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EFNS GUIDELINES

EFNS guidelines on diagnosis and treatment of primary dystonias

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Objectives: To provide a revised version of earlier guidelines published in 2006.
Background: Primary dystonias are chronic and often disabling conditions with a widespread spectrum mainly in young people.
Diagnosis: Primary dystonias are classified as pure dystonia, dystonia plus or paroxysmal dystonia syndromes. Assessment should be performed using a validated rating scale for dystonia. Genetic testing may be performed after establishing the clinical diagnosis. DYT1 testing is recommended for patients with primary dystonia with limb onset before age 30, and in those with an affected relative with early-onset dystonia. DYT6 testing is recommended in early-onset or familial cases with craniocervical dystonia or after exclusion of DYT1. Individuals with early-onset myoclonus should be tested for mutations in the DYT11 gene. If direct sequencing of the DYT11 gene is negative, additional gene dosage is required to improve the proportion of mutations detected. A levodopa trial is warranted in every patient with early-onset primary dystonia without an alternative diagnosis. In patients with idiopathic dystonia, neurophysiological tests can help with describing the pathophysiological mechanisms underlying the disorder.
Treatment: Botulinum toxin (BoNT) type A is the first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia; it is also effective on writing dystonia. BoNT/B is not inferior to BoNT/A in cervical dystonia. Pallidal deep brain stimulation (DBS) is considered a good option, particularly for primary generalized or cervical dystonia, after medication or BoNT have failed. DBS is less effective in secondary dystonia. This treatment requires a specialized expertise and a multidisciplinary team.

Background

Dystonia is characterized by sustained muscle contractions, frequently causing repetitive twisting movements or abnormal postures [1,2]. Although thought to be rare, dystonia may be more common than currently evidenced because of underdiagnosis or misdiagnosis [3]. Adult onset primary dystonia can present mainly with tremor, which could be misdiagnosed as Parkinson's disease [4]. In such cases, imaging of dopaminergic terminals with dopamine transporter (DAT) scan or F-DOPA PET may help with the differential diagnosis.

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Primary dystonias are diseases where torsion dystonia is the only or the largely prevalent clinical feature. To improve clarity of definitions and exchange of clinical information, this EFNS committee proposes to introduce a new terminology for the etiological classification of primary forms, which encompass pure dystonia, dystonia plus and paroxysmal dystonia syndromes (Table 1). Areas of specific concern include clinical diagnosis, differential diagnosis with other movement disorders, aetiology, genetic counselling, drug treatment, surgical interventions and rehabilitation.

Search strategy

Computerized MEDLINE and EMBASE searches (2005–July 2009) were conducted using a combination of textwords, MeSH and EMTREE terms 'dystonia',

Table 1 Classification of dystonia based on three axes

1. By cause (aetiology)

Primary dystonias

Primary pure dystonias: torsion dystonia is the only clinical sign (apart from tremor), and there is no identifiable exogenous cause or other inherited or degenerative disease. Examples are DYT1 and DYT6 dystonias.

Primary plus dystonias: torsion dystonia is a prominent sign but is associated with another movement disorder, for example myoclonus or parkinsonism. There is no evidence of neurodegeneration. For example, DOPA-responsive dystonia (DYT5) and myoclonus-dystonia (DYT11) belong to this category.

Primary paroxysmal dystonias: torsion dystonia occurs in brief episodes with normalcy in between. These disorders are classified as idiopathic (often familial although sporadic cases also occur) and symptomatic because of a variety of causes. Three main forms are known depending on the triggering factor. In paroxysmal kinesigenic dyskinesia (PKD; DYT9), 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; DYT8) by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (DYT10) has also been described.

Heredodegenerative dystonias: dystonia is a feature, amongst other neurological signs, of a heredodegenerative disorder. Example: Wilson's disease.

Secondary dystonias: dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals. Examples: dystonia because of a brain tumour, off-period dystonia in Parkinson's disease.

2. 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.

3. 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)

'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 Florence on 12 September 2009, until consensus was reached within the task force.

Results

In addition to the previously published literature screen [6], we found 299 papers, amongst whom 191 were primary diagnostic studies, and 108 were efficacy studies.

Clinical features of dystonia

Literature search on the clinical features of dystonia identified a report of a multidisciplinary working group [7], one workshop report [8], 64 primary studies on clinically based diagnosis and 125 primary studies on the diagnostic accuracy of different laboratory tests. The primary clinical studies encompassed 4 cohort studies, 15 case–control studies, 12 cross-sectional and 33 clinical series.

The clinical features of dystonia have been summarized in the previous guidelines edition [6]. More recent reviews and new primary studies have focused on specific diagnostic features; a recent review has assembled the features of dystonia into a diagnostic flowchart [9].

Dystonia is a dynamic condition that often changes in severity depending on the posture assumed and on voluntary activity of the involved body area. The changing nature of dystonia makes the development of rating scales with acceptable clinimetric properties problematic.

Three clinical scales are available for generalized dystonia: the Fahn–Marsden rating scale [10], the Unified Dystonia Rating Scale and the global dystonia rating scale [11]. The total scores of these three scales correlate well, they have excellent internal consistency, from good to excellent inter-rater correlation and from

fair to excellent inter-rater agreement [11]. An evidence-based review identified more than 10 rating scales for cervical dystonia [12]. However, the most frequently used ones are the Toronto Western Spasmodic Torticollis Rating Scale [13], the Tsui scale [14] and the Cervical Dystonia Severity Scale [15].

Dystonia influences various aspects of quality of life, particularly those related to physical and social functioning. Class IV studies have evaluated the predictors of quality of life in dystonia [12,16]. Functional disability, body concept and depression were important predictors of quality of life in dystonia.

Classification

The classification is based on three axes: (i) aetiology, (ii) age at onset of symptoms, and (iii) distribution of body regions affected (Table 1). The etiological axis defines primary (idiopathic) dystonia with no identifiable exogenous cause or evidence of neurodegeneration (i.e., no progressive loss of neural cells). In the pure form, dystonia is the only clinical sign (apart from dystonic tremor). We propose to call these forms 'primary pure dystonia' (PPD). In dystonia plus, instead, usually there are additional movement disorders (e.g., myoclonus or parkinsonism). In the paroxysmal form, symptoms are intermittent and provoked by identifiable triggers (e.g., kinesigenic because of sudden movement, exercise-induced or non-kinesigenic). Non-primary dystonia is because of heredodegenerative diseases or secondary (symptomatic) to known causes; these forms are characterized by the presence of additional symptoms or signs, apart from movement disorders. A number of genes and gene loci have been identified for primary as well as for other forms.

Recommendations and good practice points

1. The diagnosis of dystonia is clinical, the core being abnormal postures (with or without tremor) and the recognition of specific features, e.g. *gestes antagonistes*, overflow and mirror movements (good practice point).
2. The classification of dystonia is important for providing appropriate management, prognostic information, genetic counselling and treatment (good practice point).
3. Because of the lack of specific diagnostic tests, expert observation is recommended. Using a structured flow chart [9] may increase diagnostic accuracy (good practice point).
4. Appropriate investigations are required if the initial presentation or the course suggests heredodegenerative or secondary (symptomatic) dystonia (good practice point).
5. Assessment of dystonia should be performed using a validated rating scale (good practice point).

Use of genetic test in diagnosis and counselling

Two genes for PPD have been identified: DYT1 and DYT6 [17,18]. Three other gene loci for autosomal-dominant PPD (DYT4, DYT7 and DYT13) and two forms of recessive PPD (DYT2 and DYT17) have been described with phenotypes ranging from cranial to generalized dystonia; however, the specific gene abnormality has not yet been identified [19].

All known DYT1 mutations reside in exon 5 of the TorsinA gene, except for one in exon 3 [20]. Screening for a GAG-deletion at position 302/303 is sufficient for clinical testing (class II) [21]. Only two patients with PPD have been described with missense mutations in exon 3 (p.F205I) and exon 5 (p.R288Q), and the pathogenicity of this variant has not been proven, as no familial cosegregation has been demonstrated [20,22].

Early-onset DYT1 dystonia typically presents in childhood and usually starts in a limb, gradually and in many patients rapidly progressing to a generalized form (class II) [21]. Many exceptions to this typical presentation have been reported, especially in mutation carriers from DYT1 families with focal or segmental dystonia of adult onset (class IV) [23,24]. Family studies have assessed that the penetrance of DYT1 dystonia is around 30%.

DYT1 mutations are the most important genetic cause of early-onset PPD worldwide. Phenotype-genotype correlations have been assessed in different DYT1 dystonia populations (class II and III) [21,25]. In Ashkenazi Jews, DYT1 testing is positive in close to 100% in patients with limb onset dystonia before age 26. Recommendation 1 below is based on such evidence [21,26]. In the western-European population, the proportion of DYT1 mutation negative dystonia is considered higher than in North America [25]. Patients with early-onset PPD not caused by the DYT1 gene tend to have later age at onset, less commonly limb onset, more frequent cervical involvement, and a slower progression than DYT1 PPD cases (class IV) [27] In patients with generalized dystonia with cranio-cervical onset DYT6 mutations should be considered [28]. thanatos associated protein (THAP1) has been identified to cause autosomal-dominant DYT6, 'mixed'-type dystonia, in Amish-Mennonite families with cranial or limb onset at young age (from 5 to 48 years) [18,29]. DYT6 mutations have been described in other populations with clinical presentations from focal to generalized dystonia in a few per cent of cases. In particular, early-onset generalized PPD with spasmodic dysphonia is a characteristic phenotype caused by DYT6 mutations (class IV) [28].

Four dystonia-plus syndromes have been characterized genetically: dopa-responsive dystonia (DRD, DYT5), myoclonus-dystonia (M-D, DYT11), rapid-onset dystonia-parkinsonism (RDP, DYT12) and autosomal-recessive (AR) dystonia-parkinsonism (DYT16).

The most common form is DRD linked to the GTPcyclohydrolase I (GCH1) gene. As this is a treatable and often misdiagnosed condition, a particular effort should be made to establish a correct diagnosis. The classical phenotype comprises onset with walking difficulties before 20 years, and progression to segmental or generalized dystonia, sometimes with additional parkinsonism and sustained response to levodopa [30,31]. Three additional DRD categories with different courses have been recognized: (i) young-onset (<20 years) cases with episodic dystonia, toe walking or progressive scoliosis throughout life; (ii) compound heterozygous GCH1 mutation carriers, who develop young-onset severe DRD with initial hypotonia similar to AR-DRD caused by tyrosine hydroxylase (TH) mutations; and (iii) adult-onset DRD patients manifesting above age 30 with mild dystonia or resting tremor or non-tremulous parkinsonism [31,32]. To date numerous GCH1 mutations but no phenotype-genotype correlations to specific heterozygous GCH1 mutations have been detected.

Inclusion of screening for gene dosage alterations of GCH1 [33,34] in addition to direct sequencing has increased the rate of detected mutations to over 80% [35,36].

If genetic testing of GCH1 is negative, other genes of the tetrahyhdrobiopterin and dopamine synthesis pathways like TH and sepiapterin reductase should be considered, especially if inheritance is recessive or atypical features like mental retardation or oculogyric crises are present (class IV) [36,37]. Parkin mutations are a rare differential diagnosis of DRD, and the diagnosis can be made by dopamine transporter imaging (class IV) [38]. For the TH gene, sequencing of the 3′-promoter sequence is recommended to increase mutation detection (class IV) [39].

A therapeutic trial with levodopa has been proposed for diagnostic purposes (class IV) [40]. Alternatively, studies on pterin and dopamine metabolites from cerebrospinal fluid (CSF) or a phenylalanine loading test have been suggested as diagnostic complements [41–43], but there is no clear evidence regarding their diagnostic accuracy and both may only be performed in specialized centres. Hence, the practical recommendation still remains that every patient with early-onset dystonia without an alternative diagnosis should have a trial with levodopa. The initial symptoms at the onset of M-D emerge in childhood and usually consist of lightning jerks and dystonia mostly affecting the neck and the upper limbs, with a prevalent proximal involvement and slow progression [44]. In a subset of patients, M-D presents as a gait disorder with lower limb onset and evolves into the typical clinical presentation until adolescence [45,46]. Myoclonus and dystonia are strikingly alleviated by alcohol in many but not in all patients [47]. However, a response to alcohol is not specific for DYT11 (class IV)[48–50]. In patients with the typical M-D phenotype, mutations in the epsilon-sarcoglycan gene (DYT11) may be detected in over 50% with an age at onset generally below 20 [51–54]. As in DRD, the rate of mutation detection in the epsilon-sarcoglycan gene is increased by screening for exon or whole gene deletions (gene dosage) [50,55–57]. Complex phenotypes with additional features may be related to chromosomal deletions and rearrangements of the 7q21 region [50,57–59].

In DYT12, RDP, the mutated gene is ATP1A3. RDP is an extremely rare disease with onset in childhood or early adulthood in which patients develop dystonia, bradykinesia, postural instability, dysarthria and dysphagia over a period ranging from several hours to weeks with triggering factors [60]. In addition to rapid onset, features suggesting an ATP1A3 mutation are prominent bulbar symptoms and a gradient of dystonia severity with the cranial region being more severely affected than arms and legs. Tremor at onset or prominent pain could not be found in ATP1A3 mutation-positive patients [61].

Protein-kinase RNA-dependent activator (PRKRA) has been identified as the DYT16 gene on chromosome 2q31.2. Mutations cause a novel form of non-degenerative, early-onset AR dystonia-parkinsonism [62]. The phenotypic spectrum of DYT16 has not been determined yet.

Four forms of paroxysmal dystonias have been genetically defined to date. In two, only the locus has been mapped: paroxysmal dystonic choreoathetosis with episodic ataxia and spasticity (DYT9) and paroxysmal familial kinesigenic dyskinesia (DYT10). Paroxysmal non-kinesigenic dystonia (PNKD, DYT8) is caused by mutations in the myofibrillogenesis regulator 1 (MR-1) gene in all families with a typical PNKD phenotype [63–65]. This condition is characterized by episodes of choreodystonia with onset in infancy or early childhood. Attacks typically last 10 min–1 h and are induced by caffeine or alcohol [66].

Paroxysmal exertion-induced dyskinesia (PED) is caused by mutations in the gene for the glucose transporter 1 (SLC2A1, DYT18). In addition to PED, patients with DYT18 gene may present with epilepsy (absence or generalized tonic-clonic seizures), migraine, cognitive deficits, haemolytic anaemia or developmental

delay. A diagnostic marker is a decreased CSF/serum glucose ratio below 0.5 (class III) [67,68].

Recommendations and good practice points

1. Genetic testing should be performed after establishing the clinical diagnosis. Genetic testing is not sufficient to make a diagnosis of dystonia without clinical features of dystonia [26,69,70] (level B). Genetic counselling is recommended.
2. DYT1 testing is recommended for patients with limb-onset, primary dystonia with onset before age 30 [70] (level B), as well as in those with onset after age 30 if they have an affected relative with early-onset dystonia [26,70] (level B).
3. In dystonia families, DYT1 testing is not recommended in asymptomatic individuals (good practice point).
4. DYT6 testing is recommended in early-onset dystonia or familial dystonia with cranio-cervical predominance [28,29] or after exclusion of DYT1 (good practice point).
5. A diagnostic levodopa trial is warranted in every patient with early-onset dystonia without an alternative diagnosis [40] (good practice point).
6. Individuals with early-onset myoclonus affecting the arms or neck, particularly if positive for autosomal-dominant inheritance and if triggered by action, should be tested for the DYT11 gene [51] (good practice point). If direct sequencing of the SGCE gene is negative, gene dosage studies increase the proportion of mutation-positives (level C).
7. Diagnostic testing for the PNKD gene (DYT8) is recommended in symptomatic individuals with PNKD (good practice point).
8. Gene testing for mutation in GLUT1 is recommended in patients with paroxysmal exercise-induced dyskinesias, especially if involvement of GLUT1 is suggested by low CSF/serum glucose ratio, epileptic seizures or haemolytic anaemia (good practice point).

Use of neurophysiology in the diagnosis and classification of dystonia

Neurophysiological tests are helpful in the characterization of functional abnormalities in patients with dystonia. However, all neurophysiology studies are class IV, not providing evidence-based results. The need for standardized study designs and methods to investigate the diagnostic sensitivity and specificity of neurophysiological tests in dystonia has been emphasized in a recent review [71]. A number of studies have been reviewed previously [6] and will not be dealt with here. Alterations in cerebellar functions suggest a role of the cerebellum in the pathophysiology of dystonia [72,73]. Cortical excitability is abnormally enhanced in symptomatic and non-symptomatic DYT1 carriers, whilst this is not the case in DYT11 M-D syndrome [74].The induction of plastic changes in the motor cortex by repetitive transcranial magnetic stimulation (rTMS) at theta burst frequency has been found to be excessive in patients with dystonia (either genetic or sporadic) and abnormally reduced in asymptomatic DYT1 carriers [75]. It is possible that such decrease in gene carriers with no symptoms indicates a form of protection against the propensity or susceptibility of DYT1 patients to undergo plastic changes that could eventually lead to clinical manifestations of dystonia.

Disturbed sensory processing has been for the past years recognized as one of the main pathophysiological agents of dystonia [76,77]. Many authors have contributed recently to confirm these findings and expand in the implication of altered sensory processing in the disordered motor control of patients with dystonia: abnormal sensory perception has been reported with studies of mental rotation and two point discrimination [78]. Several reports have shown abnormal enhancement of sensory evoked potentials (SEP) in patients with dystonia [79]. Notably, however, the only study in which the assessment was carried out blindly showed that differences in the size of the SEPs were not significant between patients and controls or between patients before and after botulinum toxin treatment [80]. Somatosensory stimuli cause abnormally reduced inhibitory effects on the motor evoked potentials (MEP) to TMS, regardless of whether the stimulus is applied on homotopic or heterotopic peripheral nerves [81]. A recent study indicates that somatosensory temporal discrimination threshold abnormalities are a generalized feature of patients with primary focal dystonias and are a valid tool for screening subclinical sensory abnormalities [82]. Using the paradigm of paired associative stimulation (PAS), i.e., applying a sensory stimulus followed 15–20 ms later by a single pulse TMS, Tamura *et al*. [79] reported a transient enhancement of cortical excitability, manifested by an increase in the P27 of the somatosensory evoked potentials tested 15 min after PAS. The same intervention was reported to cause an abnormal increase in the MEP, which is not only limited to the territory depending on the nerve stimulated but includes other muscles as well [83].

In most instances, neurophysiological abnormalities are not specific but, rather, they reveal a trend towards functional defects that may or may not become clinically relevant. This is the case in non-affected relatives of patients with dystonia [78] or in non-dystonic sites of patients with focal dystonia. Changes in neuronal excitability have been found in patients with forms of dystonia akin to psychogenicity [84,85].

Recommendations and good practice points

1. Neurophysiological tests are not routinely recommended for the diagnosis or classification of dystonia; however, multiple simultaneous electromyography (EMG) recordings from various muscles may contribute to the clinical assessment by showing characteristic features of dystonia [9] (good practice point).

Use of brain imaging in the diagnosis of dystonia

Conventional or structural MRI studies in primary dystonia are normal, and a normal MRI study is usually considered a pre-requisite to state that a patient's dystonia is primary. Recent class III [86] and class IV [87–89] diffusion magnetic resonance studies found signal abnormalities in various brain areas (including corpus callosum, basal ganglia, pontine brainstem and pre-frontal cortical areas) in cervical dystonia, writer's cramp and generalized dystonia, but not in blepharospam.

Interesting prospects of 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 [90], writer's cramp [91–93] or other focal dystonia of the arm [94] demonstrated that several deep structures and cortical areas may be activated in primary dystonia, depending on the different modalities of examination. A class II study on blepharospasm and cervical dystonia demonstrated increased basal ganglia activation in a task not primarily involving the dystonic musculature [95].

Recent class II [96] and class IV [97–100] voxel-based morphometry studies demonstrated an increase in grey matter density or volume in various areas, including cerebellum, basal ganglia and primary somatosensory cortex. This increase might represent plastic changes secondary to overuse, but different interpretations have been considered. Another class IV study found that non-DYT1 adult-onset patients with dystonia and asymptomatic DYT1 carriers have significantly larger basal ganglia compared to symptomatic DYT1 mutation carriers, with a significant negative correlation between severity of dystonia and basal ganglia size in DYT1 patients [101].

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) [102,103]. A significant reduction in caudate and putamen D2 receptor availability and reduced [^{11}C] raclopride binding in the ventrolateral thalamus were evident in DYT6 and DYT1 dystonia in a class III study [104]. The changes were greater in DYT6 than DYT1 carriers without difference between manifesting and non-manifesting carriers of either genotype.

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 DRD have normal studies, whereas patients with early-onset Parkinson's disease show reduction of striatal ligand uptake (class IV) [105]. It has been suggested that patients with tremor resembling parkinsonian tremor who have normal DAT scans may be affected by dystonia [4].

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 [106] (good practice point).
2. Structural brain imaging (MRI) is necessary for screening of secondary forms of dystonia [107] (good practice point). Computed tomography may be required to differentiate between calcium and iron accumulation.
3. Pre-synaptic dopaminergic scan (DAT or ^{18}F-DOPA) is useful to differentiate between DRD and juvenile Parkinson's disease presenting with dystonia (good practice point). This can also be useful to distinguish dystonic tremor from parkinsonian tremor (good practice point).

Treatment

Botulinum toxin (BoNT) treatment continues to be the first choice treatment for most types of focal dystonia. Pharmacological and neurosurgical treatments have also a role in the treatment algorithm.

Medical treatments: BoNT
It is established that BoNT, in properly adjusted doses, are effective and safe treatments of cranial (excluding oromandibular) and cervical dystonia [6]. In the last years long-term studies on the efficacy and safety of BoNT/A have become available, a new formulation of BoNT/A has been marketed, and new studies on BoNT/B have been performed. Further to systematic reviews already reported in the previous guidelines version, a new evidence-based systematic review released by the

American Academy of Neurology [108] recommended that BoNT injections should be offered as a treatment option for cervical dystonia (established as effective) and may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia (probably effective). A lower level of evidence was detected for focal lower limb dystonia (possibly effective).

The efficacy and safety profile of BoNT treatment has been evaluated in long-term observational studies. In patients with different dystonia types followed for >12 years, there was no decline of efficacy and the main side effects consisted in muscle weakness in or around the injected region [109]. Also, immunogenicity was found to be low for BoTN/A in long-term use, although might be higher for BoTN/B (Class III, [110]). Four class I [111–114], two class II [115,116], two class III [80,117] and 29 class IV new studies on BoNT were identified. These reports have confirmed the long-term safety of BoNT products for dystonia and other conditions. A meta-analysis performed on children with cerebral palsy found that adverse events are more frequent amongst children with cerebral palsy than in individuals with other conditions [118]. Occasional occurrences of botulism-like symptoms have been reported in children and in adults treated with BoNT products; therefore, the United States Food and Drug Administration has ordered the manufacturers to add a boxed warning to the prescribing information for each product about the potential for serious side effects at sites distant from injection [119]. No similar initiative has been taken by the European Medicines Agency. Furthermore, the possible occurrence of central effect following BoNT because of axonal migration and neuronal transcytosis has been recently suggested [120], but not unequivocally demonstrated.

Three recent studies compared different BoNT/A products and three compared the A and B serotypes. Two class II trials reported that Xeomin is as effective and safe as Botox for the treatment for cervical dystonia [115] and blepharospasm [121]. A class IV trial found that in cervical dystonia and blepharospasm, Botox is more efficacious than Dysport and has a longer duration of effect [122]. A class IV study with longer follow-up reported that in blepharospasm the mean duration of improvement was higher for Dysport than for Botox [123]. Two class I studies found that improvement of cervical dystonia was comparable following BoNT/A and B treatments, but dry mouth and dysphagia were more frequent with BoNT/B [112,114]. A class II study reported that patients treated with BoNT/B had less saliva production and more severe constipation than those treated with BoNT/A [116].

A class IV study reported that using EMG guidance can improve outcome in patients with cervical dystonia [124]. A class III trial evaluated that the association of ad hoc rehabilitative programme with BoNT injections in patients with cervical dystonia [117] provided more marked improvement and a longer duration effect than BoNT injections alone.

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 [125,126] (level A).
2. BoNT/A is effective for writer's cramp [113] (level A) and is possibly effective in other types of upper limb dystonia, but controlled dose adjustments are needed because of frequent muscle weakness (good practice point).
3. BoNT/A is probably effective for adductor-type laryngeal dystonia, but there is insufficient evidence to support efficacy in abductor-type laryngeal dystonia and in muscular tension dysphonia (good practice point).
4. BoNT are safe and efficacious when repeated treatments are performed over many years (good practice point), but doctors and patients should be aware that excessive cumulative doses may be dangerous, particularly in children (good practice point).
5. BoNT injections can be performed by direct inspection; EMG- or ultrasound-assisted targeting may improve clinical outcome (good practice point).
6. BoNT should not be used in patients affected by a disorder of neuromuscular transmission or in presence of local infection at the injection site. The recommended dosage should not be exceeded (good practice point).

Other medical treatments

No new class A or B data are available for oral medications. Therefore, the previously reported recommendations and good practice points are retained [6].

Neurosurgical procedures: Deep brain stimulation

Long-term electrical stimulation of the globus pallidus internus (GPi) is now established as an effective treatment for various types of dystonia [127]. The use of deep brain stimulation (DBS) for dystonia currently addresses in particular primary generalized or segmental forms, complex cervical dystonia and tardive dystonia in patients who do not achieve sufficient relief with conservative approaches [128]. Other manifestations are still being explored, such as status dystonicus, task-specific dystonia, camptocormia and secondary

dystonias including hemidystonia, pantothenate kinase-associated neurodegeneration, Lesch-Nyhan and cerebral palsy-related dystonia-choreoathetosis. DBS for dystonia is widely available in Western countries and in Japan. After it received FDA approval in the form of a humanitarian device exemption in the United States and CE certification in Europe, it is uniformly being reimbursed by health-insurance carriers.

In August 2006, the National Institute for Clinical Excellence (NICE), UK, published a guideline for treatment of tremor and dystonia with DBS [129], which was based on data from a systematic review and two primary studies. According to this evidence, GPi DBS provided marked benefit of dystonia, with improvement of dystonia motor scores ranging between 34 and 88% and disability scores between 40 and 50%. A meta-analysis using a regression analysis published in 2006 revealed that longer duration of dystonia correlated negatively with surgical outcome [130]. The German DBS Working Group recently provided recommendations on several practical issues [131].

One class I randomized sham-controlled study with a crossover design at 3 months found that in patients with primary generalized and segmental dystonia the change from baseline in the mean dystonia motor score was significantly greater in the neurostimulation group (-15.8 ± 14.1 points) than in the sham-stimulation group (-1.4 ± 3.8 points) [132]. In addition, patients in the sham-stimulation group had a similar benefit when they switched to active treatment during the open label phase of the study. A total of 22 adverse events occurred in 19 patients (the most frequent adverse event was dysarthria) during an overall follow-up of 6 months.

There are several studies with some form of blinded assessment, including either blinded video evaluation or double-blind assessment randomized to off or on DBS [133–136] which provide class II-III evidence and support the efficacy and safety of DBS GPi in selected patients with primary generalized or segmental dystonia [133,134], primary cervical dystonia [135] or tardive dystonia [136].

Numerous class IV studies with either prospective or retrospective design have been published over the past few years. The efficacy of GPi DBS was related to disease duration in one study [137]. Quality of life was shown to improve both in patients with primary segmental and generalized dystonia [138–141]. Stimulation via contacts located directly within the posteroventral portion of the GPi provided the best overall effect [142]. Whilst high-frequency stimulation at 130 Hz or higher has been used in most studies, stimulation < 100 Hz has been shown to be a possible alternative in selected patients with dystonia [143,144].

It is clear that improvement of dystonia after DBS frequently follows a particular pattern, with phasic, myoclonic and tremulous elements improving earlier than tonic elements, the latter often with a delay of weeks or months [145–147]. More recently, it has also been shown that upon recurrence of dystonia after switching off DBS, phasic elements manifest again within minutes and tonic elements within hours [148]. The GPi has been used in most studies on chronic stimulation, whilst there is limited experience with other targets [128] such as thalamus [149], STN [150] and cortex [151].

Overall, the most beneficial results with pallidal DBS were reported in children with primary generalized dystonia. DYT1 dystonia was shown to improve in the range of 40% to 90% [152–154] and also, adult patients with non-DYT1 primary generalized dystonia can achieve equivalent benefit [145,146,155]. The French Spidy Study on patients with primary generalized dystonia reported a mean motor improvement of 54%, and a mean improvement of disability of 44% at 1-year follow-up [133].

Long-term efficacy was reported to be sustained after more than 5 years of follow-up [156–159]. Bilateral pallidal stimulation did not negatively affect cognitive performance [160].

In patients with cervical dystonia, GPi DBS has been used primarily in those who were thought not to be ideal candidates for peripheral denervation, including patients with head tremor and myoclonus, or marked phasic dystonic movements [147,161,162]. In the past few years, however, indications have been widened. In a recent class II trial, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) dystonia severity score improved from a mean of 14.7 ± 4.2 before surgery to 8.4 ± 4.4 at 12 months post-operatively [135]. Disability and pain scores improved similarly.

Patients with primary craniofacial dystonia may achieve similar benefit than patients with other segmental dystonia with regard to the severity score. In a study on six patients with Meige syndrome, a mean improvement of 72% of dystonia motor scores was seen at 6 months post-operatively [163]. The impact of GPi on secondary dystonia, in general, is much less pronounced. Patients with dystonia and choreoathetosis because of cerebral palsy may achieve limited benefit with motor scores improving between 10 – 40%, but nevertheless yielding acceptable patient satisfaction in some patients [164]. Tardive dystonia, as opposed to other dystonias appears also a good indication for Gpi DBS with benefits similar to those seen in primary dystonia [136].

Safety aspects which have to be considered include surgery-related complications, stimulation-induced side

effects and hardware-related problems. Recently, it was noted that Gpi DBS in patients with segmental dystonia may induce a parkinsonian gait or bradykinesia in extremities which were not affected by dystonia at chronic stimulation with high voltage [163,165].

Chronic stimulation in dystonia uses both higher pulse width and voltage than in PD which results in earlier battery depletion; replacement may be needed sometimes every 2 years or less. Sudden battery depletion may induce acute recurrence of dystonia, sometimes resulting in a medical emergency. No study, thus far, has evaluated if rechargeable pulse generators are more useful than non-rechargeable ones for patients with dystonia.

Recommendations and good practice points

1. Pallidal DBS is considered a good option, particularly for primary generalized or segmental dystonia, after medication or BoNT has failed to provide adequate improvement [132] (level A).
2. Pallidal DBS can be considered a good option for cervical dystonia, after medication or BoNT has failed to provide adequate improvement [135] (level B).
3. Pallidal DBS, in general, is less effective in secondary dystonia with the exception of tardive dystonia [164,166] (level C).
4. This procedure requires a specialized expertise and a multidisciplinary team and is not without side effects (good practice point).

Other surgical procedures

In the past 5 years, there have been no new studies providing class I or II evidence for selective peripheral denervation, myectomy and myotomy, intrathecal baclofen or radiofrequency lesioning. Therefore, the previously reported recommendations and good practice points are retained [6].

Physical therapy and rehabilitation

Recently, there have been an increased number of publications showing that physical therapy and rehabilitation procedures have an important role in the care of patients with dystonia [167,168]. A number of studies have reported motor improvement in patients with writer's cramp and other forms of focal dystonia following physical treatment, and sensory and motor retraining [169–171].

A class II study showed that transcutaneous electrical nerve stimulation caused a significant beneficial effect in patients with writer's cramp [172]. A class IV study of patients with primary writing tremor showed beneficial effect of writing after training with a device that supported the hand and held the pen [173]. This evidence adds to the already reported class III study [117] where physical therapy was combined with BoNT/A injections in patients with cervical dystonia.

Musicians with dystonia may have specific benefit from motor retraining. A class IV study reported the long-term subjective outcome in a large series of musicians with focal dystonia after treatment with different medical and physical options: 54% of patients reported an alleviation of symptoms, 33% improved with trihexiphenidyl, 49% with BoNT, 50% with pedagogical retraining, 56% with unmonitored technical exercises and 63% with ergonomic changes [167].

Recommendations and good practice points

1. Transcutaneous electrical nerve stimulation to forearm flexor muscles administered is probably effective in patients with writer's cramp [172] (level B).
2. We encourage the conduction of new randomized controlled studies on these potentially useful interventions, particularly for patients with upper limb dystonia (good practice point).

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