National Consensus Statement
for Diagnosis and Treatment of Hyperkinetic Motor Disorders

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Today, 27 March 2018, we, the undersigned experts reached consensus on diagnosis and treatment of hyperkinetic motor disorders:

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Motor disorder is a term, used for diseases, manifested by abnormal or excessive movements, occurring in patients, who are conscious. Motor disorders are subdivided into hyperkinetic and hypokinetic. The hyperkinetic disorders are characterized by excessive movements, while the hypokinetic are presented with scarcity of movements. Hypokinetic motor disorders are manifested by Parkinson's syndrome. Hyperkinetic motor disorders are characterized by tremor, dystonia (dyskinesia), chorea, tics, myoclonias and muscular hypotonia. Though tremor is a hyperkinetic symptom, it also accompanies the hypokinetic Parkinson's syndrome and is an integral part of its differential diagnosis.

For diagnosing hyperkinetic motor disorders, **the general practitioner** should verify the presentation of one or more of these symptoms:

- Tremor
- Dystonia
- Chorea
- Tics
- Myoclonias
- Muscular hypotonia

Upon detection of these symptoms, it is necessary to refer the patient to a neurologist without using any other diagnostic methods.

The neurologist should set the diagnosis for the symptom. The etiological clarification of the disease is done in a specialized motor disorder center.

1. **Dystonias**

Dystonia is a motor disorder, characterized by continued or intermittent muscular contractions, resulting in abnormal, frequently repetitive movements or postures or both. Usually dystonias are one-type, of torsional character and may be accompanied by a tremor. Quite often dystonia is caused or worsened by voluntary motor acts and is associated with abnormal muscular activation. There are two major types of tremor in the dystonias: postural, which is similar to the essential tremor, and dystonic. The

dystonic tremor is fast, abrupt, variable in amplitude and gets worsened in specific positions of the affected limb and/or when performing certain movements.

The prevalence of primary dystonia is approximately 225 per 100,000, and for the age over 50 it reaches up to 732 per 100,000. The prevalence of focal dystonias is around 29.5 per 100,000, of cervical dystonia – 8.9 per 100,000, and of generalized dystonia – 3.4 per 100,000.

The etiology is multifactorial and represents a combination of a genetic background, which is of prime importance, and environmental triggering factors. Both family (10%), and non-family dependent cases are observed. Until now 15 gene loci have been identified from DYT1 to DYT15, localized in different chromosomes and associated with dystonias of different phenotype. The classic generalized idiopathic torsional dystonia with an onset during childhood is inherited by autosomal-dominant pathway of reduced penetrability. The focal dystonias with a late age onset are genetic heterogeneous diseases of autosomal-dominant inheritance and reduced penetrability (5%).

Genetic DYT Classification of Dystonia				
DYT Number & Name	**Inheri-tance**	**Clinical Characteristics**	**Gene**	**Existing Tests**
DYT1	AD	Primary generalized dystonia with an early onset	DYT1	Yes
DYT2	AR	Recessive primary dystonia of an early onset in a Spanish Gipsy family	HPCA	No
DYT3 X-associated dystonia Parkinsonism	XR	Dystonia Parkinsonism in Philippine males	TAF1	Yes, of scientific interest

DYT4, whispering dystonia	AD	Laryngeal dystonia +/- limb dystonia in an Australian family	?	No
DYT5 Levodopa responsive dystonia	AD	Early onset dystonia Parkinsonism, responding to levodopa	*GTPCH1*	Yes
DYT6	AD	Two Mennonite families, with variable manifestation of primary craniocervical and limb dystonia	Associated with 8p21-p22	No
DYT7	AD	German family with primary craniocervical dystonia	Associated with 18p	No
DYT8, PNKD	AD	Dystonia and chorea outbursts, deepening by fatigue or consumption of coffee, alcohol	Myofibrillogenesis regulating-1 gene	Yes, of scientific interest
DYT9	AD	Episodic chorea and ataxia of progressive interictal spasticity	Associated with 1p	No
DYT10, PKD	AD	Episodes of chorea and dystonia, deepening by sudden movement	Associated with the center-metering region of chromosome 16	No

DYT11 Myoclonus dystonia	AD	Myoclonus & dystonia	Epsilon Sarcoglycan gene	Yes
DYT12 Rapidly progressing dystonia syndrome Parkinsonism	AD	Acute onset of dystonia following an infection or physical strain	ATP1A3	Yes, of scientific interest
DYT13	AD	Italian family with primary craniocervical dystonia	Associated with1p36.13-36.32	No
DYT14	?	Levodopa-responsive dystonia Parkinsonism	Associated with 14q13 beyond the region of GTRPCH1 gene	No
DYT15 Myoclonus dystonia	AD	Myoclonus dystonia	Associated with 18p11	No
AD, autosomal-dominant; AR, autosomal-recessive; XR, X-associated recessive; GTPCH1, guanosine triphosphate cyclohydrolase 1; PNKD, paroxysmal non-kinesigenic dyskinesia; PKD, paroxysmal kinesigenic dyskinesia				

The pathogenesis is associated with disturbed inter-neuronal inhibition at basal ganglia, cortex, and brain stem and spinal cord levels. The inhibiting activity is disturbed

both in the motor and sensory systems, with increased plasticity of the central nervous system.

The classification presumes multi-diagnostic approach and is carried out mainly in two directions – clinical characteristics and etiology. Clinical characteristics include: age at the onset of the disease, anatomic dissemination of the symptoms, time specifics and associated characteristics.

On the basis of clinical characteristics dystonias are subdivided into isolated (earlier known as primary) and combined dystonia (secondary, dystonia-plus syndromes and heredodegenerative). According to their etiology dystonias are subdivided into induced by certain nervous system pathology, inherited, acquired or idiopathic.

Dystonia Classification

Directions	Classification Measurement	Subgroups
Division I: Clinical characteristics	Age at onset	Infantile (up to 2 years)
		Childhood (3–12 years)
		During teenage and adolescence (13–20 years)
		Early adult age (21–40 years)
		Late adult age (over 40 years)
	Anatomic dissemination	Focal (involves isolated part of the body, e.g. arm)
		Segmental (2 or more adjacent body parts, e.g. arm and neck)
		Multifocal (2 or more not adjacent body parts)

		Hemidystonia (affects one half of the body)
		Generalized (torso plus 2 other regions)
	Time specifics	Disease course (static or progressive)
		Short-term variations (e.g. persisting, provoked by a certain motion, diurnal sways, daily fluctuations, paroxysmal)
	Associated characteristics	Isolated (with or without tremor)
		Combined (with other neurological or systemic symptoms)
Division II: Etiology	Nervous System Pathology	Degenerative
		Structural (such as focal permanent lesions)
		Without degenerative or structural pathology
	Heredity	Inherited (e.g. gender associated, autosomal-dominant, autosomal-recessive, mitochondrial)
		Acquired (e.g. cerebral injury, medicines/toxins, vascular, neoplastic)
	Idiopathic	Sporadic

		Family type

According to the associated characteristics the isolated dystonia (earlier called primary) is the type, where dystonia, with or without tremor, is the only clinical sign. There is no secondary cause, nor neurodegeneration.

Combined dystonia covers several types, subdivided in earlier classifications as *dystonia plus syndromes (*other symptoms and signs may occur with the dystonia, but there are no secondary causes or neurodegeneration), *secondary dystonia (*there is a clear secondary cause for the dystonia, such as cerebral trauma, toxic noxa, etc.), *hereditary-degenerative dystonia (the* dystonia is part of a wider neuro-degenerative syndrome).

In paroxysmal dystonia episodic attacks of dystonia are being observed, often with no clinical symptoms between the attacks. *The paroxysmal dystonia* can be *paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia or paroxysmal dystonia, induced by physical strain.*

Psychogenic dystonia usually goes with fixed postures/positions, with other signs, suggesting psychogenic motor disorder.

Dystonias according to clinical characteristics	
Isolated dystonia	**With an onset in young age:** *generalized* (primary torsional type or Oppenheim dystonia) Due to DYT1 gene mutations **With an onset in a more mature age:** *specific* at performing certain activity (e.g. graphospasm, musician's dystonia, etc.) *Focal* (e.g. oromandibular, torticollis , blepharospasm dystonic tremor) *Rare genetic idiopathic dystonias* (e.g. DYT6, DYT7, DYT13)
Combined dystonia	
Dystonia plus syndromes	*Levodopa responsive dystonia* (DYT15) *Myoclonus dystonia* (DYT 11)
Secondary dystonia	As a result of cerebral injury (most often putamen) *Drugs/toxic substances*: many medicinal products can cause acutely emerging dystonia; dopamine receptor blockers may cause acute or late dystonia *Post-encephalitic*

Hereditary-degenerative dystonia	Parkinson's disease Cortical-basal degeneration (CBD) Progressive supra-nuclear paresis (PSP) Multiple systemic atrophy (MSA) Huntington's chorea Wilson's disease Spinocerebellar ataxias Neuronal brain iron accumulation syndrome/NBIAS, Hallervorden-Spatz's disease) Dentorubropalladoluysic atrophy Neuroacanthocytosis X-associated dystonia Parkinsonism (Lubag) Rapidly emerging dystonia-Parkinsonism syndrome Mohr-Tranebjaerg syndrome (deafness-dystonia) Metachromatic dystrophy GM1/GM2 gangliozidosis Aminoacidemias Niemann-Pick type C Ataxia teleangiektasia

Clinically abnormal movements are of different velocity: slow and torsional, usually in the distal muscular groups (athetosis), faster myoclonic (myoclonic dystonia), muscle spasms or progressing in dystonic postures. Regardless of the number of muscle groups affected, dystonia is always predominant in certain muscle groups. This results in movements in specific direction, which even for a short time end up in specific posture: bending one's head, ulnar deviation, plantar flexion, closing the eyes, and so on. Dystonia starts from one part of the body, but it is not a static phenomenon and may remain focal or encompass other body parts as well. One of the typical symptoms is the involvement of adjacent muscle groups, for example in cervical dystonia the upper limbs are also affected. Dystonia is associated with a feeling of muscle strain and pain. The

pain is stronger in the abnormal posture than during movement. The dystonic movements and postures are relieved by certain voluntary movements (geste antagoniste) or sensory practices.

Characteristics of the isolated (primary) dystonias			
Age at occurrence	<25 years	25–45 years	>45 years
Anatomic dissemination	**Generalized** Typical involvement of a limb, spreading to the head and the neck	**Focal** Dependent on certain movement (e.g. graphospasm)	**Focal** Head and neck, lower limbs are almost never involved

The differential diagnosis is focused first on differentiating dystonias from other motor disorders, such as tics and tremors. Second is the need to differentiate primary from secondary dystonia types. It requires searching for other clinical symptoms and signs, accompanying the dystonia. Similar ‘syndrome associations’ (e.g. dystonia and peripheral neuropathy, dystonia and Parkinsonism) may prove very useful in differential-diagnostic aspect. Medical history, suggesting symptomatic dystonia, includes encephalitis, intoxication with medicines or toxins (manganese and methanol), intake of neuroleptics, some anti-emetics and anti-vertiginous agents or levodopa and perinatal anoxia.

There are many reasons for hereditary-degenerative dystonias and the tests can be rather invasive and taking long period of time.

The diagnosis can be set by an expert in motor disorders interviewing and observing the patient and using clinical tests.

1. Medical History

- Is the dystonia mobile or fixed?
- Is it depending on certain movement or posture?

- Does it improve by touching or *geste antagoniste*?

- Caused by parallel contractions of agonist and antagonist muscles (it can be palpated by the examiner or recorded using EMG).

Does the patient have primary or secondary/degenerative dystonia? The most important is to estimate whether there are other symptoms and signs except dystonia, which differ from it (e.g. epileptic seizures, cognitive deficit, and Parkinsonism). Nevertheless, patients with secondary/degenerative dystonia may have clinical picture of dystonia only. The primary dystonias are characterized by anatomic distribution, depending on the age of occurrence. Provided the patient has unusual clinical picture for the age of its occurrence, for example lower limb dystonia in an adult patient, in such a case secondary/degenerative dystonia should be excluded.

In these cases there are other signs suggesting that dystonia is due to secondary/degenerative cause:

- Abnormal birth (perinatal medical history);
- Developmental retardation;
- Exposure to medical products in the past (dopamine receptor blockers);
- Sustained progression of the symptoms;
- Arrant bulbar inclusion by the dystonia;
- Unusual dystonia dissemination, related to the age of its occurrence;
- Atypical dystonia characteristics (such as fixed dystonia);
- Hemidystonia.

2. Neurological Status Investigation

The patient should be observed at rest, with arms stretched in front of his body and during slow pronation/supination of the arms to look for an abnormal position and tremor.

Examining the patient while walking (best without shoes and trousers rolled up) – screening for abnormal postures of the lower limbs/ the feet.

Watching the patient while writing to look for abnormal position of the writing hand, abnormal pressing of the sheet of paper by the other hand, as well as any movements of the hand, which does not write (mirror movements).

One should also look for other neurological signs and syndromes: Parkinsonism, myoclonus, pyramidal signs, retinopathy, eye movement distortions, and neuropathy. The patient should be examined also for systemic pathology (such as organomegaly).

The diagnostic test with levodopa should be administered in all young patients to exclude the possibility for presence of levodopa-responsive dystonia. The therapeutic dose is 300-600 mg/daily. It is taken at least for 2 months before assessing its effectiveness.

Neuroimaging methods such as computer tomography and magnetic resonance imaging could be helpful for differentiation of the secondary dystonias.

The genetic test may confirm mutation in DYT gene. The existence of mutation in the gene is not sufficient to verify the diagnosis of dystonia against lack of clinical evidences, because of the reduced penetrability (below 40%).

The neurologist should establish:

- Evidence for preceding intake of medications, traumas or illnesses
- Symptom dissemination and localization
- Presence of other motor disorders
- Presence of other neurological symptoms besides motor disorders
- Should conduct the diagnostic test with levodopa
- Should perform neuroimaging tests

Upon identifying the symptom, it is necessary to refer the patient to center of motor disorders with no use of other diagnostic methods.

The neurologist at the Center of motor disorders should define the etiological diagnosis using genetic test.

I. Primary (isolated) dystonia of an early onset

It is also known as primary, generalized, torsional dystonia or Oppenheim dystonia.

About 50–60% of the patients have DYT1 gene mutation of chromosome 9p.

DYT1 early onset primary dystonia is a result of GAG deletion in the DYT1 (dystonia 1) gene. DYT1 gene codes torsin A protein, which has a chaperon function within the cell and is expressed in highly dopaminergic areas in the brain. The DYT1 gene mutation appears in all ethnic groups, but it has high penetration in the Eskenazi Jews.

It is of autosomal-dominant inheritance, but it has strongly reduced penetrability: only 30% of the mutation carriers develop the illness. The penetrability is age-determined; provided mutation carrier reaches the age of 25 without developing any symptoms, it is very likely not to develop dystonia during his lifetime.

In **non-DYT1 primary dystonia of an early onset** the patients are negative to DYT1 mutation, so secondary or degenerative dystonia should be excluded and one should look for or monitor the development of newly emerging symptoms with time.

Clinically the onset of the dystonia is in the late childhood or early adolescence. Very typical is the onset from the distal parts of a particular limb. Most frequently, it starts from a lower, more seldom from an upper limb. The progression of the dystonia starting from a lower limb is more rapid (average 4.7 years) compared to the one started from an upper limb – average 11.4 years. Subsequently the dystonia disseminates within months to 2 years and usually ends up as generalized dystonia. Some patients may also develop focal/segmental symptoms. After that the symptoms reach plateau and though they may deepen or decrease, the development of new dystonic symptoms should turn the focus to revision of the diagnosis. It is unusual cranial and bulbar structures to be affected by the dystonia.

In **DYT1** some patients develop severe generalized dystonia, while others may just have mild focal dystonia of the limbs. Once the condition has reached its plateau, further progression is unusual. In the course of time, neurological complications may arise as a result of the dystonic poses (scoliosis, peripheral-nervous compression, myelopathy, associated with the spondylosis).

Non-DYT1 runs with a similar clinical phenotype and response to the treatment as in the patients with DYT1 mutations.

The differential diagnosis requires first and foremost excluding levodopa responsive dystonia. Some degenerative forms of dystonia may onset at early age, the first evidence being dystonia (Wilson's disease, NBIAS).

Investigations: If there are no signs suggesting secondary/degenerative dystonia it is reasonable to conduct the following tests:

- DYT1 gene testing. The genetic testing of DYT1 mutation is affordable and technically easy to perform.
- Copper, ceruloplasmin, testing for Kayser-Fleischer ring
- MRT of the cerebrum
- Diagnostic-therapeutic test with levodopa in all young patients.

II. Combined dystonias

1.2. Dystonia-plus syndromes

Only 2 dystonia-plus syndromes have been described: levodopa responsive dystonia and myoclonus dystonia

Levodopa Responsive Dystonia

Segawa syndrome (Dopa responsive dystonia/DRD) is completely curable illness, which may result in serious disability if not treated.

Etiologically it is associated with mutations of the quinidine triphosphate cyclohydrolase 1 gene of 14p chromosome (GTPCH1). The enzyme is responsible for the limitation of one step in the production of tetrahydrobiopterin (THB), which in its turn is an important co-factor in the production of dopamine from the tyramine. THB is needed for the conversion of phenylalanine into tyramine. Deficit of the central dopamine synthesis occurs. It has autosomal-dominant inheritance, of incomplete penetrability.

The morbidity rate is 0.5 - 1 per 1 million inhabitants, without ethnic predilection. Girls are affected 4 times more often than boys.

It is clinically manifested between the age of 2 and 5 years with progressing lower limb dystonia, often Parkinsonism and spasticity are being added. There is frequent diurnal variability of the symptoms, which get worse at the end of the day. The

improvement after sleep is due to the reduced use of dopamine. The dystonia gradually progresses, involving the arms, the axial musculature with deepening of the lumbar lordosis, scoliosis and occasionally torticollis and retrocollis. Within 4 – 5 years, all body parts are affected. The clinical expression is quite variable. Some patients have non-progressing dystonia of the arm, emerging in their twenties, which imitates graphospasm. The majority have severe early onset symptoms with additional signs due to inclusion of upper motor neuron (vivid tendon reflexes, spasticity, positive reflexes from the group of Babinski and Rossolimo), resembling children's cerebral paralysis or Strumpell's disease.

The differential diagnosis in the generalized torsional dystonia is very important in view of the different therapy. It should also be differentiated from the children's cerebral palsy. The Parkinson's disease, emerging in young age may start with levodopa responsive dystonia. Treatment with levodopa in young patients having Parkinson's disease should be postponed in time and therefore clear differentiation is required.

Investigations: It is recommended that all patients below 25 years, with dystonia having started at early age, to get *a diagnostic test with levodopa*.

Genetic test for mutations in GTPCH1 gene cannot be performed everywhere. The gene is very large and there are descriptions of many mutations, which makes the test very difficult.

In the *test for loading with phenylalanine*, a dose of 100 mg/kg is taken per os and immediately after that the level of phenylalanine is measured at 1, 2, 4 and 6 hour interval. The high levels after the loading suggest considering DRD.

The SPECT test (Datscan) is normal for DRD and abnormal in Parkinson's disease.

Myoclonus-dystonia and essential myoclonus

These are various manifestations of non-degenerative pedigree forms of myoclonus.

Most frequently, it has autosomal-dominant inheritance. About 30% of the patients have mutations in the epsilon-sarcoglycan gene of 7q chromosome. This gene

reveals ‘maternal imprinting’, which means that the children inheriting this defect from their mother almost never develop the disease.

Clinically it occurs in early childhood. The symptoms could be very mild and not detected immediately after their onset. The clinical status is usually expressed in myoclonic twitches, affecting mostly the neck and the arms. These twitches are so quick that they are also described as ‘flash’ or ‘tic-tac’ myoclonic twitches. There might be accompanying neck and arms dystonia, but usually it is very mild compared to the myoclonus. Usually both myoclonus and dystonia are influenced by alcohol consumption. Some patients may have additional psychiatric comorbidity such as obsessive-compulsive behavior, anxiety and depression.

Investigations: The myoclonus has a subcortical origin and neither encephalographic abnormities, nor gigantic somatosensory evoked potentials are found. Genetic testing is available only in few centers.

III. Status dystonicus

This is an urgent neurological condition in patients with existing dystonia, having acute and severe dystonia exacerbation. It is preceded by a triggering factor such as recent infections or change in the therapeutic regimen. The dystonic spasms can be quite severe, often causing bulbar and respiratory failure. Such patients should be hospitalized as an emergency in the intensive care unit for permanent monitoring. The continuous muscular spasms may result in rhabdomyolysis and subsequent renal failure.

IV. Isolated (Primary) Dystonias of Late Onset

1. Segmental dystonias

Cranial dystonias

Cranial dystonias pervade the face, mouth and mandible and are manifested as combinations of various focal dystonias: blepharospasm, lingual, orofacial, orofaciolingual, oromandibular, cervical dystonia, dystonic dysphonia and dysphagia. They may remain focal or progress into segmental.

Meige's Syndrome

The sporadic occurrence of the combination of oromandibular dystonias and blepharospasm is called cranial dystonia or Meige's syndrome.

This is the most frequent form of segmental cranial dystonia.

The blepharospasm and the oromandibular dystonia, when occurring independently, are in fact incomplete forms of Meige's syndrome. In some cases cervical dystonia, spasmodic dysphonia, dystonia of the limbs and tremor is being added.

Sometimes it is difficult to differentiate Meige's syndrome from the focal cranial dystonias.

Facial Hemispasm

This is chronically progressing form of segmental dystonia. Recently it is not considered as real dystonia.

Most often occurs in average age and both genders are equally affected.

Etiologically in many cases it is due to mechanical irritation of abnormal blood vessels in the area of the Obersteiner-Redlich zone of the radices of VII cranial nerve. More rarely some tumors, bone anomalies, Paget disease, multiple sclerosis and peripheral-stem injury of the nerve may cause the disease.

The pathophysiology is associated with impulse generation from the injured zone, exciting the nerve motor nucleus antidromically.

Clinically it starts just from the eyelids (m. orbicularis oculi), but later ~~on~~ other facial muscles on the same side are also affected. It is characterized by sudden, unilateral, synchronous, involuntary, episodic spasms of the muscles, innervated by VII cranial nerve. Occasionally the spasm can be bilateral. The muscular contraction may turn for a few seconds into tonic spasm.

The differential diagnosis is done with the blepharospasm, which causes bilaterally synchronic spasms of the muscles around the eye.

2. Focal Dystonias

Blepharospasm

The idiopathic blepharospasm is characterized by involuntary, transient or permanent, bilaterally synchronous spasms of the periorbital muscles.

The morbidity rate ranges between 13.3 and 30 per 100,000 inhabitants. Women are twice more affected than men.

Clinically it starts around 50 – 60 years of age. It is often preceded for years by a more frequent and strong blinking. 40 – 60% of the patients have photophobia, dryness, irritation, pain and discomfort of the eye, associated with the dry eyes syndrome, blepharitis or conjunctivitis. They play the role of triggering factors in patients with predisposition to this disease. In 20% of the patients it begins with unilateral spasms of the eye surrounding muscles (mm. orbicularis oculi), which results in closing the eyelids. The spasms gradually get stronger and after differently long period of time they involve both eyes. At the beginning the spasms are of clonus and later on of tonic nature. In some patients the clonus form (blepharoclonus) prevails during the entire course of the illness, distinguished by repetitive, rapid spasms closing the eyes, which resemble the normal blinking. In other patients (essential or dystonic blepharospasm) the continued muscular spasms, lasting seconds or minutes, prevail. In some patients as a result of contraction of the pre-tarsal part of m. orbicularis oculi, the blepharospasm resembles apraxia of the opening of the eyelids. The eyes of these patients are closed, with no visible spasm and they cannot open them.

The muscular spasms lead to closure of the eyes, inability to open them and functional blindness. Driving, reading, watching TV, walking and all social and labor activities get difficult.

Many patients invent their own tricks to suppress the spasms, such as touching or slightly pulling the eyelids, chewing, yawning, laughing, singing, mouth opening or talking.

Often during the first 5 years since the disease onset other facial muscles in the craniocervical area (frontalis, platysma и risorius) or the tongue, vocal strings, mandible and the neck are also involved turning it into segmental craniocervical dystonia. Most often Meige’s syndrome is being developed. Particularly predisposed to dystonia expansion are the females, the patients with onset of the disease at a more mature age

or who have had preceding head trauma. Frequently Parkinsonism and postural tremor, having the characteristics of the essential, are added.

Differentially-diagnostically it should be distinguished from conjunctivitis, which may cause frequent blinking; therefore consultation with ophthalmologist is required. The Sjogren's syndrome leads to dry eyes and closure of the eyelids. It must be differentiated from the eyelid ptosis due to paresis of III cranial nerve, myasthenia and Horner's syndrome (lesion of the cervical sympathetic fibers). The apraxia of the eyelid opening in progressive supra-nuclear paralysis, Parkinson disease, Wilson disease and Huntington disease is characterized by inability for voluntary opening of the eyelids due to disturbed contraction of the levator muscle. The tics imitate blepharospasm or facial hemispasm and the differential diagnosis is difficult if the tics involve other body parts ~~as well~~. Psychogenic blepharospasm is characterized by pressing the eyelids, which twitch all the time.

The disease is chronically progressive. Spontaneous partial or full remissions are observed rarely (13%), in the first 5 years and are followed by variably long period of new exacerbation of the disease.

Oro-mandibular dystonia

It can rarely be just isolated, more frequently it combines with blepharospasm such as Meige's syndrome or with blepharospasm and cervical dystonia under the name of craniocervical dystonia.

It is observed more often in females.

Clinically it starts between 40 and 70 years of age, affecting bilaterally the lower facial, masticatory and lingual muscles. The involvement of the masticatory muscles may cause any combination of mandible opening, closing, and dislocation laterally, inwards or outwards. These movements bring about involuntary teeth clenching, tongue, lips, cheeks biting and difficulties to talk and chew. The spasm of the mandible closing muscles, together with the contractions of m. temporalis and m. masseter, can cause trismus and bruxism. The involvement of the lower facial muscles (orofacial dystonia) results in making grimaces involving m. platysma and the lips. The tongue involvement is manifested in movements outwards, upwards or to one side. These

movements disturb the articulation, feeding and pronouncing some sounds. The impact on neighboring areas is frequent and dysphonia or nasal muscle contraction may be added. Also the pharyngeal muscles may get affected with occurrence of dysarthria, dysphagia, dysphonia, breathing difficulty and involuntary giving out of sounds. The dystonia may go on permanently, even during sleep or be associated only with certain actions, such as speaking, chewing. Some sensory tics such as touching the chin, chewing gum or tooth pick, talking or the submental area pressure alleviates the dystonia. In some patients however dystonia is provoked by talking or chewing. Often essential tremor may also be added.

This disease is strongly incapacitating because it causes jaw pains, dysarthria and difficulty in chewing and feeding

The differential diagnosis includes tics, bruxism, facial hemispasm, tetanus, disease of Whipple and of Huntington, myotonia and myasthenia.

Cervical dystonia (torticollis spastica)

It may be manifested independently or as part of a segmental (cervicobrachial or craniobrachial) or generalized dystonia.

The morbidity rate is 30 patients per 100,000 inhabitants. This is the most common focal dystonia. It is twice more frequent in females.

Etiologically the idiopathic form prevails, while the symptomatic dystonia may occur following a neuroleptic treatment.

Clinically it starts between the age of 40 and 50 years, but it may well be manifested at any age. The onset of the disease is acute or subacute, with clamping or pulling sensation in the neck area. The first symptoms can be pain in the neck or head tremor. Gradually distortion of the head and shoulder posture appears due to clonic or tonic contractions of the cervical musculature.

20 pairs of muscles take part in the head and neck movements, which allow moving the head in three directions (flexion - extension, rotation and lateral bending). Many of the neck muscles are involved in various combinations and because of that the strength and the direction of the movements is differently expressed. It predetermines the various cervical dystonia types as well. Most often (in torticollis) affected are m.

sternocleidomastoideus on the one side and the posterior cervical muscles (m. splenius capitis) on the other, where the head is turned laterally and bends to the side of the contralateral shoulder, which might be raised and dislodged forward. Occasionally mildly expressed dystonia in the proximal muscles of the arm is also found. More seldom the head can be bent forward (anterocollis), backward (retrocollis) or to the side (laterocollis) due to participation of other muscle groups. Many other cervical muscles may be involved, such as trapezius, levator scapulae и scalenus.

The dystonia manifestation varies from mild to very severe, when the patient cannot be looked into the eyes. It gets intensified by stress, pressure, in certain postures and while walking; diminishes when lying or using various sensory tricks and disappears during sleep.

The presence of salient pain is particularly typical because of the participation of large muscles in the dystonia as well the multitude of pain receptors, localized in the cervical muscles. The pain is more pronounced in patients with permanently fixed head deviation. In long lasting disease, there is muscular hypertrophy and contractures, as well as spondylotic changes in the cervical vertebra and subsequent radicular myelopathies, with a strongly expressed pain, spreading out to the arm.

During the progression of the disease, 30% of the patients may experience head or arms tremor, myoclonia, facial spasms, graphospasm, dystonia of the shoulder, arm or the whole body, as well as other dystonia types.

The disease progresses slower or faster. Its development goes into three stages. The first stage of slow progression continues ~~for~~ 5 years, followed by a second five year period of stationing and a third period of mild improvement. For 30% of the patients this dystonia type may turn into segmental, involving the shoulder zone, the arm or the oromandibular area. The disease is incapacitating for the patients and disrupts their daily routines, even when mildly expressed.

The differential diagnosis is verified against damages of the cervical vertebrae (malformations, subluxation of the atlantoaxial joint, cervical osteomyelitis), muscles (fibrosis) and discs (disc prolapse), causing mechanical difficulties in the neck motion. Quite common is the congenital contracture of m. sternocleidomastoideus, malformation of Arnold-Chiari and of Klippel-Feil. Lesions in VIII and XI cranial nerves, tumors in the

rear cranial axilla as well as lesions in the cervical section of the spinal cord may result in changing the position of the head and should be taken into account in the differential diagnosis. It is also necessary to differentiate it from the neck tremor, which does not cause deviation of the head but only rhythmic oscillations.

Laryngeal (spasmodic, spastic) dysphonia

This is an idiopathic motor disorder of the vocal strings.

It is **more common** in females.

Clinically the onset of the disease is between 30 and 50 years of age. It starts gradually with disturbed control of the voice volume and amplitude in stressful situations, which progresses in the next years. No damages or limitations in the movement of the vocal string are found except for the speech and the symptoms get more intense after speaking for a long time. The disease is associated with performance of certain acts by the larynx – the speech gets disturbed, whispering and singing is slightly disturbed too, which does not show in laughter, crying or cough. As in the other focal dystonias some sensory tricks, such as pressing the neck or the abdomen with a hand, may temporarily relieve the dysphonia. It occurs in two forms – adductor and abductor. Combined forms are rare.

The adductor form is displayed by transient and not rhythmic hyperadduction (closure) of the vocal strings at the beginning and during the phonation, especially when pronouncing vowels. It results in a difficult air passage through the vocal strings and disturbance of their vibrations.

Clinically it is manifested by a slower speech requiring more effort, drop of the voice volume, voice interruptions and periodically getting hoarse. The speech fluency is disturbed, yet the singing ability is relatively preserved.

The abductor form is more seldom and is characterized by hyperabduction (opening) of the vocal strings due to contraction of mm. cricoarytenoideus posterior, expressed predominantly when pronouncing consonants, which results in their delayed pronunciation and changes in the voice tone.

The patients often have a gasping, poor voice because of disturbed coordination between breathing and speaking. The voice volume is dropped; some words are whispered in aphonic voice.

Voice tremor may be noticed in about 20% of the patients in both forms of the disease and it may precede the manifestation of the dystonia.

The disease progresses during the first 1-2 years, thereafter it stabilizes and remains chronic. In 20-30% of the patients this form of dystonia may involve the cranial or cervical area.

The diagnosis can be verified following observation via nasolaryngoscopy of the vocal strings movement.

The differential diagnosis includes structural injuries of the larynx and vocal strings, myasthenia, amyotrophic lateral sclerosis, cerebellar or Parkinson's dysphonia, essential voice tremor.

Limb dystonias

They are characterized by involuntary transient or constant muscle contraction resulting in torsional, repetitive movements or abnormal limb positions.

They are classified according to the area, which is affected as: focal – affecting one limb joint, segmental – affecting one limb joint and adjoining body part, multifocal – affecting a multitude of non-adjacent limb parts, hemidystonia – affecting upper and lower limb and generalized – affecting several joints in the four limbs. The limb dystonias can be divided into fixed and associated with certain muscular activity.

Fixed dystonias are most often of action type, laid onto performing voluntary movement. They may involve any joint of the upper and lower limbs. More often they affect the distal joints of the lower limbs – ankle joints with plantar flexion and foot inversion and toes flexion. If they start in early age this is most often an onset of a generalized dystonia. If occurring after the age of 20, it is possible to originate due to structural lesion of the central nervous system, Parkinson's syndrome or an early onset of Parkinson's disease.

Clinically at the beginning the symptoms are manifested primarily with an attempt to walk and are absent at rest. They can be suppressed with running and walking backwards. The initial equinovarus foot position in walking may transform into fixed dystonic position, causing plantar flexion, knee joint extension, extension, inner rotation and abduction of the coxal joint. Fixed poses are more typical for the lower limbs.

When the upper limbs are affected, primarily the distal sections are involved, but it may also involve the shoulder joint and the neck. There might be wrist flexion, ulnar deviation, supination, inner rotation, elevation or abduction of the arm. They are frequently combined with essential tremor or other focal dystonias – cervical or blepharospasm.

Dystonias, associated with specific muscular activity, (occupational dystonias) are characterized by disturbing the movements, associated with specific motor activity. They may be present in any profession, requiring performance of repetitive, accurate and complex coordinated movements. More often are affected the upper limbs and the flexor muscle groups in people, performing precise and frequently repeated rehearsed movements. The lower limbs are affected more seldom, since they are not usually used for precise and repetitive movements. This group of dystonia types includes the graphospasm, occupational dystonias, dystonias in musicians and dystonias in sportsmen. They are of focal and action type – the dystonic pose is super-pronated onto the voluntary movement, associated with performing certain action.

Clinically the disease starts gradually with a feeling of discomfort and constriction in the respective limb. Gradually these complaints get stronger and the attempt to perform the specific movement causes muscle spasms, which makes its performance harder. All other movements are performed with no causing of muscular spasm. In the course of development of these simple cramps (covering one automated act), difficulties may also occur in performing other actions, such as handwriting or typing, playing various musical instruments, buttoning buttons, use of screwdriver, bottle opening, use of a knife and a fork, etc. The patients try to compensate their awkwardness by inclusion of more proximal muscle groups. When there are muscular cramps in performing several actions we speak about dystonic cramps, while in case of progressive difficulty in performing more and more new actions the word is about

progressive cramps. In some patients with the disease progression the dystonia persists even when the limb is at rest. Tremor, myoclonias and Parkinson's symptoms in the same limb may add up.

Graphospasm is the most common occupational dystonia. It is well manifested still with taking the pen or writing a few words by tightly holding the pen. The position of the hand and the fingers is strange, with hyperflexion of the fingers (most often the first three) and hyperflexion, hyperextension, pronation or supination of the wrist, raising the elbow and hyper-adduction and raising of the shoulder. It results in constriction, heaviness and pain in the hand and writing disturbance. Writing gets difficult, uneven and with trembling. Upon having written a few words writing becomes impossible. Hyperextension of the fingers may occur, which does not allow holding the pen. Trying to cope with this problem the patients include the proximal muscle groups of the hand in writing or start writing with the other hand. It results in the proximal muscle groups the other limb also being affected by the dystonia. Some patients succeed to write on a blackboard or stabilize their writing hand with the healthy one or write with a thinner pen. When the dystonia affects just the writing, it is called 'simple'. If the ability to perform other activities, such as buttoning up, using a screwdriver, shaving or playing a musical instrument is disturbed, then the dystonia is called 'dystonic'. 30% of the patients may experience postural symmetric tremor of the hands or tremor at writing.

The disease course can be stable or progressing. The dystonia progresses from simple to dystonic in 30% of the patients. In 15-25% of the patients the other hand may also be affected. Months or years after the onset of the disease it may also cover adjacent areas.

As to *differential diagnosis,* one should take into account that graphospasm can be an onset of idiopathic generalized torsional dystonia, Parkinson's diseases or progressive supra-nuclear paralysis.

Dystonia when typing on a typewriter or computer is rarer than graphospasm and it usually starts from the last fingers of the hand.

Other occupational dystonias incorporate dystonia in tailors, watchmakers, milkmen, shoemakers, painters, knife grinders, dancers, traders and many other occupations. Laryngeal dystonia may be present in teachers.

Dystonia in musicians is extremely unfavorable for the professional career of the patients. It can appear in using any musical instrument, but it is more common with piano and keyboard instruments. It may also occur in playing a guitar and other string instruments, trumpet, violoncello and other brass musical instruments. The musicians rehearsing precise and complex movements to achieve professional success are particularly predisposed to the disease. It occurs in 1 of each 200 musicians, while for the population the incidence is 1 of each 3400. Usually dystonia is focal and non-progressive. In musicians using their upper limbs to play it starts from the last fingers. In pianists there is flexion predominantly on IV and V finger, in guitar players – flexion of III finger and in clarinetists – extension of III finger. Musicians playing on brass instruments may get dystonia of the mouth and the neck.

Dystonia in sportsmen involves various sports activities. It may occur in playing golf, tennis, billiard, bowling, javelin throw, etc. In rare cases it may affect the lower limbs in bicyclist. It is present in 28% of the golf players and is more frequent in those, who have played for many years.

The differential diagnosis includes tendovaginitis, carpal syndrome, and distortion of handwriting in patients with Parkinson and tremor of other etiology.

Axial dystonias

They encompass the axial body muscles and result in abnormal postures, more seldom — in abnormal movements. These dystonia types include scoliosis and camptocormia.

Primary scoliosis appears in adolescence in 80% of all the cases and can be hereditary. It is not manifested by dystonias in other anatomic areas, but can well be just an early manifestation of the primary torsional dystonia.

Dystonic camptocormia is a postural dystonia, which progressively bends the trunk forward and is manifested or reinforced in standing position or when walking. Occasionally the dystonia is more rapid and is denoted by the term of ‘woodpecker dystonia’. The term ‘Pisa syndrome’ designates the progressive lateral bend of the body when standing up and walking.

The sensory tricks, which temporarily improve the axial dystonia, include leaning the body against a wall, pressing the neck or the thighs.

Treatment of Isolated (Primary) Dystonias

1. Generalized dystonias: Pharmacotherapy is used for treating generalized dystonia. The botulinum toxin has a tiny role in the treatment of generalized dystonia. Isolated parts, covered by the dystonia, such as the dominant hand, can be treated with botulinum toxin to reduce the disability.

The treatment starts with **levodopa** in order to check if the patient does not fall in the group of levodopa responsive dystonia. Dosing is gradually increased at least to 4 times of 250 mg daily. Moreover the side effects (motor fluctuations and dyskinesia) are the least and appear seldom and late in time.

It is assumed that levodopa is not effective provided there is no clinical response after 3 month therapy.

The treatment of ***levodopa responsive dystonia*** is conducted with levodopa. Usually excellent long-term control of the symptoms is achieved and all this by administering low doses (200-400 mg levodopa daily). Levodopa should be gradually introduced.

Dopamine agonists also have an effect in levodopa responsive dystonia.

Provided levodopa is not effective the patient should start treatment with trihexyphenidyl.

Anticholinergic medications (trihexyphenidyl 12 mg daily) are second choice medication, following levodopa. Given in high doses they are effective in 20-40% of primarily the younger patients. The doses are gradually increased from 2 mg daily to the maximum tolerable by the patient. Sometimes a daily dose of 60-100 mg is needed to have an effect. The side effects are numerous (hallucinations, memory disturbances) and the activity of these medications is depleted in about 1 year.

Anti-dopaminergic medications – blockers of dopamine receptors (haloperidol) and medications, depleting the dopamine depots (tetrabenazine, reserpine) are well tolerated by some patients. The most frequently used anti-dopaminergic medications are the phenotiazines, clozapine, haloperidol, risperidone and tetrabenazine. Using this

group of medications is not recommended because of the numerous adverse effects, including also late dyskinesias.

Tetrabenazine 100-200 mg daily is effective in patients having late dystonia and it has the advantage of not causing late dyskinesia, but it may cause transient acute dystonic reactions.

Baclofen is $GABA_B$-receptor agonist and has a good effect in 20% of the patients, especially in patients with segmental cranial dystonia. Baclofen in a daily dose ranging from 75 to 100 mg is administered if there is no effect of the anticholinergic medications or in case of individual intolerance.

Benzodiazepines (clonazepam), carbamazepine and phenothiazine preparations may occasionally render good result, particularly in cases of facial hemispasm, blepharospasm and Meige's syndrome.

Combined therapy includes triple combination of dopamine depot depleting medication, dopamine receptor blocker and anticholinergic medication or anticholinergic medications and benzodiazepines.

Status dystonicus is treated with benzodiazepines, anticholinergic products, botulinum toxin and respiratory resuscitation. In some patients the urgent pallidotomy or deep brain stimulation are successful methods of treatment. Most patients recover spontaneously just on maintenance therapy.

Deep brain stimulation (DBS) of nucleus medialis of globus pallidus internus (GPi) may enjoy excellent and long-lasting effect in patients with primary dystonia. This method has replaced long ago the destructive neurosurgical operations, such as pallido- and thalamotomy.

Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex zones is getting more and more used as therapeutic method in most forms of generalized dystonia, where the therapeutic alternatives are often ineffective.

2. Focal and segmental dystonias are treated by injecting locally type A botulinum toxin in the affected muscles. AbobotulinumtoxinA (Dysport – clostridium botulinum type A toxin-haemagglutinin complex) in small bottles of 300 U, onabotulinumtoxinA (Botox) in small bottles of 50 and 100 U or incobotulinumtoxinA (Xeomin) in small bottles of 100 U is being administered. The recommended neurotoxin

doses differ for the different symptoms and depend on the particularly affected muscles. The average administered dose is up to 600 U Dysport or up to 200 U Botox or Xeomin in one session. The most commonly used ratio in the clinical practice is approximately Dysport : Botox : Xeomin = 2,5 : 1 : 1

The botulinum toxin, registered in China, contains bovine gelatin protein, which has the potential to trigger immune responses and allergic reactions. The risk of transmitting spongiform encephalopathy (‘wild cow’ illness) should not be underestimated.

The most common fast transient adverse effects are local muscle weakness in case of higher dose injection or weakness in adjacent muscles due to diffusion of the toxin. The potential long term effects resulting from the frequent toxin use include formation of neutralizing serum antibodies to the botulinum toxin and clinical resistance to subsequent application. Applying botulinum toxin type B (rimabotulinumtoxinB) in such cases has clinical effect. In order to avoid these side effects minimum effective quantities of the toxin should be administered not more often than each 4 months.

Dystonia treatment

Dystonia severity	**Dystonia localization**	**Core treatment**	**Supplementary treatment**	**Comments**
Mild	Focal	AT/None	-	AT or the treatment is postponed
	Disseminated	AT/ None	-	
Moderately severe	Focal	BT	RT (by choice)	In anterocollis and alternating torticollis - DBS
	Disseminated	BT	RT (by choice)	
Severe	Focal	BT	RT ADP (by choice) AT (by choice)	If BT has unsatisfactory effect - DBS

	Disseminated	BT	RT ADP (by choice) AT (by choice)	Initially BT or directly DBS
		DBS	RT BT (by choice) ADP (by choice) AT (by choice)	

AT – Adjuvant Therapy (analgesics, anxiolytics), ADP – Anti-Dystonic Products, BT – botulinum toxin, DBS – Deep Brain Stimulation, RT – Rehabilitative Therapy

The therapy with botulinum toxin should be ambulatory, conducted by a specialist especially trained in botulinum therapy.

Criteria for treatment of focal dystonia with abobotulinumtoxinA (Dysport – clostridium botulinum type A toxin-haemagglutinin complex), onabotulinumtoxinA (Botox) or incobotulinumtoxinA (Xeomin)

I. Inclusive:

- Focal dystonia diagnosed in a University hospital
- Injected by a neurologist, trained to inject botulinum toxin.
- Injected once each 4 months in a minimally required doses (abobotulinumtoxinA 300-600 U or onabotulinumtoxinA and incobotulinumtoxinA 100-200 U).
- Each 4 months prior to the injection neurological check-up in a University hospital should be conducted aiming to establish any change in the dystonia pattern.
- Follow up check should also be performed 1 month after each injection by the neurologist, having injected the medication for verifying the therapeutic effect and the necessity of correction of the botulinum toxin dose.

II. Excluding:

- Pregnancy

- Severe somatic disease

III. Treatment is not applied or if started is discontinued if:

- The patient gets pregnant
- There are serious adverse reactions from the treatment
- The dosing scheme is systematically not adhered by the patient
- Clinical effectiveness of the treatment is lacking

2. Chorea

'Chorea' originates from the Greek word *horos* – dance.

It represents involuntary, uninterrupted, rapid, scattered, non-rhythmic and useless motion, which runs from one body part to another. People with chorea seem restless and nervous.

Chorea can be generalized, localized only in one area (e.g. the face) or affecting half of the body (hemichorea). Hemichorea and hemibalismus may occur with any interruption of the strio-pallido-subthalamic-paladar connections due to lesions of the contralateral subthalamic nucleus, putamen, outer pallidum, and thalamus or corona radiata. The reduction of the suppressing efferentation to the lateral pallidum and the sub-thalamic nucleus releases the outer segment of globus pallidus from the suppressing impact of the striatum with subsequent excessive suppression of the activity of the sub-thalamic nucleus, reduced activation of the inner segment of globus pallidus and decreased inhibition of the thalamus. All this results in enhanced cortical excitation and choreic hyperkinesis.

Clinically the chorea severity varies from inability to stay calm and awkward movements, imitating nervousness to tempestuous movements of the limbs and the axial muscles, which hinder the voluntary activity. These movements vault over to various parts of the body, shoulders, abdominal muscles, fingers and toes, head, lips and forehead with no tendency of repetitiveness in one and the same muscle group. Phenomenon, known as parakinesia, namely inclusion of involuntary choreic movements in visibly purposeful movements and gestures, can be observed quite often. The choreic movements themselves are not disabling for the patients and they can

manage well their daily routine. These patients are more frequently disabled by the accompanying symptoms: bradykinesia, rigidity, dystonia and postural instability.

Often the muscle tone of the limbs is reduced (hypotonia), and the tendon reflexes are ‘bouncing’. This is due to the muscle contraction, occurring immediately after the reflexive response due to the stretch of the muscle.

The differential diagnosis when compared to the tics, myoclonia and dystonia is based on the key sign of chorea, namely the transfer of the muscle activity to various muscle groups, which distinguishes it from them. The tics can be suppressed for a long time, while the myoclonic movements are very fast and do not spread out as a wave along the affected section, as is the case with chorea.

The choreoathetosis is being used as an alternative concept for chorea. The athetose movements are distal, slow and resembling convulsions. It is proper for them to be defined as dystonic, not as choreic. It is recently recommended this term to be avoided, as the slow, convulsion-like movement can be seen within the frames of dystonia and are entirely different from the chorea.

Ballismus is a severely manifested proximal chorea, in which the patient has very vividly displayed scattered movements. If these movements involve only one limb, then it is called monoballism, if only one part of the body is involved - the phenomenon is called hemiballismus. Usually the etiological cause of hemiballismus is vascular. Lesion is detected in or very close to the contralateral sub-thalamic nucleus.

The neurologist should establish:

- Data about preceding intake of medicines, traumas or illnesses
- Dissemination and localization of the symptom
- Existence of other motor disorders
- Presence of other neurological symptoms besides motor disorders
- Perform neuroimaging tests

Upon identifying the symptom it is necessary to refer the patient to a Center of motor disorder, without using any other diagnostic methods.

The neurologist in the center of motor disorders should clarify the etiologic diagnosis using:

- Genetic test
- Neuropsychological tests

2.1. Huntington's Chorea

The disease is described first by George Huntington and has taken his name.

It is characterized by progressing behavioral disturbances as well as motor disorders, usually chorea.

The morbidity ranges from 4 to 8 patients per 100,000 people. Some populations in Scotland and Venezuela have higher morbidity rates. The morbidity rate is lower among Japanese, Finns and Afro-Americans. Genders are equally affected.

Its etiology is associated with mutation of gene IT15, localized in the short arm of 4 chromosome. The gene codifies a protein, consisting of over 3140 amino-acids, called huntingtin, whose function is unknown. It has autosomal-dominant inheritance.

The pathogenesis is degenerative, associated with premature death of neurons in the basal ganglia due to aggregation of the mutant huntingtin protein in the cytoplasm and the neuronal nuclei. During the early stages of the disease primarily the middle sharp-pointed efferent striatal neurons (containing GABA and enkephalin), connected with projections to the outer segment of globus pallidus perish. This preferential loss of neurons leads to breaking the balance between the direct and indirect extrapyramidal pathway and the appearance of chorea. Later on the striatal efferents to the medial pallidum are affected, which results in rigidity and dystonia.

Pathoanatomically widespread brain lesions are found – frontal and parietal cortex atrophy, atrophy of nucleus caudatus, putamen and of the outer pallidary segment.

Clinically the age at onset varies; most frequently it is manifested in the fourth decade. Early onset of the disease is rare and can be manifested more with Parkinsonism rather than with chorea (variant of Westphal).

The disease is of heterogeneous phenotype and may start with psychic and behavioral disorders, neurological symptoms or with both.

The initial mental and behavioral symptoms are revealed in lack of inhibitions, having inadequate and indecent behavior in public, disorganization, apathy, depression or paranoia. Usually the cognitive functions are intact. Later on the attention and concentration are disturbed, as well as the ability of acquiring new information. The intellect is on a decline; the patients become less communicative and socially withdrawn. Dementia gradually develops, which is characterized as subcortical due to the prevalence of bradyphrenia and attention disturbances with lack of cortical deficit, aphasia, agnosia and apraxia. The executive functions – capacity for planning and performing complex tasks – are selectively damaged, due to an injury of the frontal-striatal circles.

The initial neurological symptoms and signs are chorea with or without tics, gait disturbance and coordination disorders. The chorea and the tics often affect the face, resulting in the typical rapid change of the facial expression in these patients (‘grimacing’). They always experience difficulty to keep one pose, for example sticking out the tongue, for a longer period. The gait is strange and more impaired than it can be related to the chorea phase. Hypotonia may be present, which later ~~on~~ is replaced by increased muscle tone and affecting the upper motor neuron. With the disease progression chorea is replaced by more clear dystonias and Parkinson’s syndrome.

The supra-nuclear paresis of the oculomotor nerve is one of the earliest manifestations. The disturbances of the ocular movements include delayed hypo-metric saccades, impossible keeping and ‘distracting’ of the gaze and difficulty in the saccades initiation. The patients blink or use ‘swaying’ the head in order to move their gaze from one point to another.

Sleep disturbances are frequent, revealed by daily hyper-somnolence, night insomnia, difficulty falling asleep, frequent wake-ups and shortened slow-waved sleep.

The differential diagnosis is verified with huntington-like syndromes. These are rare hereditary diseases, having clinical picture similar to Huntington’s disease.

- HDL-1 – prion disease with dominant inheritance, due to 192 base pair insertion in the coding region of the prion protein gene.

- HDL-2 – autosomal-dominant disease of similar clinical characteristic as Huntington's disease, due to mutations in juctophillin-3 gene. It is reported only in Afro-Americans.
- HDL-3 – autosomal-recessive disease, associated with chromosome 4p15.3. The patients are children with Huntington-like phenotype. The gene, causing this disease is still unknown.
- HDL-4 is the same disease as spinocerebellar ataxia type 17 (SCA17), with autosomal-dominant inheritance and variable presentation. It is due to extended CAG repeats in TBP gene in chromosome 6.

It is also necessary that the disease is differentiated from other autosomal-dominant choreic syndromes such as the benign hereditary chorea and dentorubropallidoluysic atrophy (DRPLA), other choreic syndromes with non-dominant inheritance, such as Wilson's disease, neuroacanthocytosis and mitochondrial diseases as well as a number of disease with choreic symptoms. The gluten enteropathy (celiac disease) may also progress with chorea and cognitive decline. One should also have in mind immune, metabolic, vascular, drug, infectious and intoxication-dependent choreic syndromes.

The diagnosis is verified by genetic testing. The presence of huntingtin gene (with many repeats of CAG) does not mean that the patient's symptoms are caused by Huntington's disease, as this gene is detected during the entire lifetime. Testing for the gene requires blood sampling, but other tissue can also be used, such as skin, amniocytes (or cells from the chorionic villi) or autopsy material.

The imaging tests display atrophy of nucleus caudatus and putamen. Measuring the bi-caudal diameter (the shortest linear distance between the heads of the two nucl. caudatus) is an easy and real marker of the disease.

2.2. Early Onset Huntington's Disease Forms

The occurrence of the disease before the age of 20 is classified as juvenile Huntington's disease, while this starting earlier at the age of 10 is known as Huntington's disease during childhood. The earlier the disease occurs, the shorter the survival time and is usually less than 15 years.

The most common juvenile form is transmitted from the father, due to the instability of the length of the CAG repeats during the spermatogenesis, which is increased, if the father has many repeats.

Clinically the characteristic of the juvenile form differs from that in adult patients. Chorea, as clinical manifestation, is presented in a much milder degree and it may be totally lacking.

The initial symptoms include disturbance of the attention and behavior, failure at school, dystonia, bradykinesia and occasionally tremor. Speech and language problems may emerge at the very onset of the disease and thus hint to the diagnosis. The cognitive disorders are progressing. Later on depression, anxiety, obsession, attention deficit hyperactivity disorder (ADHD), apathy, impulsiveness and irritability occur. With time comes weight loss, poor hygiene and during the late stages of the disease – aspirational pneumonia.

Epileptic seizures, which are very rare in adult patients, may be present in the juvenile form (30% of the adolescents with Huntington's chorea), as well as psychosomatic symptoms.

Quite often the clinical picture is dominated by cerebellar symptoms, rigidity, bradykinesia, dystonias with torsion, inclining, turning, twisting of the neck (torticollis), opisthotonus, as well as feet equinovaris. The dystonias are symptoms of the disease or result of the neuroleptic treatment. Rigidity and spasticity are often manifested at the very onset of the disease in children. These symptoms may impede the gait, cause falls and outline the need to use a wheelchair.

The diagnostic criteria for an onset in childhood (≤10 years) require exploring family history for Huntington's disease (usually the father) and 2 or more of the following:

- Poorer grades at school
- Epileptic seizures
- Oro-motor dysfunction
- Rigidity
- Gait disturbance

The course of the disease in young age is rapid and progressive. Three phases of the disease in children are being described: Initial phase of behavioral disorder, school problems, gait disturbance and mild chorea; more violent phase with signs of mental retardation, rigidity, speech disorders and epileptic seizures; and terminal phase, when the patients are bed-stricken, with muscle hypotonia and frequent epileptic seizures.

Investigations: More than 60 repeats of CAG in the genetic test presume juvenile Huntington's disease.

MRI findings display changes in the volume of the striatums and other brain areas, such as thalamus, hypothalamus, hippocampus, amygdala, cerebellum, frontal and insular cortex as well as atrophic changes of nucleus caudatus and putamen.

PET is more sensitive and specific methodology for the juvenile form as it can register hypometabolism in n. caudatus and putamen, as well as in the posterior thalamic nuclei.

The electroencephalography (EEG) in the juvenile form reveals paroxysmal phenomena.

Treatment of Huntington's Chorea

The treatment is symptomatic since the slowly progressing degeneration of the basal ganglia cannot be ceased.

Dopamine antagonists (haloperidol 2 to 10 mg daily) and dopamine depot depleting medications (reserpine, tetrabenazine) can sustain chorea for certain period of time, but they reinforce the rigidity, bradykinesia and depression. When the choreic hyperkinesias disable the patient, treatment with minimal effective doses of neuroleptics should be initiated. With time the chorea expression decreases, necessitating dose reduction.

Tetrabenazine 100-200 mg daily is medication at first choice since it does not provoke late dyskinesia. The therapy starts with a dose of 12.5 mg twice daily and dosing is slowly titrated increasing it by 25 mg weekly. The major adverse effects are somnolence, general weakness, depression, Parkinson symptoms and acute akathisia, which respond positively to dose reduction.

The selective D_4 receptor antagonist *clozapine* (50-200 mg/day) is also effective in choreic hyperkinesias.

The pharmacological effect on the choreic syndrome does not affect the motor act. Bradykinesia and rigidity respond to levodopa or dopamine agonists, yet it may lead to intensifying the chorea and dystonia symptoms as well as provoking psychosis and hallucinations. Dystonia cannot get relieved by medications.

As to the irritability and impulsiveness, combination of haloperidol and lithium carbonate has better effect than monotherapy. Risperidone improves the abnormal involuntary movements and psychotic occurrences.

Olanzapine is an alternative primarily for controlling the psychotic manifestations.

The treatment of epileptic seizures is dependent on their nature. In case of juvenile onset of the disease, myoclonic epilepsy or generalized seizures, treatment with divalproex sodium should start.

3. Tics

These are sudden, short time (about 100 ms), fast, useless, non-rhythmically repetitive stereotype movements or sounds. They are preceded by inner tension and necessity of performing the movement, which cannot be voluntarily suppressed for long and disappears after the movement is being performed.

The morbidity rate is highest in the childhood, reaching up to 20% of the school-age children. For the majority of children in this age group these tics are transient and spontaneously disappear.

The etiology of the primary (idiopathic) tics is associated with a genetic predisposition. The secondary (symptomatic) tics are associated with various neurological diseases like encephalitis, cerebral infarction, cerebral trauma, carbon oxide poisoning, neuroacanthocytosis and multitude degenerative neurological diseases, damaging the basal ganglia. Various medications may provoke or strengthen the tics.

The pathogenesis is associated with hyper-function of the central dopaminergic pathways.

They are classified according to their *origin* as primary and secondary, according to *the affected* muscle groups as motor and vocal, and according to *the complexity* – as simple and complex. The motor tics are subdivided into fast (clonic) and dystonic (slower). The simple motor tics are sudden, short-time repetitive stereotype movements of isolated muscles. The complex motor tics consist of coordinated muscular contractions in various muscle groups, organized in a certain order, which results in complex series of movements, which seem purposive. They involve copropraxia (obscene gestures) and echopraxia (repeating movements, performed by other people).

The vocal tics are sounds, caused by the air passing through the nose, mouth or throat. Simple vocal tics include various non-articulated noises and sounds like clearing up throat, tussiculation, grunting. The complex vocal tics have linguistic meaning and consist of full or fractured words as echolalia (repetition of the words of others), palilalia (repetition of own words) and coprolalia (obscene words).

The primary (idiopathic) tics are divided into transient and chronic. The transient tics continue over 1 month but less than 1 year and the diagnosis is set retrospectively after they disappear.

Clinically the tics have sudden onset. They may engage one muscle or numerous muscle groups. Tic severity varies from barely visible ‘neurotic habits’ to severe and complex. In the same way the severity of the vocal tics varies from separate sounds to words and sentences. The tics are characterized by their dependence on the situation – they get strengthened by some medications (primarily stimulants), tension, pain, excitement and fatigue, while during sleep they may either disappear or persist.

The differential diagnostics should distinguish tics from the other fast movements such as chorea, myoclonia, late dyskinesia, levodopa-induced dyskinesia, hyperekplexia, psychogenic motor disorders, and obsessive rituals, the stereotypies in psychotic patients, akathisia, habitual gestures and mannerism. Tics are differentiated from other hyperkinesias by the possibility for their voluntary suppression, inconstant manifestation in time and persistence during sleep.

3.1. Idiopathic motor tics

The etiology is associated with hereditary predisposition. They are often reported in patients from families, where there is a patient with the syndrome of Tourette.

They affect three times more frequently the boys.

Clinically they first manifest in childhood or early adolescence, most often around the age of 7 years. As an exception they may occur in 1 year old or even at the age of 70. During maturity (after an age of 21) tics occur rarely, if they are not secondary. The tics appear as isolated phenomenon – acute, transient tics. Transient idiopathic tics are reported in many children, but in the majority of cases they disappear before reaching mature age. Tics that have started in childhood may not go away, but remain as chronic simple, complex or multiple tics or reappear later. Chronic tics differ from the syndrome of Tourette in lacking simultaneous appearance of motor and vocal tics.

The neurologist should establish:

- Data about preceding intake of medicines, traumas or illnesses
- Dissemination and localization of the symptom
- Existence of other motor disorders
- Presence of other neurological symptoms besides motor disorders
- Perform neuroimaging tests

Upon identifying the symptom it is necessary to refer the patient to center of motor disorder, without using any other methods.

The neurologist in the Center of motor disorders should clarify the etiologic diagnosis using the clinical criteria for the syndrome of Tourette.

3.2 Syndrome of Tourette

In 1885 George Gilles de la Tourette depicted a disease manifested by motor and vocal tics, in some patients with accompanying echo-phenomena and coprolalia.

It affects up to 1.6% of the population. It can be seen in all races and social-economic categories. The coprolalia is almost not reported in Japan. It is 3 times more frequent in males.

Its etiology is still not known. It is assumed that the disease is hereditary with autosomal-dominant inheritance. The penetrability is incomplete and depends on the gender; the clinical expression is variable and covers the syndrome of Tourette, chronic tic disorders and the obsessive-compulsive disorders.

According to some authors it is provoked by autoimmune process following an infection with group A β-hemolytic streptococci in childhood. The autoimmune mechanism interacts with the genetically determined susceptibility of the individual and causes obsessive-compulsive disorders. The term introduced is pediatric autoimmune neuropsychiatric disorders, associated with streptococci infection (PANDAS).

Pathoanatomically injuries of the basal ganglia and some areas of the limbic system are detected. There are supra-activity of the dopamine receptors and disorders in the mesocortical dopamine projections. Damage of the stem tegmental periaqueductal grey matter, as well as reduction of dinorphine in the striatal fibers to globus pallidus is assumed.

Clinically it is displayed between the age of 2 and 15 years (average age of 7 years) and its expression fluctuates in time. It goes with tics and behavioral disorder. It has heterogeneous clinical picture with multiple repetitive motor and vocal tics around the clock, obsessions and rituals, stereotypies, coprolalia, copromimia, echo-phenomena (repeating own words or the words and movements of others), touching other people, self-injuring conduct and inability of remembering.

Tics first appear in the upper part of the body, most often as facial tics. They do not disappear during sleep. More rarely the disease starts with vocal tics. Coprolalia is not mandatory symptom for verifying the diagnosis. Most patients just mentally pronounce obscene word (mental coprolalia). The tics change in type and they intensify and subside both in different hours during the day and in the different days. There are periods lasting days and week, in which the tics worsen, followed by periods of improvement. The movements may resemble dystonia, chorea and myoclonias. With the disease progression new tics are added while the old ones change their type and

expressiveness. They reach their maximum around the age of 10 and in a few years may drastically subside or even disappear. In other patients the tics disappear for several years after which they reappear, while in some they persist for life. In 5-8% of the patients these tics go away forever during adolescence.

Sleep disturbances, somnambulism and night fears are present.

Behavioral disorders precede the appearance of tics. Most common (in 50%) are the obsessive-compulsive disorders. Typical are the compulsive check-ups, counting, perfectionism and obsessive worries and fears. Also attention deficit and hyperactivity disorder is existent. Tourette's syndrome has close clinical association with various other behavioral disorders such as panic attacks, phobias, depressions, manias, anxiety, stammering, obesity and alcoholism. Often the patients have personality peculiarities such as aptitude to dispute, defensiveness, impulsiveness and negativism. It is not so much common to witness self-injuring behavior, difficulties in reading writing and arithmetic, irrespective of the lack of cognitive disorders. Another socially unacceptable behavior such as offending or damaging the property of people around and humiliating remarks may also be reported.

The diagnosis is set up based on clinical criteria, requiring presence of a number of motor and one or more vocal tics, manifesting themselves simultaneously or separately during some period of the disease progression. Tics should be present almost every day or intermittently for a period over a year, emerging many times during the day (usually in fits). During this period of time there should be no more than 3 consecutive months without any tics. The disease should cause distress and significant impairment of the social, professional and other functions. The onset of this disease should be below 18 years of age. It should not be provoked by intake of substances (stimulants) or by another disease (Huntington's chorea or post-viral encephalitis).

The differential diagnosis verifies it against the chronic tic disorders by the presence of motor and vocal tics concurrently. Transient tic disorders last for not more than a year. The chronic motor and vocal as well as the transient tic disorders are considered by most authors as a clinical version of the more severe syndrome of Gilles de la Tourette.

Tic Treatment

It starts with **clonidine** 0.05 mg in the evening and the dose is gradually increased until reaching effect. Most patients respond well to 3 times 1 tablet of 0.1 mg daily. The minimum effective dose should be used.

In case of lack of adequate effect **neuroleptic** should be added or if there is no effect the treatment should be switched only to a therapy with a neuroleptic. Dopamine antagonist administration and blockage of the dopamine receptors results in tic suppression.

Haloperidol is started at a dose of 0.25 mg in the evening and is increased until having effect, which is usually attained with 2 mg in the evening.

If there is no effect other neuroleptics can be administered, such as risperidone 0,25 – 16 mg, olanzapine 2,5 – 15 mg, ziprasidone 20 – 200 mg daily, clozapine or tetrabenazine.

Dopamine agonists (pergolide 0,45 mg daily) have an effect on the tics.

Antagonists of calcium channels are effective.

Administering **botulinum toxin** is also effective.

Sensory and dystonic tics are more difficult to treat.

Attention deficit and hyperactive disorder (ADHD) responds well to clonidine, tricyclic antidepressants, serotonin reuptake inhibitors and some stimulants.

Obsessive-compulsive disorders respond well to serotonin reuptake inhibitors.

4. Myoclonias

These are sudden, fast, short-timed, involuntary, non-rhythmic single or repetitive contractions of one muscle or a group of muscles or only part of it, provoked by neuronal trigger. The myoclonic movement consists of single muscular contraction, which can be repeated and may provoke limb or body movement.

The morbidity rate is 8.6 per 100,000 persons, showing that myoclonia is quite common motor disorder.

They are classified per their clinical manifestations, etiology and pathophysiology.

According to the *clinical manifestations* they may occur spontaneously, be induced by voluntary muscular activity (action type) or by outer sensory stimulation (reflexive type). In other cases the myoclonias may persist almost constantly. The action type myoclonias (positive and negative) are the most severely disabling motor disorder as they repeat frequently in some rhythm, which impedes the performance even of the most simple movements.

According to *the anatomic areas involved* they can be focal (affecting several adjacent muscles), generalized (involving the majority of the muscle groups), multifocal (affecting many muscles but with different myoclonic type) or segmental.

The etiologic classification provides information about the underlying disease, causing myoclonias, the options for its treatment and the expected outcome for the patient. According to their etiology myoclonias are classified as physiological, essential or symptomatic (epileptic or due to another reason).

Symptomatic myoclonias occur in numerous neurological diseases, affecting the cerebrum, the spinal cord and the peripheral nerves. Myoclonia etiology includes almost all possible neurological injuries. They cannot be independently used to verify the diagnosis, but are usually accompanied by other neurological symptoms. The diseases where myoclonias are the only or key neurological symptom are the anoxia (syndrome of Lance-Adams), traumas, intoxication with bismuth and metabolic disorder (renal failure, hyponatremia, hypokalemia, etc.). Degenerative diseases of late onset, such as progressive supranuclear paralysis, olivopontocerebellar atrophy and Huntington's chorea can be manifested with action type myoclonias as major symptom. The reflexive myoclonias are the key symptom in the cortical-basal degeneration and olivopontocerebellar atrophy, as well as in some families suffering from Huntington's chorea. Focal lesions of the central nervous system may provoke focal or segmental myoclonias. Many medicines can cause myoclonias.

Idiopathic epilepsy may be manifested predominantly with myoclonias. Typical examples for it are the child's benign myoclonia, myoclonic absences, juvenile myoclonic epilepsy of Janz and the photosensitive epileptic myoclonias. In these cases the myoclonias are generalized, emerge spontaneously and are provoked by insomnia and alcohol; they can be triggered by ocular stimuli. Myoclonias may emerge in patients

with generalized tonic-clonic epilepsy in progressive encephalopathy (progressive myoclonic epilepsy).

Various myoclonia types may combine in the same patient and in the same anatomic area. Often the reflex and action type myoclonias are found combined or the spontaneous myoclonias are reinforced during movement, while the focal can get generalized.

Pathophysiological classification identifies the mechanisms of the origination of myoclonias. Often myoclonias of different etiology, genetics and prognosis fall into the same pathophysiological group, because they share the same pathophysiological mechanisms of origin. According to the localisation of the generator in the nervous system myoclonias are broken down in three large groups: cortical, subcortical (stem) and spinal. Pathophysiology divides them in two large groups: epileptic and non-epileptic.

The group of the epileptic includes the reflex myoclonias (cortical, reticular and generalized – primarily generalized epileptic myoclonias and photic cortical reflexive myoclonias). The group of the non-epileptic includes the physiological, essential, palatal, spinal, peripheral, night type and psychogenic myoclonias, as well as the reinforced startle reflex. Cortical and epileptic myoclonias as well as subcortical and non-epileptic myoclonias are interchangeable terms. The reticular reflex myoclonias from the epileptic group are distinguished, since they are of stem origin, i.e they fall in the subcortical group.

According to the rhythmicity myoclonias can be rhythmic or non-rhythmic. Rhythmic myoclonias are almost always spontaneous, focal or segmental. They may persist during sleep and respond slightly to sensory stimuli. The frequency varies, but it is usually low- from 1 to 4 Hz. Most common are the spinal myoclonias.

According to the muscle contraction myoclonias are subdivided into positive, associated with muscle contraction and negative. The negative presents short-timed interruption of the muscle contraction being performed, which may cause disturbance in the position of the limbs.

The pathophysiology is associated with abnormal activity of motor-neurons and inter-neurons due to enhanced activity or reduced inhibition.

Clinically the myoclonias can be of different amplitude ranging from low amplitude type to high amplitude type, which may provoke movement of the limb.

The differential diagnosis is verified against other motor disorders like clonus, tics, chorea, postural tremor, dystonia and facial hemispasm.

The neurologist should establish:

- Evidence about preceding intake of medicines, traumas or illnesses
- Dissemination and localization of the symptom
- Existence of other motor disorders
- Presence of other neurological symptoms besides motor disorders
- Perform neuroimaging tests

After identifying the symptom it is necessary to refer the patient to center of motor disorder, without using any other methods.

The neurologist in the center of motor disorders should clarify the etiologic diagnosis using:

Electroencephalography

Genetic test

4.1. Non-epileptic myoclonias

This group of myoclonias is included into the motor disorders, contrary to the epileptic myoclonias. They affect the proximal muscle groups, while the epileptic type affect the distal ones.

Physiological myoclonias emerge in healthy people in certain circumstances and are not due to pathological injuries. The night myoclonias, affecting the legs and much more rarely spreading over the whole body before falling asleep, are most typical.

Essential (familial) myoclonias are hereditary diseases of autosomal-dominant inheritance and include the myoclonus-dystonia. Though the myoclonias are their core clinical manifestation, they often combine with dystonic postures and movements. They also often combine with postural tremor.

Spinal myoclonias are rare and occur as a result of stem or spinal cord lesions and abnormal discharges in the spinal neurons. Infrequently they are idiopathic, most often found in disc prolapse, cervical myelopathy (including post-traumatic), syringomyelia, tumors, myelitis, degenerative and demyelinating diseases, spinal anesthesia and contrast spinal test. The myoclonias are spontaneous, rhythmic, symmetric and focal, encompassing small myotomes and are rarely stimuli-dependent.

Propriospinal myoclonias affect the axial flexion and in rarer cases the extension muscles of the body and the abdominal muscles. They lead to repetitive, symmetric flexion of the neck, body, thighs and knees.

Peripheral myoclonias are found in case of lesions of the spinal radices, plexuses or peripheral nerve and Sudeck's atrophy.

Facial myoclonias may emerge in healthy people following overstrain, alcohol abuse or smoking, in case of facial hemispasm or following a focal brain stem injury.

Axial myoclonias of the neck and the body are segmental and rhythmic. They happen in case of stem lesions, Arnold-Chiari's malformation and injuries of the upper cervical section of the spinal cord.

Treatment of Myoclonias

Spinal myoclonias do not have specific treatment and the underlying disease should be treated. Administering clonazepam, the glycine inhibitor levetiracetam, carbamazepine and tetrabenazine may render some effect.

If the night myoclonias disturb the process of falling asleep, they respond to a dose of 1-3 mg clonazepam before sleep.