**What is new in Tics, Dystonia and Chorea?**

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**ABSTRACT**

Movement disorders comprise hyperkinetic involuntary movements (e.g. tremor, myoclonus, tics, dystonia and chorea) and hypokinetic (parkinsonism) disorders. Tics are cardinal features of primary tic disorders encompassing Tourette syndrome (TS), but are also found in some neurodegenerative conditions and may be induced by psychoactive substances. The first line treatment approach for tics includes pharmacological (mainly dopamine receptor blockers or alpha-2A agonists) and behavioural. Dystonia and chorea syndromes are considerably heterogeneous in aetiology, and age at onset, body distribution of the movement disorder, accompanying neurological motor and non-motor features, and systemic manifestations are all important to reach a correct aetiological diagnosis. Whereas symptomatic pharmacological treatment remains the mainstay of treatment for choreas, deep brain stimulation surgery has a well defined place in the management of medically refractory dystonia.

**INTRODUCTION**

Movement disorders comprise hyperkinetic involuntary movements (e.g. tremor, myoclonus, tics, dystonia and chorea) and hypokinetic (parkinsonism) disorders.1 Due to the complex aetiology of movement disorder syndromes, accurate phenomenological characterization of the clinical features of these syndromes is an important first step to plan the correct diagnostic work-up and guide further management and referral to the appropriate Neurology services.

Here, we provide a brief overview of three subtypes of hyperkinetic disorders (tics, dystonia and chorea), discussing their clinical diagnosis and therapeutic approach. Despite the lack of disease-modifying treatment for the great part of these neurological disorders, an effort to improve diagnostic acumen remains paramount for the provision of prognosis to the patients and their families, and for patient recruitment in future therapeutic trials.

**TICS**

**Clinical approach**

Tics are repetitive and patterned movements or phonic utterances that appear out of context, may be partially suppressed under volition, and are often preceded by uncomfortable urges that are temporarily relieved by tic production. Tics are the defining feature of neurodevelopmental chronic tic disorders, among which Tourette syndrome (TS) remains the most clinically relevant *primary* tic disorder. According to the recent DSM-V criteria, TS is diagnosed by the presence of motor and vocal (or phonic) tics manifesting before the age of 18 for more than 12 months in the absence of secondary causes.2 Tics are less commonly secondary to other conditions or causative factors (Table 1).3

In a meta-analysis of prevalence data from 1985 to 2011, studies applying a school-based assessment yielded a combined prevalence of 0.77% for TS, 1.61% for chronic tic disorders, 2.99% for transient tic disorders, and 2.82% for the “all tic disorders” category in the population up to 16 years of age.4 Recent population-based data have confirmed that only about 15% of TS patients do not suffer from any other psychiatric comorbidity, with the majority of patients affected by attention-deficit/hyperactivity disorder or obsessive compulsive disorder (72% cumulatively), mood, anxiety and disruptive behavior (impulsive behaviors, rage attacks) disorders (each approximately 30%).5 This striking comorbidity profile should be taken in great account during the assessment of TS patients, in order to identify treatment priorities in each individual patient.

Tics are now viewed as the result of altered inhibitory control mechanisms modulating action selection. Importantly, tics are highly influenced by sensory, cognitive and emotional inputs, suggesting dysfunctional crosstalk between all three of the main cortico-basal ganglia circuits (motor, associative and limbic). Recent advances coming from neurophysiological,6 imaging (MRI and magnetoencephalography),7,8 neurobiological (animal models)9 and neuropathological studies confirmed the involvement of dysfunctional inhibitory control at the level of both inhibitory projection neurones or interneurones in the striatum and cortical microcircuits. Vocal tics have been put in relationship to abnormal connectivity of the ventral striatum within cortico-subcortical limbic circuits in a recent primate model. Importantly, *post mortem* studies documented reduced numbers and function of striatal interneurones in adults with TS.10

**Treatment approach**

Therapeutic algorithms like those published by the European Society for the Study of Tourette syndrome (Figure 1) identify three main decisional stages in the treatment of tics. After diagnosis and comprehensive assessment, a more active intervention for tics (i.e. beyond psychoeducation) is necessary only when tics impact on social and academic functioning, are stigmatizing, or potentially physically harmful.11 Once a decision to treat tics more actively is taken, the following step to undertake is to decide between behavioral and pharmacological treatment.

A behavioral approach like the Comprehensive Behavioral Intervention for tics, which applies Habit Reversal Training, is supported by high quality trials on youth and adults with TS.12 Other approaches, such as Exposure Response Prevention and cognitive psychophysiological models, still require to be tested in higher quality trials, and the efficacy of their combination with pharmacological treatments remains to be investigated. Moreover, behavioral treatments may be difficult to apply in younger children (below age 10) or in patients with severe comorbid ADHD.13

Several randomized controlled trials and meta-analyses support α-2 adrenergic agonists and dopamine receptor blockers as first line agents for the treatment of tics. The former group of drugs (clonidine and guanfacine, the latter unavailable in several European countries) appears to be effective against tics predominantly in TS patients with comorbid ADHD.14 Amongst dopamine receptor blockers, aripiprazole, risperidone, pimozide and haloperidol were confirmed effective in meta-analyses, although the poor tolerability of first generation antipsychotics (pimozide, haloperidol) strongly limits their routine use.15 Although not supported by a similar degree of evidence quality, fluphenazine and benzamides are often favoured due to their better tolerability profile, like a non-antipsychotic dopamine depletor like tetrabenazine. Botulinum toxin may have great utility in cranial and cervical motor tics, as well as in vocal tics.

Patients with severe, highly disabling tics who are unresponsive to first line interventions are now more and more frequently considered for neuromodulation strategies, above all deep brain stimulation (DBS) surgery. More than 130 patients with TS have been treated with DBS worldwide, with less a dozen cases under age 18.16 In these patients, DBS should be considered only in those patients in whom psychiatric comorbidities are stable and who do not present with suicidality or high risk of aggressiveness directed against others. Although priority anatomical targets are still being debated, crossover sham-controlled trials support the efficacy of globus pallidus internus (limbic portion particularly)17 and centromedian/parafascicularis nuclei stimulation,18 with acceptable short- and medium-term adverse effect profile.

**DYSTONIA**

**Clinical approach**

Dystonia is a movement disorder characterized by sustained muscle contractions, which frequently cause abnormal postures (tonic component) or repetitive movements (phasic component). The typical clinical features of dystonic contractions are marked directionality, long duration, and simultaneous involvement of agonist and antagonist muscles.19 Dystonic movements can less commonly be more rapid and have a rhythmic pattern, resembling tremor. However, in most cases dystonic tremor may show an evident directionality, unlike the typical sinusoidal oscillations of other forms of tremor.20

Dystonic movements and postures can occur at rest, but are typically aggravated by voluntary movement, and in some forms dystonia is almost exclusively triggered by specific complex motor actions performed with the same body part (e.g. writing dystonia, musician’s dystonia). Dystonic contractions within a specific body region can also be triggered by voluntary movements occurring at distant segments (overflow phenomena).21 A rare phenomenon is the suppression of dystonia during voluntary movements (paradoxical dystonia) and involves the facial muscles.19,21

*Gestes antagonists* (also known as ‘sensory tricks’) are typical features of dystonic movements and indicate the temporary reduction in the severity of dystonia using an alternative motor action, which often conveys tactile or proprioceptive stimulation; typical *gestes* include touching the chin or the neck in cervical dystonia.22

The clinical classification of dystonia has been recently revised, and comprises two main axes: clinical characteristics and aetiology (Figure 2).23

Isolated (formerly known as primary) dystonia encompasses all those conditions in which dystonia is the sole relevant clinical feature, with the exception of associated tremor. This is a genetically heterogeneous group of disorders. Early onset forms (i.e. age at onset <26 years) become frequently generalized and are associated with *TOR1A* (DYT1, without cranio-cervical involvement) and *THAP1* (DYT6, with cranio-cervical involvement) gene mutations. More than five other potentially causative genes have been described in the last 3 years, which are also associated with adult-onset (focal) forms, but their role in aetiology and diagnosis is still under investigation.24 Combined dystonia syndromes include myoclonus-dystonia syndromes (also genetically heterogeneous) and dystonia-parkinsonism syndromes; the latter group includes dopa-responsive forms and heredodegenerative diseases that include the complex family of neurodegeneration with brain iron accumulation disorders (Table 2).

**Treatment approach**

The mainstay of the treatment of dystonia remains pharmacological for isolated dystonias and the majority of secondary dystonias, even though early deep brain stimulation for monogenic forms of isolated generalized dystonia is now extensively applied. Anticholinergic drugs, e.g. trihexyphenidyl, remain first line agents for multifocal or generalized dystonias, and their dose should be titrated gradually to minimize side effects, particularly of dry mouth, gastrointestinal upset, urinary retention and confusion.25 Muscle relaxants such as baclofen (available also in intrathecal pump infusion formulation) and clonazepam can be helpful, when spasticity or tremor, respectively, are associated with dystonia; lethargy, dizziness and confusion may be associated with these drugs. Dopamine-depleting drugs such as tetrabenazine may be helpful in a smaller proportion of cases. L-dopa in small doses (50-200 mg) represents the first line treatment for dopa-responsive dystonias, and, given the costs of genetic screening for these forms, an empiric trial of L-dopa is usually offered to all patients with early onset dystonia in whom there is no evidence of neurodegeneration or brain structural lesions.26 Chemodenervation with botulinum neurotoxins (three forms of botulinum toxin A and one of botulinum toxin B are available in the UK) is a very effective and widely available treatment for segmental/focal dystonias, in which the topography of the muscles involved can be determined.27 Electromyographic and ultrasound guidance techniques have greatly advanced recently for those body regions, like upper and lower limbs, in which the superficial injection approach is hindered by the complexity of anatomical localisation of the muscles contributing to dystonia.25, 28

Deep brain stimulation (DBS) surgery is considered for highly disabling, medically refractory dystonias. DBS of the globus pallidus internus (GPi) has shown to be very effective for the treatment of DYT1 dystonia, and, to a slightly lesser extent, for non-DYT1, early onset generalized dystonias. A 35-45% improvement in severity was reported for GPi DBS also in refractory cervical dystonia. There is a lower degree of evidence quality for DBS of the subthalamic nucleus in cervical dystonia and for GPi DBS of secondary dystonias or other focal dystonias (cranial, upper limb).29 The full benefit of GPi DBS in dystonia is usually achieved in several months, with stable efficacy above 5 years. 30, 31

**CHOREA**

**Clinical approach**

Chorea is a movement disorder characterized by rapid, purposeless, non-stereotyped movements flow randomly from one part of the body to another.32 Chorea is caused by a multitude of conditions with different pathophysiological mechanisms. In the majority of cases, the clinical context in which chorea develops is the key to defining its aetiology. The different causes of chorea may be recognized based on course (acute/subacute, i.e. reaching a peak of severity within days/weeks, or chronic, i.e. gradually progressing over months or years) and body distribution (focal, segmental, unilateral, generalized). An updated list of the different aetiologies of chorea, and relative diagnostic work-up, is provided in Table 3.

Within the rubric of acute/subacute chorea, the spectrum of immune-mediated causes of chorea has broadened extensively in the recent past, to include a vast group of autoantibody-induced encephalopathies such as those associated with anti-LGI1, anti-GAD65, anti-CASPR2, anti-GABA-B receptor antibodies, in addition to the choreiform movements documented in anti-NMDA-receptor antibody-related encephalitis33. Furthermore, there is increasing interest on the behavioural and cognitive aspects of the prototype of immune-mediated choreas, i.e. Sydenham’s (or rheumatic) chorea (SC).34 Executive dysfunction, obsessive-compulsive disorder, mood disorders, anxiety, attention-deficit–hyperactivity disorder, tic disorders, and rarely also psychosis, are important comorbidities in patients with SC.33

Amongst chronic or progressive chorea, Huntington’s disease (HD) remains the most frequent cause, and is an autosomal dominant trinucleotide repeat disorder related to the *IT15* gene coding for the protein huntingtin.35 Usually chorea is the prominent movement disorder of adult-onset HD, whereas juvenile HD (Westphal variant) typically presents with an akinetic-rigid syndrome and progresses more rapidly.36 Personality changes, depression, hostility and/or increased interpersonal sensitivity, obsessive-compulsive symptoms, phobias and anxiety appear early in the course of the illness. As disease progresses, global cognitive decline appears, initially manifesting mainly as loss of cognitive flexibility, executive dysfunction, memory and attention deficits, and reduced psychomotor speed.37-38

A number of HD-look alikes has been described. Within this group, *c9orf72* expansions, spanning across all age groups, have recently been described as the most commonly identified genetic cause (1.95%), followed by spinocerebellar ataxia type 17, Huntington’s disease-like 2, Friedreich ataxia, and inherited prion disease (HDL-1). The group of HD phenocopies is in continuous expansion.39

Among the forms of chorea beginning in youth and showing a slowly progressive or apparently non-progressive course, there have been recent advances on the characterization of benign hereditary chorea (BHC), which was confirmed to be genetically heterogeneous. This condition is mostly caused by *NKX2.1* autosomal dominant mutations, which should be screened in the presence of a history of neonatal hypotonia, motor developmental delay, and early-onset hyperkinetic movement disorder (often generalized chorea and/or dystonia), with possible comorbid lung or thyroid symptoms.40 Early-onset chorea and dystonia can be distinguishing features also of the recently identified autosomal dominant inherited adenylate cyclase-5 (*ADCY5*) mutations.41

**Treatment approach**

The treatment of chorea aims at reversing treatable conditions, followed or accompanied by symptomatic management. Symptomatic pharmacological management is necessary when chorea is not fully reversible (e.g. neurodegenerative or vascular causes) or if aetiologic treatment is complex and the patient needs fast and effective improvement. Three main classes of medications are used to alleviate chorea: a) D2 dopamine receptor blockers (antipsychotics); b) tetrabenazine, indicated to treat chorea in HD and tardive choreiform dyskinesias; c) antiepileptic agents (mainly carbamazepine and valproic acid). In patients with chorea and severe behavioural symptoms (e.g. psychosis, depression, aggressive behaviour) antipsychotics may be favoured, whereas tetrabenazione may be more difficult to manage in the presence of severe depression with suicidal risk. A combination of antipsychotics and tetrabenazine can be considered, if safe, when monotherapy is unsuccessful. Antiepileptic drugs like carbamazepine and valproate are less effective anti-chorea agents, with the exception of paroxysmal kinesigenic chorea, which responds dramatically to carbamazepine.42,43

Surgical treatment (either ablative or DBS) of chorea is still at an experimental level and it should be used in selected case refractory to pharmacological treatments. Evidence supporting surgical treatment of chorea is quite limited and focuses mainly on HD and neuroacanthocytosis syndromes.44 The globus pallidus internus is the target of deep brain stimulation for relieving chorea. However, long term outcomes are still uncertain, considering the progressive course of these conditions. DBS of the GPi in tardive choreiform dyskinesias is supported by recent promising evidence45

**CONCLUSION**

In summary, because of the wide variety of different aetiological causes of movement disorders and a large number of different forms of clinical presentation, it is important to use a step-by-step organized approach to a patient with a movement disorder. The first step is to identify whether it is a hypo- or hyperkinetic movement disorder and if the latter which particular form of dyskinesia. Age and distribution and whether there are associated other signs or clinical features is to be noted.

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**Box 1. Key points and keywords**

**Key Points**

1. Tourette syndrome exhibit an important comorbidity with attention-deficit/hyperactivity disorder or obsessive compulsive disorder (72%), mood, anxiety and disruptive behaviour disorders (each approximately 30%).
2. Several randomized controlled trials and meta-analyses support α-2 adrenergic agonists and dopamine receptor blockers as first line agents for the treatment of tics.
3. Dystonic movements and postures can occur at rest, but are typically aggravated by voluntary movement, and in some forms dystonia is almost exclusively triggered by specific complex motor actions (e.g. writing dystonia, musician’s dystonia).
4. Chemodenervation with botulinum neurotoxins is the most effective and widely available treatment for segmental/focal dystonias, whereas deep brain stimulation surgery has gained an important role in the management of medically refractory dystonia.
5. The different causes of chorea may be recognized based on course (acute/subacute or chronic) and body distribution (focal, segmental, unilateral, generalized).
6. The pharmacological treatment of chorea involves D2 dopamine receptor blockers, tetrabenazine and antiepileptic agents (mainly carbamazepine and valproic acid)

KEYWORDS: Hyperkinetic movement disorders, dystonia, chorea, tics, diagnosis, treatment.

**Table 1.** **Secondary Causes of Tics**

|  |
| --- |
| **► Neurodevelopmental Disorders** |
| Mental retardation |
| Autistic spectrum disorders (including Asperger syndrome) |
| Rett syndrome |
| Genetic and chromosomal abnormalities |
| X-linked mental retardation (*MRX23*) |
| Albright hereditary osteodystrophy |
| Duchenne muscular dystrophy |
| Factor VIII hemophilia |
| Fragile X syndrome |
| Lesch-Nyhan syndrome |
| Triple X and 9p mosaicism |
| 47 XXY karyotype |
| Partial trisomy 16 |
| 9p monosomy |
| Beckwith-Wiedemann syndrome |
| Tuberous sclerosis |
| Congenital adrenal hyperplasia due to 21-hydroxylase deficiency |
| Phenylketonuria |
| Corpus callosum dysgenesis |
| Craniosynostosis |
| Klinefelter syndrome |
| Neurofibromatosis |
| Developmental stuttering |
| **► Acute Brain Lesions** |
| Posttraumatic |
| Vascular |
| Infectious |
| Varicella-zoster virus |
| Herpes simplex encephalitis |
| *Mycoplasma pneumoniae* |
| Lyme disease |
| **► Postinfectious** |
| Sydenham chorea |
| Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) |
| **► Neurodegenerative Diseases** |
| Huntington disease |
| Neuroacanthocytosis syndromes |
| Neurodegeneration with brain iron accumulation |
| **► Other Systemic Diseases** |
| Behçet syndrome |
| Antiphospholipid syndrome |
| **► Peripheral Trauma** |
| **► Medications and Toxins:** amphetamines, cocaine, heroin, methylphenidate, pemoline, antipsychotics (tardive tics), antidepressants, antiepileptics (carbamazepine, phenytoin, phenobarbital, lamotrigine), L-dopa |
| **► Functional Tic-like Jerks** |

**Table 2. Secondary dystonias**

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| **► Non-degenerative combined dystonia syndromes** |
| Dopa-responsive dystonia: results from genetic defects in enzymes that are involved in the biosynthesis of dopamine; the most common condition is autosomal dominant GTP cyclohydrolase 1 deficiency (Segawa disease) |
| Rapid onset dystonia-parkinsonism (ATP1A3 gene mutations) |
| Myoclonus-dystonia: most common cause is *SGCE* gene mutations |
| **► Dystonia associated with neurodegenerative disorders** |
| **►Autosomal dominant** |
| Huntington disease |
| Machado-Joseph disease (SCA3) |
| Basal ganglia calcifications syndromes |
| SCAs |
| Neuroferritinopathy |
| **►Autosomal recessive** |
| Juvenile Parkinson’s disease |
| Wilson’s disease |
| Neuroacanthocytosis syndromes |
| Hallervorden-Spatz disease |
| Neurodegeneration with brain iron accumulation syndromes (pantothenate kinase associated neurodegeneration, *PLA2G6* associated neurodegeneration, Kufor Rakeb syndrome, MPAN, BPAN, aceruloplasminemia) |
| Lysosomal storage disorders |
| Ataxia-Telangiectasia |
| Homocystinuria |
| **► Recessive X-linked** |
| Lubag disease |
| Lesh-Nyhan syndrome |
| Rett syndrome |
| **► Mitochondrial disorders** |
| Leber disease |
| MELAS |
| MERRF |
| Leigh’s disease |
| **► Parkinsonian syndromes** |
| Parkinson’s disease |
| Progressive Supranuclear Palsy |
| Cortico-basal syndrome |
| Multiple system atrophy |
| **► Dystonia associated with acquired causes** |
| **► Medications**  Dopaminergic (L-dopa, dopamine agonists), dopamine receptor blocking drugs  (neuroleptics, prochlorperazine, metoclopramide), selective serotonin reuptake inhibitors, MAO  inhibitors, antiepileptic drugs, ergots, flecainide, cocaine, ranitidine, calcium antagonists,  anaesthetic agents. |
| **► Toxins**  Manganese, carbon monoxide, carbon disulfide, cyanide, methanol, disulfiram |
| **► Infectious, post-infectious and inflammatory diseases**  Subacute sclerosing panencephalopathy, Reye’s syndrome, viral encephalitis, Creutzfeld-Jakob  disease, systemic lupus erythematosus, Antiphospholipid syndrome, Sjogren’s syndrome. |
| **► CNS lesion**  Brain tumour, Stroke, Hypoxia, Intracranial haemorrhage, CNS trauma, congenital  malformations, cervical cord lesions. |
| **► Perinatal cerebral injury**  Cerebral palsy, delayed-onset dystonia, perinatal hypoxia, kernicterus. |
| **► Functional dystonia** |

SCAs=spinocerebellar ataxias; MELAS=Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF=Myoclonic Epilepsy with Ragged Red Fibers

**Table 3 Clinical Approach to Chorea**

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| --- | --- | --- |
| **Clinical presentation** | **Possible aetiologies** | **Diagnostic investigations** |
| **Acute or subacute hemichorea/hemiballism**  **Acute or subacute generalized chorea**  **Episodic (paroxysmal) chorea** | *Immune-mediated*  Sydenham’s chorea  Antiphospholipid antibody syndrome  Systemic lupus erythematosus  Other connective tissue diseases (e.g. Sjogren’s syndrome)  Coeliac disease  Paraneoplastic (associated with anti-CRMP5 and anti-Hu antibodies)  Autoimmune encephalitides/encephalopathies (secondary to anti-NMDA receptor, anti-LGI1, anti-GAD65, anti-CASPR2, anti-GABA-B receptor antibodies)  *Endocrinological*  Thyrotoxicosis  Chorea gravidarum  Chorea secondary to oral contraceptives or hormone replacement therapy  *Drug- and toxin-induced*  Drugs (antiepileptics, calcium channel blockers, anticholinergics, digoxin, lithium, tricyclic antidepressants, fluoxetine, cyclosporine, ciprofloxacin, baclofen, theophylline, methotrexate, interferon-alpha, ribavirin, methadone)  Recreational drugs (D-amphetamine and derivatives, pemoline, cocaine, crack)  Carbon monoxide encephalopathy  *Infectious*  Viral encephalitides (HSV-1, VZV, measles, German measles, CMV, West Nile virus, Parvovirus B19, Japanese B encephalitis)  Bacterial infections (Diphtheria, Legionella and Salmonella species, Neuroborreliosis, Neurosyphilis)  *Other metabolic aetiologies*  Posterior reversible encephalopathy syndrome  Hypocalcaemia  Type 2 diabetes and uraemia with T2 striatal hyperintensities  Central extrapontine myelinolysis  *Vascular/haemodynamic*  Polycythemia vera  Essential thrombocytemia  ‘Post-pump’ syndrome  *Genetic*  Paroxysmal kinesigenic dyskinesias (*PRRT2* gene mutations, genetically undetermined)  Paroxysmal exercise-induced dyskinesia (*GLUT1* gene mutations)  Paroxysmal non-kinesigenic dyskinesias (*MR1* gene mutations)  *Acquired*  Intracerebral arterial stenosis or Moyamoya (episodic hemichorea) | *First level*  • Magnetic resonance imaging head (including contrast-enhanced, diffusion-weighted or susceptibility-weighted sequences; plus magnetic resonance angiography or conventional angiography, if required)  •Antistreptolysin O and anti-deoxyribonuclease B antibodies  •Anti-β2-glycoprotein I (IgG) antibodies  •Anti-double stranded DNA antibodies  •Lupus anticoagulant  •Acute phase reactants (ESR, C-reactive protein)  •Full blood count  •Electrolytes  •Thyroid function tests  •Throat culture analysis for group A Streptococcus  •Glycemic level – plasma osmolality – plasma ketones  •Doppler echocardiography  •ECG  •HIV test  *Second level*  •Anti-NMDA receptor antibodies (followed by CT pelvis, if justified by clinical presentation)  •Anti-neuronal antibodies (anti-CRMP5/CV2, anti-Hu, anti-Yo antibodies)  •Anti-SS-A and anti-SS-B antibodies  •Anti-gliadin and anti-transglutaminase antibodies  •Genetic screening for PRRT2, MR1, SLC2A1, GLUT1 gene mutations (if paroxysmal)  •Cerebral SPECT (if required)  •Carotid/vertebral arterial Doppler studies  •Pregnancy test (if justified by clinical presentation)  •EEG (if justified by clinical presentation)  *Third level (if the cause remains undefined)*  •Cerebrospinal fluid analysis (14-3-3 protein, cells, viral or bacterial antibodies/PCR)  *First level*  *•*Magnetic resonance imaging head  •Thyroid function tests  •Copper/coeruloplasmin studies  •Uric acid  •Liver function tests, calcium and phosphate  •Anti-β2-glycoprotein I (IgG) antibodies  •Anti-double stranded DNA antibodies  •Lupus anticoagulant  •Albumin  •Cholesterol  •Plasma and CSF lactate/pyruvate  •Urinary and serum organic and amino acids  •Creatine phosphokinase  •Ferritin  *Second level*  •alpha 1-fetoprotein serum  •Cerebral SPECT  •Somatosensory evoked potentials  •Genetic screening for TITF1/NKX2.1, FRDA, APTX, SETX gene mutations  •Genetic screening for IT15, JPH3, SCAs, DRPLA, PRNP and others  •Peripheral blood film for acanthocyte search  •Erythrocyte Kx and Kell antigen screening  •Skin biopsy for filipin staining on fibroblasts |
| **Chronic, progressive chorea**  **Chronic, non-progressive chorea** | *Early onset*  Friedreich ataxia  Ataxia-teleangiectasia  Ataxia with oculomotor apraxia types 1 and 2  Pantothenate kinase-associated neurodegeneration  Wilson’s disease  Aceruloplasminemia  Lesch-Nyhan syndrome  Leigh syndrome  Infantile bilateral striatal necrosis syndrome  Non-ketotic hyperglycinemia  Recessive hereditary methemoglobinemia type 2  Beta-ketothiolase deficiency  *Adult-onset*  Huntington’s disease  *C9orf72* gene expansion-related neurodegeneration  Huntington’s disease-like 2  Neuroacanthocytosis syndromes (chorea-acanthocytosis, McLeod syndrome)  Spinocerebellar ataxia 17 (much less commonly other types, e.g. 1, 2, 3, 7, 8, 14, dentato-rubro-pallido-luysian atrophy, POLG-1 mutations)  Pallido-nigro-luysian atrophy  Neuroferritinopathy  Basal ganglia calcifications  Hepatocerebral degeneration  Huntington’s disease-like 1 and Creutzfeldt-Jakob disease  *RNF216*-associated neurodegeneration (variant of Gordon Holmes syndrome)  *Mixed age at onset*  Niemann-Pick disease type C  Non-ketotic hyperglycinemia  Hereditary methemoglobinaemia type 2  Beta-ketothiolase deficiency  Neurosyphilis  Benign hereditary chorea (*TITF1/NKX2.1* gene mutations)  Dyskinetic cerebral palsy spectrum  Tardive dyskinesia  L-dopa-induced dyskinesia (may worsen over time) |

(Disorders of Movement, Martino D, Espay AJ, Fasano A, Morgante F eds. Springer Verlag 2016).

**Fig. 1 Therapeutic algorithms for treatment of tic disorders.** Decision tree for the treatment of tics (specifically focused on Tourette syndrome and other primary tic disorders). 11

**Figure 2. Classification of dystonia**. Dystonia is currently classified according to two axes: clinical characteristics and aetiology. Clinical characteristics include age at onset, body distribution, temporal pattern and associated features. The aetiological axis refers to presence of nervous system pathology and whether these are inherited, acquired or idiopathic in nature (from Disorders of Movement, Martino D, Espay AJ, Fasano A, Morgante F eds. Springer-Verlag, Heidelberg 2016).

**CME QUESTIONS**

1) What are the most common psychiatric disorders associated with Tourette syndrome?

(a) Depression and anxiety

(b) Anxiety and obsessive compulsive disorder

**(c) Attention-deficit/hyperactivity disorder and obsessive compulsive disorder**

(d) Schizophrenia and depression

(e) Attention-deficit/hyperactivity disorder and anxiety

2) What is the most successful deep brain stimulation target in patients with dystonia?

(a) Thalamus

(b) **Internal Globus Pallidum**

(c) Sub-thalamic nucleus

(d) External Globus Pallidum

(e) Substantia nigra