study found that the outreach nurse service was as effective and safe as the standard clinic-based service, and the patients preferred it. Although the costs to the National Health System were slightly higher in the nurse practitioner group, the overall costs for society were lower than in the clinic-based service [78].

Recommendations and good practice points

(1) BoNT-A (or type B if there is resistance to type A) can be regarded as first line treatment for primary cranial (excluding oromandibular) or cervical dystonia [74,75] (level A).
(2) Due to the large number of patients who require BoNT injections, the burden of performing treatment could be shared with properly trained nurse specialists, except in complex dystonia or where EMG guidance is required [78] (level B).
(3) BoNT-A may be considered in patients with writing dystonia [77] (level C).

Other treatments

One systematic review is available on other types of symptomatic treatment [77].

Anticholinergic drugs

Two small class III crossover studies have investigated if trihexyphenidyl treatment was superior to placebo for childhood onset primary or secondary dystonias [79,80]. These studies showed benefit during a follow-up period of 9 months [80] and after a mean follow up of 2.4 years [79]. In contrast, a class III crossover study on cranial adult-onset dystonia [81] did not reveal differences between centrally acting anticholinergics, peripheral anticholinergics, and placebo in patients with cranial dystonia. A retrospective class IV study on adult-onset dystonia [82] found no consistent benefit from anticholinergics in patients with adult-onset focal dystonia and concluded that only a minority of patients with cranial dystonia respond to anticholinergics.

Recommendations and good practice points

(1) The absolute and comparative efficacy and tolerability of anticholinergic agents in dystonia is poorly documented in children and there is no proof of efficacy in adults; therefore, no recommendations can be made to guide prescribing (good practice point).

Antiepileptic drugs

Two double blind randomized crossover studies of oral gamma-vinyl GABA (six patients) and valproate (five patients) were considered not representative, due to the small sample size (class IV) [83,84]. All other available studies are only case-series evaluating the effects of benzodiazepines or carbamazepine in dystonia.

Recommendations and good practice points

(1) There is lack of evidence to give recommendations for this type of treatment (good practice point).

Anti-dopaminergic drugs

No controlled-trials were available on the effects of this type of treatment. Class IV studies reported symptomatic relief with classic neuroleptics like haloperidol or pimozide [77,85].

Tetrabenazine was effective in one double-blind randomized cross-over study, that was considered class IV due to the small sample size [86]. The positive effect of this treatment was confirmed in a large class IV series of patients with different types of movement disorders, including dystonia, followed-up retrospectively for a mean duration of 6.6 years [87]. All other available studies are also of class IV, thus insufficient to prove the effect of tetrabenazine.

Two class IV studies evaluated the effects of risperidone in patients with different forms of dystonia and did not provide sufficient evidence of efficacy. One class IV study on tiapride and three studies on clozapine did not provide evidence of efficacy.

Recommendations and good practice points

(1) There is lack of evidence to give recommendations for this type of treatment (good practice point).

Dopaminergic drugs

Levodopa is the treatment of choice for dopa-responsive dystonia. There are no evidence-based data to support the use of levodopa or dopamine agonists in other primary dystonias. Patients with dopa-responsive dystonia typically experience marked long-term benefit with low doses of levodopa. The optimal dose differs amongst patients; whilst some respond magnificently to small doses, others require higher doses.

A class IV trial performed on a small sample of dopa-responsive dystonia patients showed no differences in the short- and long-duration responses [88]. Many uncontrolled studies reported improvement of Parkinsonism and dystonia with variable doses of levodopa, from 100 mg daily [89] to 750 mg daily [90]. In a case series of 20 patients, clinical benefit was observed at a mean dose of 343.8 mg daily for patients with dyskinesias, and 189.1 mg daily for patients without dyskinesias; in addition, there was an inverse correlation between the daily dose of levodopa and duration of treatment [91].

Recommendations and good practice points

(1) Following a positive diagnostic trial with levodopa, chronic treatment with levodopa should be initiated and adjusted according to the clinical response [91] (good practice point).

Other drugs

A class I study on the acute effect of nabilone (a cannabinoid receptor agonist) did not show efficacy [92]. Only class IV evidence is available regarding alcohol, lidocaine, diphenhydramine, L-tryptophan, tizanidine or oestrogens.

Neurosurgical procedures

The available studies were classified according to the following categories: deep brain stimulation (DBS); selective peripheral denervation/myectomy; intrathecal baclofen; radiofrequency lesions; rare, uncommon or obsolete procedures.

Deep brain stimulation

Long-term electrical stimulation of the globus pallidus internus (GPi) or the thalamus has been applied in patients with various features of dystonia, mainly those who do not achieve adequate benefit with medical treatment. At this time, the consensus is that patients with primary (familial or sporadic) generalized or segmental dystonia and patients with complex cervical dystonia are the best candidates for pallidal DBS [93]. Several other manifestations are currently being explored. DBS has received approval form the Food and Drug Administration in the USA in the form of an humanitarian device exemption and has received in Europe the CE-mark for dystonia.

All studies published thus far are class IV, with the exception of a recent class III study on primary generalized dystonia [94].

It has been observed that the improvement of dystonia following DBS implants follows a specific sequence. Whilst dystonic movements (including phasic, myoclonic and tremulous features) may improve immediately or within hours or days after surgery, dystonic postures (i.e. tonic features) generally have a delayed improvement over weeks or months [94–97].

Primary versus secondary dystonia

The post-operative improvement of patients with primary dystonia who receive GPi implants is within a range of 40–90% using standard dystonia rating scales. The improvement of patients with secondary dystonia is much less pronounced [93,98].

Targets other than the pallidum

The GPi is currently considered the target of choice in primary dystonia; however, the ventrolateral thalamus has been considered by some a suitable target for secondary dystonia by some. Other targets (e.g. the subthalamic nucleus) have also been considered for primary dystonia. Due to the paucity of data, no conclusions can be made at this time and no recommendations can be given.

Generalized dystonia

The most beneficial results with pallidal DBS were reported in children with DYT-1 dystonia with improvement in the range of 40–90% [99]. However, also adult patients with non-DYT-1 primary generalized dystonia can achieve equivalent benefit [95–97]. A class III French multicentre study investigated the effect of bilateral pallidal DBS in primary generalized dystonia including blinded assessment of clinical outcome [94]. The mean percentage of improvement of the Burke–Fahn–Marsden rating scale after pallidal DBS in primary generalized dystonia in this study was on

average 54%, and the mean improvement of disability was on average 44%.

Cervical dystonia

Pallidal DBS has been primarily used in patients who were thought not to be ideal candidates for peripheral denervation, including those with head tremor and myoclonus, marked phasic dystonic movements, sagittal and lateral shift, antecollis, and combined complex forms of cervical dystonia. Post-operative benefit in these patients most often was evaluated with the Toronto Western Spasmodic Torticollis Rating Scale. At 1–2 year follow-up, the improvement in severity score ranged between 50% and 70%, the disability score improved between 60% and 70%, and the pain score between 50% and 60% (level C) [98,100,101].

Chronic stimulation uses both higher pulse width and voltage than in PD, which results in much higher energy consumption and earlier battery depletion. Batteries must be replaced sometimes every 2 years or even more often. Sudden battery depletion may induce acute recurrence of dystonia, sometimes resulting in a medical emergency. Three safety aspects have to be considered: surgery-related complications, stimulation-induced side effects and hardware-related problems.

Recommendations and good practice points

(1) Pallidal DBS is considered a good option, particularly for generalized or cervical dystonia, after medication or BoNT have failed to provide adequate improvement. Whilst it can be considered second-line treatment in patients with generalized dystonia, this is not the case in cervical dystonia since there are other surgical options available (see below). This procedure requires a specialized expertise, and is not without side effects [94,98] (good practice point).

Selective peripheral denervation and myectomy

The National Institute for Clinical Excellence of the UK has produced a guideline for selective peripheral denervation in cervical dystonia which was issued in August 2004 [102]. Selective peripheral denervation should not be confused with intradural rhizotomy, which has a high incidence of complications; it is indicated in patients with cervical dystonia who do not achieve adequate response with medical treatment or repeated BoNT injections. It is indicated in non-responders to BoNT injections. Additional myectomy may be carried out if necessary. Patients with prominent (phasic or myoclonic) dystonic movements or with dystonic head tremor are not good candidates for this procedure.

In some patients selective peripheral denervation can also be an alternative to BoNT injections. Overall, about one to two-thirds of patients achieve useful long-term improvement. This proportion has been higher, up to 90%, in some studies [103]; however, it is unclear how follow-up was performed in these studies. Denervation of C2 invariably involves numbness in the territory of the greater occipital nerve in the early post-operative period. Patients should be informed about the invariable procedure-related numbness; neuropathic pain can develop rarely. Swallowing difficulties have been noted in some studies. In about 1–2% of patients the procedure causes weakness in non-dystonic muscles, in particular in the trapezius. Re-innervation can occur and may require further surgery.

Recommendations and good practice points

(1) Selective peripheral denervation is a safe procedure with infrequent and minimal side effects that is indicated exclusively in cervical dystonia. This procedure requires a specialized expertise [102] (level C).

Intrathecal baclofen

Intrathecal baclofen has been used in patients with severe generalized dystonia; in particular, patients who have concomitant severe spasticity may benefit from this therapeutic option. The number of publications has decreased since the use of DBS for dystonia has become more prevalent. All the available evidence on outcome is class IV and furthermore no standardized dystonia scales have been used; thus, results are difficult to compare. Controlled studies have only been performed on the screening procedure to select candidates for long-term treatment. There is no evidence to set the procedure in perspective with other treatments. Overall, the results from different centres are variable.

The surgical risk is low, but the method is burdened by medication-related side effects, infections and long-term hardware-related problems. Intrathecal baclofen for treatment of dystonia requires frequent pump refills and follow-up visits.

Recommendations and good practice points

(1) There is insufficient evidence to use this treatment in primary dystonia; the procedure can be indicated in patients where secondary dystonia is combined with spasticity [104] (good practice point).

Radiofrequency lesions

Until recently, unilateral or bilateral stereotactic radiofrequency ablations of the thalamus or the pallidum were the preferred surgical methods to treat patients with severe and otherwise refractory dystonia. Most of the available literature suffers from methodological flaws and there is a little data available to compare the benefits achieved with thalamotomy as opposed to pallidotomy [105,106]. In a retrospective series of 32 patients with primary and secondary dystonias, it was found that patients with primary dystonia who underwent pallidotomy demonstrated significantly better long-term outcomes than did patients who underwent thalamotomy [107]. Patients with secondary dystonia experienced more modest improvement after either procedure, with a little or no difference in outcome between the two procedures.

Recommendations and good practice points

(1) Radiofrequency ablations are currently discouraged for bilateral surgery because of the relatively high risk of side effects (good practice point). The focus of treatment has currently shifted to DBS because of its lower risk for bilateral procedures.

Rare, uncommon or obsolete procedures

Intradural anterior cervical rhizotomy was the most common operation for cervical dystonia before the advent of peripheral denervation [108,109]. Several variations of this procedure have been developed. Since the 'standard procedure' was rather non-selective and resulted in high complication rates, modified techniques aimed to denervate the dystonic muscles and to preserve normal activity. Both the reported results and the complication rates in different series were highly variable [110]. Side effects included dysphagia, weakness of the neck, cerebrospinal fluid fistulas and infection. Weak or unstable neck has been estimated to occur in about 40% of patients after bilateral rhizotomy, and transient dysphagia in about 30% of patients.

Microvascular decompression of the spinal accessory nerve for treatment of cervical dystonia has been used in analogy to the therapeutic benefit of this procedure in other cranial neuropathies such as hemifacial spasm [111]. Pathophysiological concepts do not support microvascular decompression as a valid treatment option for cervical dystonia, and data on outcome are very limited.

Recommendations and good practice points

(1) Intradural rhizotomy has been replaced by selective ramisectomy and peripheral denervation or myotomy. These procedures are no longer recommended.
(2) Microvascular decompression is not recommended for treatment of cervical dystonia.

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