Alcohol response in different tremor syndromes based on anamnestic survey
Is subjective alcohol response a discriminatory factor to distinguish between tremor disorders?

ingereicht von
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Ort, Datum ........................................... (Unterschrift)
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# Table of contents

1. INTRODUCTION .................................................................................................................. 1

1.1 Classification ....................................................................................................................... 2

1.1.1. Rest tremor .................................................................................................................. 2

1.1.2. Action tremor ............................................................................................................... 2

1.1.2.1. Postural tremor ....................................................................................................... 3

1.1.2.2. Kinetic tremor ......................................................................................................... 3

1.1.2.2.1. Simple kinetic tremor ......................................................................................... 3

1.1.2.2.2. Tremor during target-directed movements (intention tremor) ......................... 3

1.1.2.2.3. Task-specific tremor ......................................................................................... 3

1.1.2.3. Isometric tremor .................................................................................................... 4

1.2. Tremor syndromes .......................................................................................................... 5

1.2.1. Physiologic Tremor .................................................................................................. 5

1.2.2. Essential tremor ......................................................................................................... 5

1.2.2.1. Origin of Essential Tremor .................................................................................. 6

1.2.2.2. The relation between essential tremor and Parkinson’s disease ....................... 7

1.2.2.3. Treatment of essential tremor .............................................................................. 7

1.2.3. Parkinsonian Tremor ............................................................................................... 9

1.2.4. Dystonic tremor ......................................................................................................... 15

1.2.5. Cerebellar tremor ...................................................................................................... 16

1.2.6. Orthostatic tremor .................................................................................................. 16

1.2.7. Holmes tremor .......................................................................................................... 16

1.2.8. Palatal Tremor .......................................................................................................... 17

1.2.9. Drug-induced and toxic tremor syndromes .............................................................. 17

1.2.10. Tremor syndromes in peripheral neuropathy ......................................................... 18

1.2.11. Psychogenic tremor ............................................................................................... 18
1.2.12. Tremor of Wilson’s disease ................................................................. 20
1.2.13. Fragile X Tremor Ataxia Syndrome (FXTAS)....................................... 22
1.2.14. Klinefelter syndrome associated tremor ............................................. 22
1.3. Alcohol and Tremor ................................................................................. 23
  1.3.1. The effect of alcohol on the nervous system ........................................ 23
  1.3.2. Alcohol in Essential Tremor ............................................................. 24
  1.3.3. Research questions / Hypothesis....................................................... 26
    1.3.3.1. Main hypothesis ........................................................................ 26
2. METHODS .................................................................................................... 27
3. RESULTS ..................................................................................................... 29
4. DISCUSSION ............................................................................................... 33
5. REFERENCES ............................................................................................... 38
6. APPENDIX .................................................................................................. 55
  6.1. Questionnaire ....................................................................................... 55
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>ataxia telangiectasia</td>
</tr>
<tr>
<td>cAMP</td>
<td>Adenosin-5'-monophosphate cyclo</td>
</tr>
<tr>
<td>CBD</td>
<td>corticobasal degeneration</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DBS</td>
<td>deep brain stimulation</td>
</tr>
<tr>
<td>DLB</td>
<td>dementia with Lewy Bodies</td>
</tr>
<tr>
<td>DT</td>
<td>dystonic tremor</td>
</tr>
<tr>
<td>EDO</td>
<td>earlier disease onset</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>ET</td>
<td>essential tremor</td>
</tr>
<tr>
<td>FMR1</td>
<td>fragile X mental retardation 1 gene</td>
</tr>
<tr>
<td>FXTAS</td>
<td>fragile X-associated tremor/ataxia syndrome</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>IPD</td>
<td>idiopathic Parkinson’s disease</td>
</tr>
<tr>
<td>MCPs</td>
<td>middle cerebellar peduncles</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MSA</td>
<td>multiple system atrophy</td>
</tr>
<tr>
<td>MSA-C</td>
<td>multiple system atrophy cerebellar</td>
</tr>
<tr>
<td>MSA-P</td>
<td>multiple system atrophy parkinsonian</td>
</tr>
<tr>
<td>NTD</td>
<td>non-tremor dominant</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>OPCD</td>
<td>olivoponto-cerebellar degeneration</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PIGD</td>
<td>postural instability and gait disturbance</td>
</tr>
<tr>
<td>PKC</td>
<td>protein kinase c</td>
</tr>
<tr>
<td>PMD</td>
<td>psychogenic movement disorders</td>
</tr>
<tr>
<td>PNKD</td>
<td>paroxysmal nonkinesigenic dyskinesias</td>
</tr>
<tr>
<td>PSP</td>
<td>progressive supranuclear palsy</td>
</tr>
<tr>
<td>PSP-P</td>
<td>progressive supranuclear palsy Parkinsonism</td>
</tr>
<tr>
<td>PSP-RS</td>
<td>progressive supranuclear palsy Richardson syndrome</td>
</tr>
<tr>
<td>RDP</td>
<td>rapid disease parkinsonism</td>
</tr>
<tr>
<td>SNCA</td>
<td>$\alpha$-synuclein promotor</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>TaD</td>
<td>tremor associated with dystonia</td>
</tr>
<tr>
<td>TD</td>
<td>tremor dominant</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affair</td>
</tr>
</tbody>
</table>
Figure directory

FIGURE 1: Tandem gait performance ................................................................. 14

FIGURE 2: Alcohol response in the 44 patients who consumed alcohol (%) .................. 30

FIGURE 3: Numbers of patients in each diagnostic group with or without alcohol response or no statement possible. ................................................................. 31

FIGURE 4: Numbers of patients in the four main groups (ET; IPD; DT and TaD; all others) with or without alcohol response or no statement possible. ............................................. 32
## Table directory

TABLE 1: Potential Effects of Drugs on Physiologic Tremor ........................................... 1

TABLE 2: Classification and Characteristics of Tremor ..................................................... 4

TABLE 3: Oculomotor signs in parkinsonism .................................................................... 12

TABLE 4: Common causes of drug induced tremor ......................................................... 18

TABLE 5: Precipitating events of psychogenic tremor ....................................................... 19

TABLE 6: Associated diagnoses and somatizations of psychogenic tremor ......................... 20

TABLE 7: Clinical and Diagnostic Features of Tremor Syndromes .................................. 21
Zusammenfassung


in einem größeren Patientenkollektiv sowie in weiterer Folge auch mittels einer objektiven Alkohol-Tests bestätigt werden.
Abstract

**Aims:** A positive response to alcohol, commonly simply inquired by history, is used as a supportive diagnostic criterion for essential tremor (ET). In fact only a few studies exist on the effect of alcohol in ET and idiopathic Parkinson’s disease (IPD). So far no systematic studies have been performed in other tremor syndromes. Therefore we wanted to investigate if subjective alcohol response distinguishes between a broad range of tremor disorders.

**Methods:** We recruited 55 consecutive patients (28 men, 27 women) with upper limb tremor and an established diagnosis based on diagnostic criteria. Besides a neurological examination a questionnaire was used to obtain information on demographics, alcohol drinking habits, and response of tremor to oral alcohol intake. Our cohort consisted of 27 patients with IPD, three with dystonic tremor (DT), nine with tremor associated with dystonia (TaD), seven with ET, three with enhanced physiological tremor, two with atypical parkinsonian syndromes, one with Fragile-X-Tremor-Ataxia-Syndrome, two with Klinefelter syndrome associated tremor, and one with psychogenic tremor. Statistical analyses were performed comparing all groups. Due to small numbers of some diagnostic entities we also performed statistical analyses comparing the following groups: 1. ET, 2. IPD, 3. dystonic tremor (DT) and tremor associated with dystonia (TaD), 4. all others.

**Results:** Forty-four out of 55 patients were drinking alcohol (mean 5.4±5.0 units/week). Of these 44 patients, 14 reported no response, 14 improvement of tremor, and 16 had never paid attention to the effect of alcohol on their tremor. The 14 patients with a positive alcohol effect rated the improvement of tremor as 54±2%, for a duration of 3.7±3.1 hours, after a mean intake of 3.9±3.6 units alcohol. Only four patients reported to experience a rebound phenomenon and only one patient stated to drink alcohol because of its anti-tremor effect. None of the evaluated parameters differed significantly between the groups.

**Conclusion:** Subjective alcohol response inquired by history cannot distinguish between different tremor disorders and is thus unlikely to serve as a supportive diagnostic criterion for ET. However, investigations of a larger sample size combined with an objective evaluation of alcohol responsiveness in different tremor disorders are necessary to shed further light on this topic.
1. INTRODUCTION

Tremor is a rhythmical, involuntary oscillatory movement of one or more body parts, which is known to be the most common movement disorder (1-3). Physiological tremor exhibits in all normal persons as a benign, high-frequency, low-amplitude postural tremor easier to watch by holding a piece of paper on the outstretched hand or pointing a laser at a distant screen. Enhanced physiological tremor, a high-frequency postural tremor, occurs in the absence of neurological disease and is caused by many medical conditions for example thyrotoxicosis, hypoglycaemia, the use of certain drugs, or withdrawal from alcohol or benzodiazepines. See Table 1. This type of tremor is usually reversible by treatment of its cause (1,4,5).

Pathological tremor is differentiated from other involuntary movement disorders such as chorea, athetosis, ballism, dystonia, tics, and myoclonus (3). The different characteristics of tremor are important to diagnose correctly between tremor syndromes (8).

<table>
<thead>
<tr>
<th>May exacerbate physiological tremor</th>
<th>May reduce physiological tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Beta-adrenergic agonists</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Beta-adrenergic antagonists</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>(propranolol)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Primidone</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic agents</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td></td>
</tr>
<tr>
<td>Terbutalinesulfate</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Valproid acid</td>
<td></td>
</tr>
</tbody>
</table>

1.1 Classification

The phenomenological classification of tremor is helpful in diagnosing the cause of this movement disorder and still the history and physical examination remain the most important diagnostic tools available to clinicians in identifying and classifying tremor syndromes (4,8).

The main characteristics of tremor are:

- type of tremor (rest, action or both)
- frequency of tremor (low < 4 Hz, medium 4-7 Hz and high > 7 Hz)
- axis of tremor
- associated symptoms (1,8)

1.1.1. Rest tremor

Rest tremor is the most common and classical tremor seen in idiopathic Parkinson’s disease (IPD). It occurs in a body part that is not voluntarily activated and is completely supported against gravity like resting on a couch (1,8).

A way to separate typical rest tremor from action tremor in clinical routine, is to investigate the patient during target-directed movements, in which tremor amplitude in rest tremor almost always diminishes. By contrast, in action tremors, increasing or constant tremor amplitudes are found during voluntary movements. Increasing tremor amplitudes in rest tremor are typically seen during mental stress, for example counting backwards or when another body part is moving, especially during walking. It is known that rest tremor responds in most patients to dopaminergic treatment, but exceptions exist and sufficient studies on this subject are lacking (1).

1.1.2. Action tremor

Action tremor is any tremor that is produced by voluntary contraction of muscle and it is further separated into postural, isometric and kinetic tremor, where the latter includes intention tremor (1,8).
1.1.2.1. Postural tremor

Postural tremor is present when the affected body part maintains position against gravity as with extending arms in front of the body (1,4,8).

1.1.2.2. Kinetic tremor

This type of tremor occurs with voluntary movement and is further divided into simple kinetic tremor, tremor during target-directed movements (intention tremor) and task specific kinetic tremor (1).

1.1.2.2.1. Simple kinetic tremor

This tremor is present during voluntary movements which are not target directed like simple pronation/supination movements or flexion/extension wrist movements. It may persist during voluntary, goal-directed movement but without any increase in amplitude during the terminal phase of movement (1,9).

1.1.2.2.2. Tremor during target-directed movements (intention tremor)

An increase of tremor amplitude during visually guided movement toward a target (e.g., finger-nose test) at the termination of the movement, - is typical for intention tremor (1, 10). The significant fluctuation of tremor amplitude while approaching the target, is characteristic for this tremor, but this feature is not required for the definition as long as the possibility of position-specific tremor at the end of a movement is excluded. This tremor has sometimes been confused with action myoclonus and ataxia in some patients but the dominant feature of intention tremor to distinguish it from other movement disorders, is rhythmicity (1).

1.1.2.2.3. Task-specific tremor

This tremor appears or becomes exacerbated during specific activities, such as writing (1).
1.1.2.3. Isometric tremor

Isometric tremor can appear in isolation or with other tremor symptoms and is a result of muscle contraction against a rigid stationary object like making a fist or squeezing the examiner’s fingers (1).

<table>
<thead>
<tr>
<th>Type of tremor</th>
<th>Frequency</th>
<th>Amplitude</th>
<th>Occurrence</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest tremor</td>
<td>Low to medium (3 to 6 Hz)</td>
<td>High; decreases with target-directed movement</td>
<td>Limb supported against gravity; muscles are not activated</td>
<td>Parkinson’s disease; drug-induced parkinsonism (neuroleptics; metoclopramide)</td>
</tr>
<tr>
<td>Action tremor</td>
<td>—</td>
<td>—</td>
<td>Any voluntary muscle contraction</td>
<td>—</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>Medium to high (4 to 12 Hz)</td>
<td>Variable</td>
<td>Limb maintains position against gravity</td>
<td>Physiologic tremor; essential tremor; metabolic disturbance; drug or alcohol withdrawal</td>
</tr>
<tr>
<td>Kinetic tremor</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Simple kinetic</td>
<td>Variable (4 to 10 Hz)</td>
<td>Does not change with target-directed movement</td>
<td>Simple movements of the limb</td>
<td>—</td>
</tr>
<tr>
<td>Intention</td>
<td>Low (&lt; 5 Hz)</td>
<td>Increases with target-directed movement</td>
<td>Target-directed movement</td>
<td>Cerebellar lesion (stroke, multiple sclerosis, tumor); drug-induced (lithium, alcohol)</td>
</tr>
<tr>
<td>Isometric tremor</td>
<td>Medium</td>
<td>Variable</td>
<td>Muscle contraction against stationary objects</td>
<td>Holding a heavy object in one hand</td>
</tr>
<tr>
<td>Task-specific Tremor</td>
<td>Variable (4 to 10 Hz)</td>
<td>Variable</td>
<td>Occurs with specific action</td>
<td>Handwriting tremor; musician’s tremor</td>
</tr>
</tbody>
</table>

1.2. Tremor syndromes

1.2.1. Physiologic Tremor

As mentioned before, all normal persons exhibit physiological tremor, which can be enhanced by several medical conditions (1,4,5). Physiological tremor is a benign, high-frequency (8-12 Hz) (11), low-amplitude postural tremor easier to detect for example by holding a piece of paper on the outstretched hand.

Enhanced physiological tremor, a high-frequency postural tremor, occurs in the absence of neurological disease and is caused by many medical conditions for example thyrotoxicosis, hypoglycaemia, the use of certain drugs, or withdrawal from alcohol or benzodiazepines. This type of tremor is usually reversible by correcting the cause of tremor (1,4,5).

1.2.2. Essential tremor

With a prevalence ranging from 4.1 to 39.2 cases per 1,000 persons, to as high as 50.5 per 1,000 on persons older than 60 years, essential tremor (ET) is the most common movement disorder worldwide (4,12). The true prevalence, however, is unknown, because ET patients with mild tremor do not attend clinics and up to 50 percent of these mild tremor patients are unaware of it (13,14).

Clinically, the differentiation between ET and parkinsonian tremor can be difficult (3). According to two studies the estimated rates for misdiagnosing ET are 37% and 50% (15,16), and the final misdiagnosis rate of IPD was reported as 24% in 1992 (17), falling to 10% in 2001 (18).

ET diagnosis comprises several criteria (19)

1. A visible and persistent, largely symmetric postural or kinetic tremor that is bilateral
2. Additional or isolated head tremor that may occur in the absence of abnormal posturing.

Exclusion criteria are

1. Other neurological signs, especially dystonia
2. The presence of enhanced physiological tremor, including current or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state.
3. Evidence of psychogenic tremor
4. Sudden onset or stepwise deterioration
5. A primary orthostatic tremor
6. An isolated voice, tongue, chin or leg tremor,
7. Isolated position-specific or task-specific tremors, also occupational and primary writing tremor.

ET is mainly affecting the hands with a frequency of 4 Hz to 10 Hz (19). The proportional distribution of the affected body parts is 95% of the upper limbs, followed by the head with 34%, lower limbs are affected in 20%, voice 12% and face and trunk with 5% (20). There is a fluctuation of tremor amplitude and tremor frequency over time, in which the frequency decreases and the tremor amplitude may increase (5). There is also an increase of tremor amplitude during stress, fatigue, and certain medications such as central nervous system stimulants (5,22,23).

ET usually shows a slow progression, the age of onset is most often between 60 and 70 years, but may also occur before 60 years, and both sexes are equally affected (3,4).

1.2.2.1. Origin of Essential Tremor

The origin of ET is believed to be in the central nervous system, but still a reproducible neuropathology has not been described (3). ET is clinically and genetically heterogeneous, half of the cases are considered familial with an autosomal dominant pattern of inheritance (25-27). A positive family history in young-onset essential tremor patients has been found in up to 80%. In linkage analyses three possible chromosomal loci (ETM1-3) have been identified, nevertheless these loci have not led to the identification of definite sequence variants associated with essential tremor (28). In a recent genome-wide association study an association to the LINGO1 gene was found. LINGO1 is a protein that is involved in the regulation of myelination of axons in the central nervous system. People with some defect in this process are more likely to develop ET than others (29). This finding has potential to help to understand further the genetics and molecular pathophysiology of essential tremor (2).

Another controversial issue is the relationship between essential tremor and dementia (30). In recent years post-mortem studies have been published on ET patients, reporting heterogeneous structural changes on cerebellum and Lewy-bodies in the brainstem (31-33). The neurodegenerative changes are diverse ranging from widespread Purkinje-cell loss and axon swellings (torpedos) in the cerebellum to brainstem Lewy-bodies and tauopathies (32, 33). The autopsied patients were heterogeneous, and late-onset patients after the age of 60-70 years are unlikely to suffer from the classical type of hereditary ET (34,35), a fact that
questions the clinical relevance of these findings (2). Further recent imaging studies employing voxel-based-morphometry (36) and diffusion-weighted imaging (37) argue against neurodegenerative changes in essential tremor. Based on currently available evidence a generalized degenerative disease is unlikely to be the cause of essential tremor and many causes such as altered ion channels, transmitter or receptor changes should be reconsidered for future research (2).

1.2.2.2. The relation between essential tremor and Parkinson´s disease

There is a long-standing debate about the relation between these two neurological diseases (2). The main reason for this disagreement derives from frequently misdiagnosing ET as Parkinson´s disease (PD) or vice-versa (38). New studies have claimed that there is a higher risk for essential tremor patients to develop PD (27) but also an increased risk for PD patients and notably their first degree relatives to develop essential tremor (39, 40). Nevertheless the true association between ET and PD is still not defined (38).

1.2.2.3. Treatment of essential tremor

Pharmacological treatment of ET remains unsatisfactory and because of the multiple side effects of these drugs, they should not be recommended for mild cases. The reasons for unsatisfactory ET treatment are that neurotransmitter deficits in ET patients have not been identified, the way by which reported microscopic pathology might lead to tremor is still unknown, the source and mechanism of pathological oscillations are not recognized (41), and the genetic defects that cause ET have not been identified, except for a risk factor-LINGO1 (35,42). The most often used drugs are non-selective β blockers like propranolol and the anticonvulsant primidone (3). Anticonvulsants such as primidone, are thought to act through ion channel and gamma-aminobutyric-acid (GABA) receptor modulation. Drugs like benzodiazepines and calcium channel blockers possibly target the low-threshold calcium current in membrane oscillation, whereas β blockers might decrease the stretch-reflex sensitivity. Since primidone is causing side-effects such as drowsiness, dizziness, or disequilibrium, the common practice to start treatment is, to put patients on very low doses (25 or 12.5 mg) (43). It is important to clearly inform patients about these side-effects when starting primidone. Another problem is a common acute toxic reaction to the first dose of
primidone, consisting of various combinations of nausea, sedation, malaise, ataxia, dizziness, and confusion, resulting in patients refusing to take additional doses. A sufficient total daily dose is given with 150mg or less. The response to primidone is modest, about half of ET patients are showing a response (50% reduction in tremor), while patients with advanced ET are having an insufficient treatment (41).

Patients treated with propranolol are showing in 50% a lasting benefit, and about 14% are developing tolerance (44). Again, side-effects such as bradycardia, syncope, fatigue and erectile dysfunction, are known and frequently dose limiting. Treatment with propranolol should start with 30-60mg per day and then gradually increased as needed, in which most responders are adequately dose-adjusted with 60-240mg per day. Other drugs, which are also used for ET treatment, are atenolol, sotalol, alprazolam, topiramate, and gabapentin monotherapy, though none of them are having greater efficacy than propranolol or primidone (41).

Botulinum toxin for essential hand tremor was given conflicting recommendations in two American Academy of Neurology practice guidelines (45,46), concluding that the beneficial effect is modest at best (41).

As mentioned before because of the potential adverse effects of certain agents, there are limitations for its use like patients with asthma, heart failure, arterioventricular block and diabetes mellitus. In medically resistant cases thalamic deep brain stimulation (DBS) is another treatment option (3). Risks and side-effects of thalamic DBS such as dysarthria (3-18% of patients), paraesthesias (6-36% of patients), dystonia (2-9% of patients), balance disturbance (3-8% of patients), ataxia (6% of patients), and limb weakness (4-8% of patients), are well documented, and possible to be reduced by adjusting the stimulus parameters. In some cases patients stop using their stimulator because of intolerable side-effects (47).
1.2.3. Parkinsonian Tremor

Different clinical presentations of tremors can be found in parkinsonian syndromes (1), a typical initial symptom is resting tremor beginning distally in one arm at a 4- to 6-Hz frequency (4), and over time, the tremor moves proximally to the second arm, again in a distal to proximal pattern (3). In fact, there may be a combination of rest and postural kinetic tremor, but only rarely an isolated postural and kinetic tremor (4). Nevertheless, isolated postural and kinetic tremors do occur in Parkinson disease with a frequency varying between 4 and 9 Hz. In the akinetic rigid variant of Parkinson’s disease postural tremors are relatively common, but severe postural tremor and also intention tremor are unusual in Parkinson’s disease. These tremor types have often been brought in connection with essential tremor variants or they have been found indistinguishable from enhanced physiological tremor (48). On the basis of the variability of the clinical expression of tremors in PD, the definition is based on the general diagnosis of PD rather than on specific tremor features. Only resting tremor is a positive diagnostic criterion for PD but other tremor types are often seen (4). Other associated signs of PD are rigidity (cogwheel rigidity during examination of the extremities), bradykinesia (including a slow, shuffling gait, decreased arm swing while walking and difficulty rising from a seated position), impaired postural reflexes, and masked face.

Monosymptomatic rest tremor is defined in patients with rest and/or postural tremor for more than two years without any signs of bradykinesia or rigidity (49) and also existing PET or SPECT evidence for dopaminergic deficit (50).

Rest tremor in PD, which is considered an expression of nigral degeneration, is the most specific sign for idiopathic PD among the other basic symptoms, and it has been estimated that classical resting tremor has a 95% probability of indicating IPD (51). Although rest tremor is one of the cardinal symptoms of PD, the severity of the disease or its progression is not in correlation with tremor severity in contrast to rigidity and akinesia (48).

Pathology of parkinsonian tremor

The basal ganglia, primary the degeneration of dopaminergic cells within the substantia nigra and the following dopamine diminution of the striatum, are the affected regions that lead to the pathology of parkinsonian tremor (48). It is questionable whether there is a difference between tremor-dominant PD and akinesia/rigidity-dominant PD. It is known that the medial substantia nigra, specifically the retrorubral area A8, is more severely affected by
dopaminergic cell degeneration in the tremor–dominant form in contrast to more severe damage of the lateral substantia nigra (A9) in the akinetic rigid variant (52-54). Therefore, there must be an association with cell loss of the retrorubral substantia nigra and tremor, and other nuclei like the locus coeruleus are more affected in the akinetic rigid form. When talking about disease progression patients with tremor-dominant PD have better prognosis than patients with the akinetic rigid variant (55-57). However, it is not possible to exclude that these pathological findings are related to other features of the tremor-dominant variant of PD, but these findings represent the first step to assign specific pathologic abnormalities of rest tremor.

It is important to diagnose rest tremor appropriately and not to confuse it with the continuation of some postural tremors when the patient is not able to completely relax. Therefore, right diagnostics are when there is increasing amplitude during mental stress and when there is at least a diminution of tremor amplitude by moving the extremity voluntarily (49).

None of the existing theories or collected findings are fully explaining the clinical phenomenology of classical parkinsonian tremor, but throughout the years some satisfactory answers have been found. As mentioned before, the main hypothesis to explain the pathology of parkinsonian tremor is an abnormal activity within the basal ganglia, depending on a dopaminergic deficit yet unexplained changes of firing characteristics within the basal ganglia loop. There are two ways how the basal ganglia loop is mediating neuronal activity from the striatum to the thalamus; one is through the indirect way (pallidum externum-subthalamic nucleus-internal pallidum) and the second is through the direct pathway (putamen-pallidum internum). This pathway is organized in numerous topographic representations of the body and under normal conditions, these compartments are extremely separated within this pathway up to the motor cortex, but under pathologic conditions this separation seems to be abolished.

The contribution of reflex factors to parkinsonian tremors is seen critically, but it seems that reflex mechanisms modify the frequency and amplitude characteristics (48).
Heterogeneity of Parkinsonism

It is important to differentiate levodopa-responsive idiopathic Parkinson’s disease from mostly treatment-resistant atypical parkinsonian syndromes (58), because dopaminergic drugs may be destructive by potentially worsening atypical features such as orthostatic hypotension or confusion in cognitively impaired patients (59). Also, a treatment with deep brain stimulation should not be used in patients with atypical parkinsonism (60).

Parkinsonism with its four cardinal signs (bradykinesia, muscle rigidity, rest tremor and impairment of postural reflexes) can be classified into a wide-ranging spectrum of primary and secondary causes, in which Parkinson’s disease is counted as the most common type of primary parkinsonism. The aetiology of primary parkinsonism is still not fully clarified, neurodegenerative disorders of unknown or genetic origin are in discussion, where else secondary parkinsonism is lead back to drugs, vascular multiinfarct syndromes, toxins, infections and trauma. When talking about secondary parkinsonism the most common causes are vascular white matter disease (pseudoparkinsonism or lower body parkinsonism), which usually arises with gait problems (including freezing of gait) together with absent or mild parkinsonian signs of the upper extremities and drug-induced parkinsonism, which may occur in patients treated with dopamine antagonists (58).

There is a broad spectrum of atypical parkinsonian syndromes with different prognoses. The most frequent atypical parkinsonian disorders are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB).

PSP is described as symmetrical parkinsonism with supranuclear vertical gaze palsy, characterized with early falls in the beginning and pseudobulbar palsy as major Parkinson-plus features (61). Downgaze is mostly affected in vertical gaze palsy, which can be simply overcome by vestibule-ocular reflex (doll’s manoeuvre), showing that brainstem reflexes at that point are relatively well-maintained until the later stages of the disease. Other features of PSP are mild cognitive changes and progressive axial rigidity. Pathological findings in the brain have shown an accumulation of tau protein and neuropil threads mainly in the pallidum, subthalamic nucleus, red nucleus, substantia nigra, oculomotor nucleus, medulla and dentate nucleus, in which these findings are not pathognomonic for PSP (58). Recently it has been suggested that there is a second and milder variant from PSP with predominant parkinsonism, so called PSP-Parkinsonism (PSP-P), distinguishable. This variant has a better respond to
levodopa before transforming to the classical disease, relabelled Richardson syndrome (PSP-RS) (62).

CBD is characterized to refer to an asymmetric form of parkinsonism combined with apraxia (63), which variably embraces other basal ganglionic or cortical signs. Apraxia in CBD is described with gestural deficits, labelled as ideomotor apraxia, as well as decreased control of precise and individual finger movements, a hallmark of limb kinetic apraxia (64, 65). In some cases it might be difficult to differentiate apraxia from dystonia or bradykinesia, hence it is only separable on the less affected side (66).

When talking about MSA the main features are a combination of early autonomic failure (including orthostatic hypertension, bladder and erectile dysfunction) and cerebellar deficits. There are two variants, a parkinsonian (MSA-P) and a cerebellar variant (MSA-C) (67). Red flags that help to distinguish MSA from other atypical parkinsonian disorders are also abnormal postures or respiratory dysfunctions (68).

The classical description of DLB is parkinsonism arising with early dementia and the presence of additional neuropsychiatric features such as marked diurnal fluctuations in cognition and unprovoked visual hallucinations (69).

The possibility to distinguish between the various phenotypes of parkinsonism is significantly given by oculomotor signs (58). Table 3 is showing oculomotor signs in different phenotypes of parkinsonism.

**TABLE 3: Oculomotor signs in parkinsonism.**

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>PSP</th>
<th>CBD</th>
<th>MSA</th>
<th>DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supranuclear gaze palsy</td>
<td><em>None</em></td>
<td><em>Prominant early (RS)</em></td>
<td>Possible, late</td>
<td>None</td>
<td>Possible</td>
</tr>
<tr>
<td>Saccades</td>
<td>Hypometric*</td>
<td>Slowed, early</td>
<td>Delayed**, early</td>
<td>Hypometric*</td>
<td>Triggerin, abnormal</td>
</tr>
<tr>
<td>Square wave jerks</td>
<td>Possible, late</td>
<td>Prominant, early</td>
<td>Possible, late</td>
<td>Moderate</td>
<td>Probably, late</td>
</tr>
</tbody>
</table>

*PD = Parkinson’s disease, PSP = progressive supranuclear palsy, CBD = corticobasal degeneration, MSA = multiple system atrophy, DLB = dementia with Lewy bodies, RS = Richardson syndrome, MSA-C = cerebellar variant, * may be slowed late, ** may be slowed horizontally.*

*Adapted from Bohlhalter Stephan, Kägi Georg. Parkinsonism: heterogeneity of a common neurological syndrome. Swiss Medical Weekly 2011;141:w13293.*

It is necessary to look for atypical features and to examine carefully, because the frequently quoted levodopa challenge to a single dose is unreliable in early Parkinson’s disease.

Atypical disorders such as MSA-P and PSP-P are known to temporarily respond quite well to levodopa, so it is essential to emphasise that autonomic dysfunction, postural instability,
freezing or cognitive deficits are only atypical features if developing early in the course of the disease. These difficulties become also prevalent in the later stages of PD (58).

A further easier and faster alternative to distinguish Parkinson’s disease from atypical parkinsonism seems to be the examination of the gait, detecting a profound balance disorder, which is, especially when occurring early in the disease course, an atypical parkinsonian feature (70).

There is a difference in width stance during gait between patients with Parkinson’s disease and patients with atypical parkinsonism, in which those with atypical parkinsonism often show a broad stance width (71).

The best way to show the greater instability in the mediolateral plane is using the tandem gait test. An explanation for this mediolateral instability could be the neuropathological findings of involvement of the superior cerebellar peduncle in PSP or cerebellar involvement in the parkinsonian variant of multiple system atrophy (71, 72). Another explanation suggests that gait ataxia may also result from more extensive frontal lobe involvement in atypical parkinsonian disorders, such as arising in PSP and often also in vascular parkinsonism (70).

Therefore a study (70) investigated tandem gait performance in 36 consecutive patients with Parkinson’s disease and 49 consecutive patients with atypical parkinsonism. For this study patients were instructed to take 10 consecutive tandem steps along a straight line without walking aids and support and with eyes open. Additionally, they also calculated the age-dependent sensitivity and specificity for the cohort of 50-70-year-old patients. The results of this study were showing a significantly greater proportion with a completely normal tandem gait in patients with Parkinson’s disease, and an abnormal tandem gait test distinguished Parkinson’s disease from atypical parkinsonism with a sensitivity of 82% and a specificity of 92%. In the age-matched group the sensitivity was 75% and the specificity was 92%, whereas the regression analysis showed that the sensitivity increased with age but the specificity decreased a little. According to the authors the explanation for the increase in diagnostic accuracy with age was the age-dependent decrease in tandem gait performance seen only for patients with atypical parkinsonism. In this study they also calculated the accuracy of tandem gait performance for the subgroup with disease duration less than three years, because of the known difficulty of differentiating patients with PD early in the disease course. The analyses were showing only 4.8% with Parkinson’s disease and abnormal gait, whereas 85% of patients with atypical parkinsonism had an abnormal gait performance. The authors of this
study suggest that a standardised execution and scoring system of tandem gait performance has a good diagnostic ability to distinguish Parkinson’s disease from atypical parkinsonism. Although, tandem gait test is a clinical routine in standard neurological examinations used to detect cerebellar or vestibular syndromes, the authors suggest that for patients with parkinsonian disorders, who are taking just a single side step, which may usually be overlooked and classified as normal, should now be scored as an additional atypical parkinsonian sign (“red flag”). Figure 1 is showing the proportion of patients with normal tandem gait and abnormal tandem gait performance in this study.

Figure 1: Tandem gait performance, which was scored as follows: score 0, no side steps; score 1, single side step; score 2, multiple side steps; score 3, unable to take >4 consecutive steps in a straight line, with eyes open.


Returning back to the subtypes of Parkinson’s disease, traditionally PD has been subdivided into a tremor-dominant and an akinetic rigid variant, whereas the former has been considered to be more benign (58). Additionally, a variant with rapid progression of postural instability and gait disturbance (PIGD), which is frequently seen in elderly patients, is also commonly distinguishable (73). More recent clinic-pathological studies are now talking about 4
subtypes: earlier disease onset (EDO), tremor dominant (TD), non-tremor dominant (NTD) and rapid disease (RDP) (74, 75).

The age of onset of Parkinson’s disease is usually after the age of 50, but early-onset disease may appear in the 20s (76). Usually there is a remarkable improvement in parkinsonian tremor with antiparkinsonian medications such as levodopa, dopamine agonists, anticholinergics, budipine, and as second line treatments, clozapine, propranolol, and clonazepam (77).

1.2.4. Dystonic tremor

Dystonic tremor occurs in a body part, which is affected by dystonia, identified by abnormal posturing with overactivity of agonist and antagonist muscles (8). Focal tremors are usually with irregular amplitudes and variable frequency, mainly less than 7 Hz. Usually there is no postural/kinetic tremor during complete rest. This type of tremor is often jerky, irregular and variable depending on posture and activity (8), a typical example of dystonic tremor is tremulous spasmodic torticollis or dystonic head tremor (1). Involving the upper limbs, it may be particularly disabling (8). It is important to distinguish between tremor associated with dystonia, which is a tremor occurring in a body part not affected by dystonia, but the patient has dystonia elsewhere (1). Anticholinergic medications or clonazepam are used usually for treatment, but the use of botulinum toxin in the posterior neck muscles is most effectively used in patients with dystonic head tremor. Deep brain stimulation of the globus pallidus can be useful in resistant cases where dystonia is a major cause of disability (8). There are many patients using their own tricks (geste antagoniste or sensory tricks) to reduce the tremor amplitude. This fact, together with the absence of attempts at suppressing the tremor by voluntary muscle contractions are properly reliable diagnostic signs (3).
1.2.5. Cerebellar tremor

This tremor is a pure or dominant intention tremor, presented unilateral or bilateral (depending on aetiology), with a low frequency (below 5 Hz) (4,8). Usually there is no rest tremor but a postural tremor can be present (3). The cause for cerebellar tremor may be stroke, multiple sclerosis, brainstem tumour, Friedreich’s ataxia, and spinocerebellar degeneration (3,4). Other cerebellar lesion signs are abnormalities of gait, speech, ocular movements, inability to perform rapid alternating hand movements and titubation, a postural tremor of the trunk and head (4-6). Its rhythmicity, at times, may be the only sign that distinguish it from ataxia of the trunk (3).

During examinations, like finger-to-nose- or finger-to-finger tests, the tremor worsens as the extremity approaches the target (5). Drug toxicity must be excluded (8).

1.2.6. Orthostatic tremor

Orthostatic tremor is a rare and unique movement disorder of middle aged or elderly people that is characterised by unsteadiness on standing, secondary a very high tremor frequency with 13-18 Hz on electrophysiological studies (3,8). Classically, patients describe a feeling of unsteadiness when standing still for longer than a few seconds, but though, they rarely fall (8).

The tremor disappears when sitting or lying down. Diagnosis is confirmed by finding a 16 Hz pattern in the leg muscle with the patient standing by EMG. The treatment response seems to be unsatisfactory, most commonly used drugs are clonazepam, levodopa and drugs used for ET (3).

1.2.7. Holmes tremor

This term has previously been labelled as rubral tremor, midbrain tremor, thalamic tremor, myorhythmia and Benedikt’s syndrome. Holmes tremor is characterised as a rest and intention tremor with sometimes irregular presentation. In some patients there is also a postural tremor, but not as rhythmic as other tremors (1). With a slow frequency (< 4,5 Hz) it is a symptomatic tremor of predominately proximal limbs, worsening during movement and goal directed tasks (3). This tremor is usually resulting from lesions of the central nervous system (CNS) (1), particularly the midbrain and thalamus (78). Some patients with Holmes tremor may have additional dystonia (1).
1.2.8. Palatal Tremor

Palatal tremor is separated into symptomatic palatal tremor, in combination with brain stem and or cerebellar lesions, and essential palatal tremor without any identified brain lesions (1,3). Symptomatic palatal tremor is characterized by brain stem/cerebellum lesions with subsequent olivary hypertrophy, which can be verified with magnetic resonance imaging (MRI) scans. Other characteristic signs are rhythmic movements of the soft palate (levator veli palatini) and often other brain stem-innervated or extremity muscles (1), which do not abolish during sleep (3).

Patients with essential palatal tremor usually have ear clicks, rhythmic movements of the tensor veli palatine muscle; though extremity or eye muscles are not involved (1).

1.2.9. Drug-induced and toxic tremor syndromes

A drug-induced tremor occurs after a reasonable time frame following drug ingestion, toxic tremors appear after intoxication (1). Depending on the drug and the individual disposition of the patient, drug-induced tremors can have the whole spectrum of clinical features of tremor (1,8). The most common form is the enhanced physiologic tremor syndrome occurring after the intake of sympathomimetics or antidepressants. Classic parkinsonian tremor associated with neuroleptics and dopamine blocking agents is another frequent form.

Alcohol withdrawal usually has as consequence an enhanced physiologic tremor which needs to be differentiated from intention tremor secondary to cerebellar damage in chronic alcoholism (1,8). Usually toxic tremors are combined with other clinical signs of CNS intoxication such as eye movement abnormalities and gait disturbance (1). Common causes of drug-induced tremor are listed in Table 4.
TABLE 4: Common causes of drug induced tremor

<table>
<thead>
<tr>
<th>Postural</th>
<th>Intention</th>
<th>Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Alcohol</td>
<td>● Alcohol</td>
<td>● Metoclopramide</td>
</tr>
<tr>
<td>● Amiodarone</td>
<td>● Amphetamines</td>
<td>● Prochlorperazine</td>
</tr>
<tr>
<td>● Amphetamines</td>
<td>● Beta adrenergic agonists</td>
<td>● Neuroleptics (dopamine blockers)</td>
</tr>
<tr>
<td>● Caffeine</td>
<td>● Caffeine</td>
<td></td>
</tr>
<tr>
<td>● Cyclosporine</td>
<td>● Dopamine</td>
<td></td>
</tr>
<tr>
<td>● Corticosteroids</td>
<td>● Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>● Sodium valproate</td>
<td>● Theophylline</td>
<td></td>
</tr>
<tr>
<td>● Thyroid hormones</td>
<td>● Tricyclic antidepressants</td>
<td></td>
</tr>
</tbody>
</table>


1.2.10. Tremor syndromes in peripheral neuropathy

There are many peripheral neuropathies in association with tremor, as well as peripheral in origin and predominately postural and kinetic. The frequent causes for this tremor are demyelinating neuropathies, and especially dysgammaglobulinemic neuropathies. Abnormal position sense is not required for this diagnosis.

There is a possibility of the coexistence of peripheral neuropathy and ET, which could make it difficult to distinguish the aetiology in a particular patient (1). For treatment often modest doses of propranolol are needed (8).

1.2.11. Psychogenic tremor

Usually movement disorders are considered to arise because of a dysfunction of the basal ganglia and their connection, but psychogenic etiology should not be disregarded (79). There are many psychogenic movement disorders (PMD) such as dystonia (80-82), myoclonus (83), tics (84), hemifacial spasm (85), parkinsonism (86), and gait disorders (87), in which psychogenic tremor is the most common PMD (88-90).

There is no diagnostic test for psychogenic tremor, so it is defined when there are negative or exclusionary criteria such as tremor or shaking not fully explained by organic disease or
positive criteria consisting of clinical characteristics, which make the movement incongruent with any organic tremor (91).

There are many different clinical presentations in psychogenic tremors, including following criteria:

- A sudden onset and remission with unusual clinical combinations of rest and postural/intention tremors
- During distraction a decrease of tremor amplitude is seen or a variation of tremor frequency, also during voluntary movements of the contralateral hand
- A rhythmic task with the contralateral hand may induce an adaptation of tremor frequency (entrainment)
- A coactivation sign of psychogenic tremor or a past history of somatisation
- As additional evidence, an appearance of additional and unrelated neurologic signs

Patients with psychogenic tremor often experience a large number of diagnosis and therapeutic procedures before the final diagnosis is established (3). In a study (79) 12,625 patients, who have been seen in the Baylor College of Medicine Movement Disorders Clinic between 1990 and 2003, have been evaluated and 517 of them were diagnosed with PMD. Of these 517 patients 127 patients had psychogenic tremor. Precipitating events and associated diagnoses and somatizations of psychogenic tremor evaluated in this study are listed in table 5 and table 6.

**TABLE 5: Precipitating events of psychogenic tremor**

<table>
<thead>
<tr>
<th>Evidence of Precipitating Event</th>
<th>N*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal life stress</td>
<td>43</td>
<td>33.9</td>
</tr>
<tr>
<td>Trauma</td>
<td>30</td>
<td>23.6</td>
</tr>
<tr>
<td>Major illness</td>
<td>17</td>
<td>13.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>9.4</td>
</tr>
<tr>
<td>Evidence of Some Secondary Gain</td>
<td>41</td>
<td>32.3</td>
</tr>
<tr>
<td>Maintaining disability status</td>
<td>27</td>
<td>21.3</td>
</tr>
<tr>
<td>Dependence on compensation</td>
<td>13</td>
<td>10.2</td>
</tr>
<tr>
<td>Pending litigation</td>
<td>13</td>
<td>9.4</td>
</tr>
</tbody>
</table>

*N=127

Adapted from Jankovic J, Vuong KD, Thomas M. CNS Spectr. Vol 11, No 7 2006
### TABLE 6: Associated diagnoses and somatizations of psychogenic tremor

<table>
<thead>
<tr>
<th>Associated diagnoses</th>
<th>N*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>85</td>
<td>66.9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>72</td>
<td>56.7</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>39</td>
<td>30.7</td>
</tr>
<tr>
<td>Multiple somatizations</td>
<td>108</td>
<td>85.0</td>
</tr>
<tr>
<td>Headache</td>
<td>63</td>
<td>49.6</td>
</tr>
<tr>
<td>Fatigue or exhaustion</td>
<td>62</td>
<td>48.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>52</td>
<td>40.9</td>
</tr>
<tr>
<td>Memory loss</td>
<td>46</td>
<td>36.2</td>
</tr>
<tr>
<td>Pain</td>
<td>39</td>
<td>30.7</td>
</tr>
</tbody>
</table>

*N=127

Adapted from Jankovic J, Vuong KD, Thomas M. CNS Spectr. Vol 11, No 7. 2006

The authors of this study (79) also suggest that besides behavioural and supportive therapy, pharmacological treatment of underlying depression, anxiety, stress management, and physical and occupational therapy are important in the treatment of patients with psychogenic tremor.

### 1.2.12. Tremor of Wilson´s disease

This disease is rare but important, presenting at an early age (4-25 years), an inborn error of copper metabolism that can be fatal if not treated early enough. The tremor appears as an intention tremor, more commonly, a wing beating movement when the arm is abducted at the shoulder. Other associated signs are dystonia, bradykinesia and rigidity. Related to liver dysfunction ring-shaped copper pigmentation in the cornea (Kaiser–Fleischer rings) is seen (4,8).
<table>
<thead>
<tr>
<th>Tremor Syndrome</th>
<th>Clinical features</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced physiologic</td>
<td>Postural tremor: absence of neurologic disease</td>
<td>Chemistry profile (glucose, liver function tests); thyroid function tests; review of medications</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential tremor</td>
<td>Postural tremor: affects arms and head; increases with stress, fatigue, and stimulants; increases with voluntary activities, decreases with alcohol; responds to beta blocker, primidone</td>
<td>No specific test; rule out other problems with general chemistry profile; CBC, and thyroid function tests.</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Resting tremor: increases with stress, decreases with voluntary movement of limb, responds to dopaminergic agents; bradykinesia, rigidity, impaired postural reflexes</td>
<td>No testing needed for typical presentation; MRI for atypical presentations; consider PET or SPECT scanning, if available.</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td>Intention tremor (same side of body as the lesion); abnormal heel-to-shin testing, rapid alternating hand movements; gait abnormalities; Dysarthria; nystagmus</td>
<td>CT scan or MRI; cerebrospinal fluid examination for IgG gamma globulins (if multiple sclerosis is suspected); screen for alcohol abuse (if suspected); check lithium level if lithium toxicity is suspected.</td>
</tr>
<tr>
<td>Psychogenic tremor</td>
<td>Variable (resting, postural, or intention): increases under direct observation, decreases with distraction, changes with voluntary movement of contralateral limb; somatization in past history</td>
<td>Electrophysiologic testing</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Wing-beating tremor: ascites, jaundice, signs of hepatic disease, intracorneal ring-shaped pigmentation; rigidity, muscle spasms; mental symptoms</td>
<td>Liver function tests; serum ceruloplasmin; urine copper; slit-lamp examination</td>
</tr>
</tbody>
</table>

CBC= complete blood count; MRI= magnetic resonance imaging; PET= positron emission tomography; SPECT= single photon emission computed tomography; CT= computed tomography

1.2.13. Fragile X Tremor Ataxia Syndrome (FXTAS)

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a newly discovered neurodegenerative disorder that affects older, mainly male, adults, who are carriers of permutation alleles (55-200 CGG repeats) of the fragile X mental retardation 1 (FMR1) gene (92-97). There are also female carriers developing FXTAS, but with much lower incidence than male carriers (98-101, 93,95). The main features of this syndrome are progressive intention tremor and gait ataxia; additionally, affected carriers commonly have parkinsonism, autonomic dysfunction, cognitive decline, emotional problems including disinhibition and apathy, and peripheral neuropathy (94, 102, 103). MRI findings of affected patients have shown global brain atrophy and white matter alterations manifested as increased T2 signal intensity in the subcortical regions and in middle cerebellar peduncles (MCPs) (104), consistent with earlier report of spongiosis in the deep cerebellar white matter (105).

1.2.14. Klinefelter syndrome associated tremor

People with Klinefelter syndrome (KS) are having one or more extra X chromosome, in which this aneuploidy 47, XXY is the most common abnormality of sex chromosomes in humans, with an incidence of 1/500 male live births (106).

Many individuals with KS have no medical problems (107), only one-third are diagnosed as KS patients (108). Problems that may occur with this chromosome abnormality are post-natal developmental delay, hypogonadism and gynecomastia in the first eighteen years and later for infertility, and behavioural or psychiatric disorders (108). Cognitive functions in KS can vary extremely, though the majority of subjects with KS have a normal intellectual level (106). Besides language difficulties, which are distinctive traits in cognitive functioning of people with KS (106), also coordination difficulties, balance problems, motor movements together with reduced manual ability and reduced strength, and postural tremor may be present (109). Concerning the lateralization of cerebral hemispheres, which has profound implications for higher cognitive functions and behaviour (106), MRI of the brain in adults with KS has presented a lobar asymmetry, indicating a reduction in the total volume of the lateral ventricles (110), and a grey matter volume reduction in the left temporal lobe (111). However, subcortical structures like the hippocampal complex and the cerebellar hemispheres seemed more reduced in the right side (112).
1.3. Alcohol and Tremor

Alcohol’s effects on motor control are well known (113), classic clinical effects become apparent when plasma concentration reaches 2.000 mg/L (2.0 Promille), including behavioural changes, motor incoordination, and slow cognitive functioning (114). Despite its adverse effects, alcohol is also known to transiently improve clinical symptoms associated with certain neurological diseases, such as essential tremor and several other hyperkinetic movement disorders (115). Additionally to ET (115,116), alcohol has been reported to alleviate some secondary (117) and task specific (118,119) tremors, focal dystonia (120,121), myoclonus associated with progressive myoclonus epilepsy (122,123), postanoxic action myoclonus (124), essential myoclonus (125), myoclonus-dystonia syndrome (126,127), and tics (128-130). In contrast, the deterioration by alcohol intake in certain hyperkinesias, such as paroxysmal nonkinesigenic dyskinesias (PNKD) (131,132) and episodic ataxias (133,134,135) has to be mentioned. Furthermore, it is established that alcohol withdrawal could also trigger movement disorders. The so called “rebound” tremor, occurring typically in the morning after an evening of alcohol binge, or during alcohol withdrawal in alcohol addicted patients, is a well-recognized phenomenon (113). Other hyperkinesias have been seen in chronic alcoholics during alcohol withdrawal, including secondary cervical dystonia (136), vocal and motor tics (129,137,138) lingual-oral dyskinesia, facial grimacing resembling tardive dyskinesia (139) and transient, reversible parkinsonism (140,141,142). Additionally periodic limb movements may disturb sleep in alcoholic patients after few weeks of abstinence (143).

1.3.1. The effect of alcohol on the nervous system

Over the years specific interactions between ethanol and major neurotransmitter systems (namely, dopamine, serotonin, GABA, glutamate, and endogenous opioids), as well as second-messenger systems, have been identified. At an ethanol concentration up to 20 mM, a discrete set of neurotransmitter systems, which can be characterized as receptor-gated ion channels, are important in mediating the effects of such ethanol concentrations (i.e., the GABA_A receptors, the NMDA and possibly other glutamate receptors, the nicotinic cholinergic receptors, and the 5-HT_3 receptors). Other important contributors are signal transduction pathways involving adenylyl cyclase and PKC. The activity of dopaminergic neurons, mainly those of the mesolimbic dopaminergic pathways, seems to be particularly
sensitive to ethanol’s action, but changes in dopaminergic neuron activity induced by ethanol may involve ethanol’s action on a number of other neurotransmitter systems, such as serotonergic, opioid, and cholinergic systems. The cAMP generating signal transduction system may be transformed in its activity by moderate ethanol levels and may contribute in certain acute actions of ethanol, but it may also participate in the neuroadaptive consequences (tolerance) of ethanol intake (144). However, the differential contribution of each neurotransmitter system seems to be in dependence on the ethanol dose/concentration (144). Recently, it has been suggested that there are neuronal proteins that are very sensitive to ethanol, called “receptive elements” for ethanol (145,146).

It is a well-known fact that excessive use of alcohol may result in central and peripheral toxicity producing chronic pathological conditions. Wernickes’s encephalopathy, related to thiamine deficiency, is a common complication of chronic alcoholism. Typical features of this disease are cerebellar dysfunction associated with ocular motor abnormalities and altered mental status or memory impairment (113).

Although alcohol can be neurotoxic, for example, by increasing cerebellar oxidative stress, some non-alcoholic components of alcoholic beverages, predominantly red wine polyphenols, such as resveratrol, may be neuroprotective (147,148).

### 1.3.2. Alcohol in Essential Tremor

As mentioned before, alcohol is known to improve essential tremor transiently (149), and it has been suggested that the effect is specific (150). Additionally the response to oral alcohol can be used to predict responsiveness to propranolol (151).

Lou and Jankovic (152) investigated in their study that two-third of their patients who used alcohol, had an improvement in tremor after drinking alcohol. According to Koller et al. (153) alcohol ingestion was reported to decrease tremor in 74% of patients who were cognizant of the effect of alcohol on tremor. In a positron emission tomography study (154) the effect of ethanol on alcohol-responsive tremor was investigated. Patients scanned during rest had a bilateral cerebellar activation including the cerebellar vermis, whereas this pattern of activation differed from passive wrist oscillation where ipsilateral cerebellar activation was observed. Ethanol consumption led to bilateral decreases of cerebellar blood flow in both tremor patients and normal subjects from
the control group, and this was associated with suppression of tremor in the patients. Further, alcohol-associated increases of regional cerebral blood flow were detected in the inferior olivary nuclei in the patients but not in the control subjects. The conclusion of the study is that alcohol-induced suppression of essential tremor is mediated via a reduction of cerebellar synaptic overactivity resulting in increased afferent input to the inferior olivary nuclei.

In another study (151) thirty-nine patients with an action tremor due to a variety of diseases, including essential tremor, Parkinson’s Disease, olivoponto-cerebellar degeneration (O.P.C.D.), ataxia telangiectasia (A.T.), and cervical cord injury with action tremor, were evaluated for the effect of alcohol ingestion. The results of this study show that tremorilytic effect of alcohol is not universal in ET patients, only 61.9% of patients with ET had an improvement in tremor, in which total relief from tremor was not observed in any of their patients. Also the relief is short-lived, lasting in most cases not more than two hours, and followed by an increase of tremor amplitude before returning to base-line level. Action tremor subsided in 46.6% of patients with Parkinson’s disease, one patient with A.T., and one patient with C6 lesion. One patient with O.P.C.D. had deterioration in tremor. According to this study the use of alcohol to differentiate one kind of action tremor from another is unreliable, and the tremorilytic effect of alcohol is neither specific for, nor limited to, ET.

Not only tremor in ET patients improves with alcohol, but also performance of tandem gait (155). Alcohol has been also shown to have a positive effect on the vestibular-ocular system, probably by reducing Purkinje input from the flocculonodular lobe to the vestibular nuclei (156-158).

Adequate treatment of tremor requires a correct diagnosis. However, the clinical differentiation of the various tremor disorders is sometimes difficult, and misdiagnoses occur. Although systematic data regarding subjective alcohol response in patients with tremor disorders other than ET are lacking, a positive alcohol response is often considered as a supportive criterion for the diagnosis of ET which may lead physicians to overdiagnose ET. Another fact that should not be left unattended is that in mainly all ET drug trials, other tremulous patients have probably been included, so it is uncertain which patients with which disease responded to which drug (38).
1.3.3. Research questions / Hypothesis

With this study we aimed to systematically investigate if 1.) drinking habits differ between various tremor disorders and 2.) if subjective alcohol benefit inquired by history is different between a broad range of tremor disorders.

In patients who reported a positive alcohol response we evaluated 3.) the amount of alcohol needed for such a positive response, 4.) the duration of alcohol benefit, 5.) the frequency of a rebound phenomenon, and 6.) the proportion of patients who would consume alcohol because of its anti-tremor effect.

1.3.3.1. Main hypothesis

We hypothesized that subjective alcohol response of tremor can distinguish between various tremor disorders.
2. METHODS

To investigate the subjective alcohol response and drinking habits among patients with various tremor disorders we conducted a prospective study in consecutive patients visiting the movement disorders outpatient clinic of the Department of Neurology, Medical University of Graz, Austria, between July 2011 and end of December 2011. Inclusion criteria included the presence of upper limb tremor and an established diagnosis based on published diagnostic criteria. The study was approved by the local ethics committee. After patient education and written informed consent the enrolment for the study followed.

All patients underwent a full neurological examination and answered together with the examiner the questionnaire which was designed for this study. The questionnaire which was used in the study is displayed in appendix part 6. The following data were collected: age, gender, diagnosis of tremor syndrome, distribution of tremor (affected body parts), age at onset, medication, response to medication, family history, previous medical history, average alcohol consumption, subjective alcohol influence on tremor, dose of alcohol after which an effect was observed, duration of alcohol benefit, presence of a rebound-phenomenon, and alcohol consumption due to its positive effect on the tremor.

Fifty-five out of fifty-six consecutive patients (28 men, 27 women) with upper limb tremor and an established tremor diagnosis based on published diagnostic criteria agreed to participate in this study. Our cohort consisted of 27 patients with IPD, three with dystonic tremor (DT), nine with tremor associated with dystonia (TaD), seven with ET, three with enhanced physiological tremor, two with atypical parkinsonian syndromes, one with Fragile-X-Tremor-Ataxia-Syndrome, two with Klinefelter syndrome associated tremor, and one with psychogenic tremor. The mean age of patients was 62.8 years (SD: 14.89) and the average disease duration was 9.7 years (SD: 11.75).

All data were transferred into an electronic database (excel). Statistical analysis was performed using PASW Statistics 18 for Windows. Statistical analyses were performed comparing all groups. Due to small numbers of some diagnostic entities we also performed statistical analyses comparing the following main groups: 1. ET, 2. IPD, 3. dystonic tremor (DT) and tremor associated with dystonia (TaD), 4. Merged group of all other diagnostic entities). For parametric data oneway-ANOVAs were performed to compare the groups. For
non-parametric data Chi-square-tests were performed. P-Values < 0.05 were regarded as statistically significant.
3. RESULTS

Out of the 55 patients, 44 patients were drinking alcohol and 11 patients denied any alcohol consumption. The average dosage of alcohol consumption among these 44 patients was 5.4 units/week (SD 5.0).

Comparison of the number of patients drinking alcohol versus those who never drank alcohol did not reveal any significant difference between the diagnostic groups (p=0.293). The same applied for the four main groups (p=0.170).

There was also no between group difference in mean alcohol consumption per week among all diagnostic groups (F=0.418; p=0.919) and the four main groups (F=0.202; p=0.895). Referring to the four main groups, group 1 (seven patients with ET), group 2 (27 patients with IPD), group 3 (12 patients with DT or TaD), and group 4 (all others) consumed 4.4, 4.8, 3.4, and 4.1 units/week, respectively.

Of the forty-four patients consuming alcohol, fourteen reported to have no response to alcohol, fourteen reported improvement of tremor, and sixteen patients had never paid attention to the effect of alcohol on tremor (see Figure 3).
The fourteen patients with a positive alcohol response consisted of 6/27 (22.2%) patients with IPD, 2/3 DT (66.6%), 3/9 TaD (33.3%), 2/7 ET (28.57%) and 1/3 patients (33.3%) with increased physiological tremor.

Comparing the number of patients 1.) with and 2.) without response of tremor to alcohol and 3.) those who had never paid attention between the diagnostic groups did not show a statistical significant difference (p=0.195) (see Figure 4).
The following analyses are showing the comparison of the four merged groups 1. ET, 2. IPD, 3. DT and TaD, and 4. all others. 25% of the IDP patients denied any alcohol response, 25% reported improvement of tremor under alcohol intake, and 50% were not able to make a statement, because they never paid attention to it.

14.3% of the DT and TaD patients reported no response, 71.4% reported positive alcohol response and 14.3% made no statement.

Of the ET patients, 50% had no response, 33.3% had a positive alcohol response, and 16.7% paid no attention to it.

The 4th group, containing all others, showed 57.1% with no response, 14.3% with improvement of tremor, and 28.6% made no statement. Comparing the three possible answers (response YES/ response NO/ never paid attention) between the four merged groups showed no significant difference (p=0.106) (see Figure 5).
Figure 4: Numbers of patients in the four main groups (ET; IPD; DT and TaD; all others) with or without alcohol response or no statement possible.

Of these fourteen patients with reported positive alcohol effect, nine patients denied any rebound phenomenon, four reported to have a rebound phenomenon (two patients with IPD, one with TaD, and one with DT), and one patient was not able to make a statement. Only one patient (with DT), out of this fourteen patients with positive alcohol response, reported to drink alcohol because of its anti-tremor effect.

The fourteen patients with positive alcohol effect rated the improvement of tremor as $54.3 \pm 25.4\%$, for a duration of $3.6 \pm 3.1$ hours, after a mean intake of $3.9 \pm 3.6$ units alcohol.

Comparing the above mentioned parameters between the four merged groups among the fourteen patients with a positive alcohol response showed the following results: percentage of tremor improvement after alcohol ($F=1.723; p=0.225$); duration of improvement ($F=1.263; p=0.339$); units of alcohol until improvement ($F=0.427; p=0.738$). Hence, no statistically significant difference was found.
4. DISCUSSION

We have shown that in our cohort consisting of fifty-five patients with different tremor syndromes, forty-four were drinking alcohol. This is in concordance with previous reports of average alcohol consumption in the normal population in Europe (180). Out of these forty-four patients, fourteen reported no response, fourteen reported improvement of tremor, and sixteen had never paid attention to the effect of alcohol on tremor. The fourteen patients with reported improvement of tremor consisted of six patients with IPD, two DT, three TaD, two ET and one with increased physiological tremor. Hence the proportion of patients with a beneficial effect after alcohol consumption did not differ between the diagnostic groups.

As mentioned before in section 1.3., it is historically known that alcohol is able to improve essential tremor transiently (115, 149), and it has been suggested that the effect is specific, so it is often used to support the diagnosis of ET (150, 152). According to Lou and Jankovic (152), they investigated in their study “Essential tremor: clinical correlates in 350 patients”, that two-third of their patients who used alcohol, had an improvement in tremor after drinking alcohol.

In another study (153) alcohol ingestion was reported to decrease tremor in 74% of essential tremor patients who were cognizant of the effect of alcohol on tremor. This study confirms the positive effects of alcohol in ET patients. Additionally to ET (115,116), alcohol has also been suggested to alleviate some secondary (117) and task specific (118,119) tremors, focal dystonia (120,121), myoclonus associated with progressive myoclonus epilepsy (122,123), postanoxic action myoclonus (124), essential myoclonus (125), myoclonus-dystonia syndrome (126,127), and tics (128-130). The improvement of parkinsonian symptoms in a small amount (16%) of patients with Parkinson disease after alcohol ingestion has been documented as well. (113).

However, in another study (151) thirty-nine patients with an action tremor due to a variety of diseases, including essential tremor, Parkinson’s Disease, olivoponto-cerebellar degeneration (O.P.C.D.), ataxia telangietasia (A.T.), and cervical cord injury with action tremor, were evaluated for the effect of alcohol ingestion. The results of this study show that the tremorlytic effect of alcohol is not universal in ET patients, only 61.9% of patients with ET had an improvement in tremor, in which total relief from tremor was not observed in any of
their patients. In this study 46.6% of patients with Parkinson´s disease showed a significant tremor decrease.

Our results underline that subjective alcohol response cannot distinguish between different tremor disorders and is not unique to ET. Percentages of patients within each group with alcohol response: 22.2% IPD, 66.6% DT, 33.3% TaD, 28.57% ET and 33.3% patients with increased physiological tremor.

According to our findings, one may argue that a reported subjective positive alcohol response may not be suitable as a supportive diagnostic criterion for ET. However, the relatively small number of patients in each diagnostic group, is a limiting factor when interpreting our data.

According to Koller and Biary (159) the duration of tremor improvement after alcohol ingestion remained reduced for 30 to 60 minutes. In another study (160) patients with essential tremor were examined, after alcohol intake the amplitude of tremor remained reduced for 1 to 3 hours.

Other collected data are speaking of tremor amplitude reduction after given a single dose of 1-octanol, 1mg/kg orally, with duration for up to 90 minutes (113, 161), and according to Rajput et al. (151) in most cases the relief is lasting not more than two hours.

Our study results confirm those previous data as they showed an average duration of response of 3.7 hours. However, since our data represent subjective finding by the patients, they are not really comparable with the above mentioned studies, which tested the alcohol effect objectively, and used different amounts of alcohol in each study.

According to some studies most of the patients rated the improvement of tremor as 50% or more (154, 159), we had similar findings as our patients (with alcohol benefit) reported an improvement of tremor of 54± 2%. However, total relief from tremor was never observed in our and in another study (151).

The rebound tremor, which typically occurs several hours after alcohol intake, is a tremor with an increase of amplitude, often seen in the morning after an evening of binge drinking (113). According to Koller and Biary (159) several patients with ET complained about a
rebound phenomenon one to two hours after alcohol infusion. Growdon et al. (160) claimed that after the alcohol effect subsides, the tremor amplitude increases for 12 to 24 hours until it returns to base-line level. Also Rajput et al. (151) confirmed an increase of tremor after a short-lived relief in ET.

Out of our fourteen patients who had a positive alcohol response, only four patients reported to have a rebound phenomenon. Among these, there was no patient with ET; hence also the presence of a rebound phenomenon does not seem to represent a specific finding for ET.

Another topic that had been put in context with the relieving effects of alcohol in tremor syndromes is the possibility of alcohol abuse and alcoholism in tremor patients. There have been several case studies to find out the correlation of alcohol misuse in ET patients (149, 162). According to a Swedish community-based study (163) no alcoholism was found in any of the examined ET patients, however, in a large retrospective study in Rochester, Minnesota, excessive use of alcohol was noticed in 16% of the ET cases. This study involved 266 cases, 38% of them were diagnosed as alcoholics (164). According to Bain et al. (165) in a study of families with ET, 10% of the ET index subjects and 4% of secondary cases were identified among the first degree and distal relatives as being dependent on alcohol because of temporary improvement of tremor. Another study showed (166) a high risk of alcohol addiction and/or dependence in ET patients compared to controls, but the study has been criticized, because it was conducted on a population of ET patients in a Veterans Affair (VA) Medical Center, known to have a high prevalence of alcoholism (113). Additionally the results were not confirmed by another study using other diagnostic criteria, also conducted in a VA population (113, 167). By analysing case-control studies, intended to evaluate alcohol use in patients with ET, no significant risk of alcohol abuse was noticed, comparing to control subjects (113).

According to Rautakorpi et al. (168), 194 cases of ET have been compared with matching controls, showing a larger proportion of ET patients consuming higher monthly alcohol amounts than controls, but the difference did not reach statistical significance (113). In another study (169) current alcohol intake instead of lifetime consumption in ET patients have been analysed, but there were not any differences between cases and controls noticeable. A reason for these results could be the low frequency of alcohol users and the low average amount of alcohol (113). In Spanish neurological centers also no excessive alcohol consumption was detected in a population of elderly ET patients in comparison of controls.
In another Sicilian community-based study (171) 31 cases of ET have been compared with matching controls, a negative association was found, but not statistically significant results, suggesting a possible protective effect of alcohol (113).

In a recent report (172) it has been suggested that alcohol abuse is a risk factor for ET. In this prospective study 3285 elderly patients sampled from three communities in Spain showed a high risk of incident ET cases in a population sample with highest drink consumption of alcohol per year at baseline. The authors of the study suggested that the alcohol may be in part responsible for the cerebellar toxicity in association with ET. This study has been criticized, because the possibility of having patients with preclinical ET at baseline has not been considered, as well as moreover 47.4% of the incident cases of ET had no baseline in-person clinical evaluation (113).

Further investigations to link alcohol misuse to ET patients had been conducted (113), according to Bain et al. 43% of patients with task specific tremor and positive alcohol response had excessive alcohol consumption (118). In another study (173) 55 patients with myoclonus-dystonia syndrome, demonstrating a linkage to locus on chromosome 7q21, were showing a significantly increased risk of alcohol dependence among subjects who manifested the disease compared to asymptomatic carriers and non-carriers. The explanation for this condition is that patients use alcohol as “self-medication” to reduce symptoms, resulting in alcohol abuse (113). Non- manifested carriers of Ɛ-sarcoglycan mutations have also shown a high rate of substance abuse (174), as well as patients with genetic predisposition for ET, who do not manifest the symptoms (175).

As mentioned before, alcohol seems to improve also parkinsonian symptoms in some patients (113), but alcohol consumption among patients with Parkinson disease, is not any greater than in control subjects (176, 177). Certainly, a heavy alcohol use or alcohol abuse is less frequent in patients with Parkinson disease than expected (178), and alcohol consumption seems to be independent from genetic factors, such as the SNCA promoter REP1 genotype (179).

Comparing with our results, only one patient stated to drink alcohol because of its anti-tremor effect, and this person is a dystonic tremor patient. None of our patients was an alcoholic (presently or in the past) and the average alcohol consumption did not differ between the groups and was not higher than seen in the general population (180).
In conclusion, this is the first study investigating the subjective response to alcohol in patients with a broad range of tremor disorders. Our data suggest that subjective alcohol response, inquired by history, cannot distinguish between different tremor disorders and may therefore not be suitable as a supportive diagnostic criterion for ET. Importantly the main differential diagnosis to ET, which is DT, did not differ from ET with regard to alcohol response. One major limitation to our study is the currently small sample size and thus our findings need to be investigated within a larger number of patients. Secondly, we currently do not know if an objective alcohol test will show similar findings, hence a follow-up study using an objective alcohol test and comparison to the findings from the subjective questionnaire based study is warranted. Another limitation is that by inquiring alcohol response by history – as it is usually performed in clinical practice and therefore also as part of this study – a large proportion cannot answer the question, because they either do not drink alcohol at all or they had never paid attention to this. Also we cannot compare the drinking habits of our patients to a normal control population, since we did not investigate the latter group. Further investigations with larger sample size in combination with an objective evaluation of alcohol responsiveness in different tremor disorders are needed to shed further light to this topic.
5. REFERENCES


6. APPENDIX

6.1. Questionnaire

Datum: _________________

Fragebogen zur Erfassung des Einflusses von Alkohol auf Tremor
(ist vom Arzt gemeinsam mit dem Patienten zu erheben)

Name: ______________________________________________________________

Alter: ______  Geschlecht: ☐ männlich  ☐ weiblich

Diagnose (Tremor):
☐ Morbus Parkinson  ☐ Essentieller Tremor
☐ Dystoner Tremor  ☐ Tremor assoziiert mit Dystonie
☐ Verstärkter Physiologischer Tremor  ☐ Neuropathischer Tremor
☐ Psychogener Tremor  ☐ Zerebellärer Tremor
☐ Andere______________________________

Alter bei Tremorbeginn: ______

Tremor betrifft:
☐ Kopf  ☐ Gesicht  ☐ Stimme
☐ Obere Extremitäten
  ☐ rechts  ☐ links  ☐ beide
  ☐ Ruhe  ☐ Aktion
☐ Untere Extremitäten
  ☐ rechts  ☐ links  ☐ beide
  ☐ Ruhe  ☐ Aktion

Nehmen Sie Medikamente gegen den Tremor ein?
Wenn ja, besteht ein positiver Effekt auf den Tremor?

☐ Levodopa ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Dopaminagonist ☐ ja ☐ nein ☐ keine Angabe möglich
☐ MAO-B-Hemmer ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Amantadin ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Anticholinergikum ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Propranolol ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Primidon ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Topiramat ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Gabapentin ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Clozapin ☐ ja ☐ nein ☐ keine Angabe möglich
☐ Clonazepam ☐ ja ☐ nein ☐ keine Angabe möglich
☐ andere__________________________ ☐ ja ☐ nein ☐ keine Angabe möglich
                                                                                       ☐ ja ☐ nein ☐ keine Angabe möglich

Positive Familienanamnese (mindestens 1 erstgradig Verwandter): ☐ ja ☐ nein

Fragen zum Alkoholkonsum:

Wie häufig trinken Sie Alkohol:

☐ täglich
☐ regelmäßig, an ca. ___ Tagen in der Woche
☐ gelegentlich, < 1x/ Woche

Wie viel Alkohol trinken Sie?
_____________ Einheiten Alkohol pro Tag

(500 ml 5% Bier – 2,5 Einheiten, ¼ l Wein 12% - 3 Einheiten, 25 ml Schnaps 37,5% bis 40% - 1 Einheit)

Haben Sie das Gefühl, dass sich der Tremor nach Alkoholkonsum bessert:

☐ keine Angabe möglich, ich trinke nicht
☐ keine Angabe möglich, habe noch nie darauf geachtet
□ nein
□ ja, der Tremor bessert sich
(bitte die geschätzte prozentuelle Besserung in der visuellen Analogskala mit einem Kreuz markieren)

Wo bemerken Sie die positive Alkoholwirkung auf den Tremor?

□ Kopf □ Gesicht □ Stimme
□ Obere Extremitäten
□ rechts □ links □ beide
□ Ruhe □ Aktion
□ Untere Extremitäten
□ rechts □ links □ beide
□ Ruhe □ Aktion

Kommt es nach Abklingen des positiven Alkoholeffektes zu einer vorübergehenden Tremorzunahme? Ja □ Nein □ Keine Angabe möglich □

Trinken Sie Alkohol wegen seiner positiven Tremorwirkung?
□ ja □ manchmal □ nein