DRUG INDUCED TREMOR

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Drug induced tremor describes a heterogeneous group of tremors caused by a variety of drugs. Drug-induced tremor may produce a resting tremor (e.g. metoclopramide), an intention tremor (e.g. epinephrine) or an action/postural tremor (e.g. SSRIs). Drug induced tremor may also enhance normal physiologic tremor or pathological tremors. Patients should be directly asked about exposures to recreational drugs, alcohol, and caffeine after the clinician takes a full medication history (1). Factors that aid the clinician in the diagnosis include: (a) a temporal relationship between drug and tremor onset, (b) a dosage dependent change in tremor severity, (c) lack of tremor progression, (d) exclusion of an underlying medical cause. Drug reduction or elimination is usually the treatment strategy. A 2015 case report discussed successful intervention with ViM deep brain stimulation in a woman with neuroleptic induced tremors.(2)

I. Drugs of abuse: Ethanol, nicotine, cocaine, psychostimulants, 3,4-methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), inhalants (3-12)

II. Neuroleptics and dopamine depleting agents: 15-60% of patients who are exposed to antipsychotics develop tremor. Risk factors for developing tremor include (1) older age, (2) women, (3) familial predisposition, and (4) AIDS (13). The type of antipsychotic used and the total daily dose consumed can also influence the development of tremor. Resting tremor is typically present in the arms and is asymmetric. After drug discontinuation, symptoms are generally reversible but might take as long as 15 months to wash out. Patients can develop a tardive tremor which is a 3-5 Hz and improves with rest and goal-directed movements. Tardive tremor usually improves with antipsychotic or dopamine depleting agents.

III. Antidepressants and mood stabilizers:
   a. Tricyclic antidepressants TCAs are associated with an enhanced physiologic tremor; Amitriptyline is the drug most commonly associated with this tremor.
   b. Selective serotonin reuptake inhibitors (SSRIs): A tremor is commonly seen in SSRIs, affecting up to 20% of tremor-naïve patients (14).
   c. Postural tremor may also be an early manifestation of serotonin syndrome. The tremor is more prominent in the legs in these cases (15).

IV. Lithium: Tremor is often associated with lithium, with incidence estimates of 4-65%. Development of tremor is frequently early in the treatment course but may occur any time after drug initiation. It may occur over a wide range of serum concentrations. Tremor may improve over time; tremor can deteriorate in the elderly. However age (elderly), sex (men>women), and personal or family history of tremor, increases the likelihood of developing tremor. The most common tremor is an enhanced physiologic (postural) tremor with a frequency of 8-12 Hz. It mainly affects the hands. Tremor may worsen with activities requiring fine control. This tremor may be seen in cases of neurotoxicity and careful screening of cognition (mental confusion), eye movement (nystagmus), and coordination (ataxia) should be performed when tremor emerges. Rarely, patients taking lithium may develop parkinsonism associated with a resting tremor. Risk factors are older age, duration of treatment, and high serum concentrations of lithium.

V. Anti-epileptic drugs (AEDs): Valproic acid (VPA) is the most common AED associated with tremors. Twenty-five to twenty-eight percent of patients may have symptoms or signs of tremor. Tremor may be postural, action induced, or at rest. Using slow preparations or lowering total dose of VPA may reduce tremor. Clinically, the tremor often has similar features to essential tremor. The frequency is 8-12 Hz. Tremor may be present in the limbs, head, mouth, or tongue. VPA may rarely cause parkinsonism and cognitive impairment. This is associated with a resting tremor (16). Other AEDs such as lamotrigine, oxcarbazepine, gabapentin, and tiagabine may produce an enhanced physiologic tremor.

VI. Others: Bronchodilators (β_2-adrenergic agonists) enhance postural tremor. Chemotherapeutics such as thalidomide, cytarabine, ifosfamide, vincristine, cisplatin, and tamoxifen can cause tremor (17, 18). Some gastrointestinal drugs are dopamine receptor-blocking drugs such as prochlorperazine and metoclopramide and are thus associated with a parkinsonian-like tremor. Cimetidine may cause an enhanced physiologic tremor. Some hormones can cause tremor. Levothyroxine overdose is associated with enhanced physiologic tremor and action tremor. Epinephrine and norepinephrine may cause an intention tremor. Medroxyprogesterone was associated with a resting tremor in breast cancer patients who received this treatment (19). Some immunosuppressants and immunomodulators can cause tremor. These include cyclophosphamide, tacrolimus, and interferon alpha (20-23).

Functional Tremor (FT)

Also known as psychogenic or hysterical tremor, functional tremor is estimated to occur in up to 10% of cases seen in tertiary care centers. It represents approximately 50% of psychogenic movement disorders. Functional tremor is a complicated diagnosis and should be considered a diagnosis of exclusion.

I. Historical clues to diagnosis: (a) Identification of a physical or psychological precipitant prior to tremor onset, (b) acute tremor onset, (c) periods of remission, (d) rapid generalization of tremor, (e) absence of family history of tremor, (f) presence of other somatic complaints without obvious cause or signs, (g) presence of other psychiatric illness, (h) patient is employed in the health profession, (i) patient has a secondary gain: pending litigation, monetary compensation, (j) history of childhood trauma (24-26)

II. Examination clues to diagnosis: (a) combination of tremors with some or all of the components of rest, postural and intention tremor; rest tremor does not usual manifest as finger tremor, (b)tremor varies in amplitude, frequency, and direction (c) tremor varies with concentration and decreased attention (distractibility), (d) selective disability,(e) entrainment, (f) presence of a co-activation sign, (g) dual task interference, (h) worsening tremor with weighted objects, (i) suggestibility, (j) presence of unrelated neurological signs (K) presence of other psychogenic movement disorders (25, 27). A “Whack-A-Mole” sign may be present during which the tremor of the affected limb is suppressed when the limb is held and subsequently the involuntary movement emerges in other limbs. (26)

CLINICAL PEARL: TESTING TREMOR FOR DISTRACTABILITY

Alternative finger tapping: With arm extended, the patient is asked to tap alternatively D2, D5, D3: 10x.
Serial 7s: The patient is asked to hold his/her arms outstretched and perform serial 7s.

CLINICAL PEARL: ENTRAINMENT

Ask the patient to perform a repetitive activity on an unaffected limb: tapping a foot, tapping the thumb and D2 together, opening and closing a hand, etc:
Changing the task, especially the directionality of task (change from opening/closing hand to pronation/supination) mid-task may be helpful.
Try to have the patient demonstrate the activity at a speed that is different than the speed of tremor in the affected limb.

The diagnosis is a clinical diagnosis that is best made by a neurologist, preferably a movement disorder specialist. A battery of electrophysiological studies was shown to have high sensitivity and specificity when used to assess patients suspected of a functional disorder. The test length was brief, approximately 15 minutes. The battery was most predictive in patients with less than 10 years of disease. (28)

Orthostatic tremor

Orthostatic tremor (OT) is a high frequency tremor (14-18 Hz), most commonly associated with the lower extremities, though present in the upper extremities in more than half of the OT patients (29). OT is sometimes categorized as either primary OT ± postural tremor where there are no other neurological deficits and OT “plus” associated with other neurological abnormalities, such as progressive supranuclear palsy (30). Research suggests cerebellar dysfunction in affected patients (31). Symptom presentation occurs in the middle-aged and the elderly, with a mean age of onset in the sixties. Women are more often affected than men (32). Symptoms frequently progress in frequency and severity. Onset latency decreases over time. A 2016 report published in *Neurology* reviewed 184 cases of OT seen between 1976 and 2013 at the Mayo Clinic (29); Records indicated

that of 155 patients who were asked about symptom changes over time, 91% endorsed progression of symptoms. A study of the long term outcomes of OT also reported progression of symptoms in almost 80% of patient regardless of primary vs OT “plus” classification (33).

Clinical and examination characteristics of primary OT are described as follows:

I. Patients have no complaints at rest but upon standing feel unsteady. They may describe their legs as shaky, tremorous, or quivering. Initial latency may be in minutes but can be reduced to seconds with disease progression.

II. Patients often stand on a wide base. When trying to stand still, patients may shift weight between their legs, walk in place, or lean against a wall (34). Symptoms remit when walking, leaning on an object, or when sitting.

III. Tremor is often not visible. When observable, only a fine ripple of muscle movement may be seen.

IV. The tremor may be palpable or audible. Using the diaphragm of the stethoscope, the clinician may auscultate a thumping sound over the quadriceps and hamstrings when the patient is standing. This high frequency sound is often termed the "helicopter sign" as it sounds similar to the rotor blades of a helicopter. When walking, the tremor disappears on the non-weight-bearing limb. Conversely, if the patient is asked to support their weight equally on all four limbs, a 16-Hz tremor in the proximal limbs of the upper extremities may be seen (35). When placed in the supine position, isometric contraction of the arms or leg muscles can induce a 16 Hz tremor in some patients. This implies that OT is not truly orthostatic (36). One study of 26 patients with orthostatic tremor reported eighteen patients complained of tremor in other locations including lips, jaw, hands, and whole body (37). Postural tremor in the upper extremities is a common finding associated with OT. Essential tremor is present in 30-40% of patients with OT.

Although clonazepam is the most common medication tried, reports indicate only a moderate response to this medication with little over half of the patients with any response. Patients responsive to the medication may lose some of this responsiveness over time. A blinded placebo crossover trial showed treatment efficacy using gabapentin (600-900 mg three times daily) as an adjunctive to other treatments, with most patients taking clonazepam (38). In the recent Mayo clinic study, approximately one-third of patients prescribed propranolol had some response to the medication, although the response was mild. Primidone and sodium valproate may be useful in some cases (34).

Palatal Tremor

Palatal tremor, formerly labeled as palatal myoclonus, is defined by short, mostly rhythmic contractions of the palatal musculature. The tremor may be unilateral or bilateral. Palatal tremor is classified into one of two categories: essential palatal tremor (EPT) and symptomatic palatal tremor (SPT). While there are clinical distinctions between the two classifications, there is some overlap.

Essential Palatal Tremor (EPT)

EPT represents approximately 25% of all palatal tremor cases and has no identifiable etiology. There is no sex preference. A review of the literature reported the mean age of onset is 29.4 ± 16.8, range: 4-74 (39). The spectrum of presentation is heterogeneous and may represent a variety of etiologies. Imaging studies are normal. Transoral or transnasal endoscopy may be helpful in a definitive diagnosis (40).

1. Palatal movements with ear clicking: Patients with EPT complain of a clicking sound in the ear. Descriptions of clicking have included “ticking”, “banging”, “cracking”, “popping”, “clattering”, “crunching”, and “crackling”. Clicks can be loud and audible by others. The sound is produced by contractions of the tensor veli palatini, a muscle which attaches to the Eustachian tube. This muscle is innervated by cranial nerve V (CN V). When the muscle contracts, the tube opens, causing a breakdown of the surface tension with the tube. The frequency of the contractions ranges from 20-420/ clicks a minute, with a range of 125 ± 70. Clicks are equally likely to be fully or partially rhythmic. When the clicks are described as unilateral, they more often originate from the left side (39).

2. Cessation of symptoms in sleep: Older literature suggested that EPT universally ceased in sleep (41). This was used as a distinctive characteristic of EPT. However, a more recent review of the literature found that tremor persists in sleep in almost half of the cases.

3. Involvement of other muscles: In approximately one-third of cases, other muscles are involved. Typically these are oropharyngeal muscles; reports indicate that the masseter, temporalis, and other muscles of the periorbital and perioral regions are occasionally involved.

Botulinum toxin may improve symptoms. Resection of the stapedius muscles is another approach, although the stapedius muscles are rarely the source of the click.

Symptomatic Palatal Tremor (SPT)

Lesions producing SPT are localized to the brainstem or cerebellum. Typically the lesion is located in the Guillain-Mollaret triangle. MRI imaging typically reveals the lesion, often seen as a hyperintense signal on T2 weighted images or on proton density weighted images. Stroke (46%), trauma (11%), demyelinating lesions (10%) and posterior fossa tumors (6%) are the most common etiologies identified (42). Pseudohypertrophy of the inferior olive is a characteristic finding on imaging. The hypertrophy is not seen immediately and evolves approximately three weeks after the lesion. Post-mortem pathological studies have found degeneration of the inferior olive. Symptom onset is thought to occur 2-49 months after the neurologic event.

1. Palatal movements without ear clicking: Most cases of SPT do not involve clicking of the ear. Patients are often unaware of the palatal movements. These movements are caused by the levator veli palatini, a muscle which is innerved by the facial (CN VII) and ambiguus (CN IX) cranial nerves. This muscle lifts the palate posteriorly, pulling the free edge of the palate against the upper pharynx.

2. Persistence of symptoms in sleep

3. Oscillopsia: While not present in EPT, up to 30% of patients with SPT have oscillopsia on exam. Two different types of movements are described. The first is a bilateral symmetric vertical pendular nystagmus. The second type of movement is nonconjugated. Eye movements are asymmetric and are associated with simultaneous oblique and rotator nystagmus (40).

4. Tremors or myoclonus of the head or extremities: Although less common, tremors of the head or extremities may be seen in up to 10% of SPT patients. These movements are often in sync with palatal movements, suggesting that both movements may be generated from the same oscillator.

5. Involvement of the pharynx and/or larynx: Rarely, but unique to SPT, the larynx and pharynx are involved in some cases. Vocal production may be rhythmically modulated, producing a vocal tremor. Spasmodic dysphonia is described in some patients. Rhythmic involvement of the larynx and pharynx may affect airflow, causing breathing abnormalities.

6. Cerebellar findings: Ataxia, dysarthria, and other cerebellar signs are sometimes seen.

Psychogenic Palatal Tremor

Voluntary control of the tensor veli palatini is possible and has been reported in musicians and scuba divers. Some reports mentioned cessation of ear clicking with maneuvers such as wide mouth opening. Thus, it is possible for a palatal tremor to be caused volitionally and ultimately have a psychogenic origin. There are several reports of psychogenic palatal tremor (43-45).

Geniospasm

Geniospasm is the term used to describe paroxysmal tremor of the chin and lower lip (46-49). Symptom onset usually occurs in infancy or childhood, but can present in adults. The frequency of episodes may reduce with age. Contractions are typically confined to the mentalis muscle and may last from minutes to hours. The tremor is high

frequency ranging between 8-10 Hz. Tremor can be stress induced and exacerbate when the affected individual is stressed, concentrating or emotional. Some cases are associated with otosclerosis and deafness. Nocturnal tongue biting, bruxism, somnambulism, and REM sleep behavior disorder have been reported. Botox into the mentalis muscle is used as first line therapy.

Holmes Tremor (aka 'rubral tremor', 'midbrain tremor')

Holmes tremor is a low frequency tremor (<4.5 Hz), predominantly affecting the proximal limbs. The upper extremities tend to be more involved than the lower. The tremor typically presents at rest, posture, and during action; postural tremor is not mandatory to make a diagnosis. A vascular etiology is the most common identified source. Other reported causes include head trauma, infection, multiple sclerosis, tumors, and radiotherapy. There is typically a delay (4 weeks- 2 years) between the underlying insult and symptomatic presentation. The mean latency is approximately two months (50). A 2016 review of 29 cases with Holmes tremor reported all patients had at least one other neurological finding on examination, most commonly hemiparesis ipsilateral to the side of the tremor and ataxia (50). Because there is often an identifiable cause of symptoms, an MRI brain should be performed in all patients. Lesions are commonly seen in the midbrain, thalamus, or cerebellum and more than one lesion is common.

Holmes tremor is often poorly responsive to medications. In the 2016 case series, approximately half of the patients had tremor improvement with levodopa; Dosing ranged from 300 mg- 1000 mg daily with mean dosing at approximately 700 mg daily. Sustained improvement in Holmes tremor with levodopa has been reported (51). Levetiracetam may be effective in some cases (52, 53). There are reported cases of improved of Holmes tremor with botulinum toxin injections (54, 55). Deep brain stimulation may be an option for patients who are refractory to medication. Although thalamic ViM (56) was the traditional target for Holmes, recent studies suggest GPi could also be an effective target (57-59).

Cerebellar Tremor

Similar to Holmes tremor, a cerebellar tremor is an irregular, slow frequency tremor (<5 Hz) that may have a unilateral or bilateral presentation. Causative lesions are often due to stroke, multiple sclerosis, or a tumor located ipsilateral to clinical symptoms. Drug toxicity due to medications such as phenytoin, valproic acid, and amiodarone can produce a cerebellar tremor. Clinical characteristics of the tremor are as follows: (a) Cerebellar tremor appears at initiation and along the course of movement and has a coarse side-to-side component. This is seen during finger-to-nose testing with the examiner's finger in a fixed position. The patient should demonstrate a full range of movement. The examiner should take note of any change in tremor as the patient approaches the target. Cerebellar tremor is seen during action and sometimes posture. It is not seen at rest. (b) Midline cerebellar or vermal lesions may produce bilateral arm tremor often involving the head and trunk (titubation). These finding are often more prominent when the patient is asked to stand. (c) Other cerebellar findings may be seen on examination including (1) a broad based ataxic gait, (2) incoordination of the limbs, (3) cerebellar speech, and (4) impaired oculomotor movements and/or nystagmus.

Fragile X associated tremor-ataxia syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that develops due to premutation range (55-200) CGG repeat expansion in the fragile X mental retardation 1 (FMR1) gene. Patients often present with tremor in their sixties and seventies. Tremor severity correlates with the number of inherited CGG repeats.

Clinical criteria for diagnosis have been established. The major criteria include the presence of intention tremor and cerebellar ataxia. Minor criteria include parkinsonism, Although symptoms of parkinsonism are common, rest tremor is rare. When present, rest tremor often presents as a re-emergent postural tremor. (60). Rest tremor may be seen in approximately 25% of patients. Bradykinesia and postural instability are more common. (61) Cognitive difficulty is another minor criterion and include moderate to severe short term or executive function deficits. Women are less likely to develop cognitive dysfunction than men. The third minor criterion is the presence of neuropathy. The pattern is typically axonal and may be less severe in women (62).

Major radiological findings include the presence of T2 hyper-intensities in the middle cerebellar peduncles (the "MCP sign") and MRI white matter lesions in the splenium of the corpus callosum. The 'MCP sign' is more common in men than women**.** Corpus callosum splenium hyperintensity may be as common as the MCP sign (63). Minor radiological criteria include MRI lesions in the cerebral white matter and moderate-severe general atrophy. The table below outlines how the diagnosis is labeled as "definite", "probable" or "possible" FXTAS.

Clinical criteria for FXTAS (64, 65)

	Clinical Criteria	**Radiological Criteria**	**Other**
Definite FXTAS	1 major	1 major	
	1 major	-	Intranuclear inclusions (post-mortem)
Probable FXTAS	2 major	-	-
	1 minor	1 major	-
Possible FXTAS	1 major	1 minor	-

Genetic testing should be considered in (a) women with a history of ovarian insufficiency, (b) patients who have family members or who themselves have intellectual disability symptoms on the autistic spectrum, (c) a family history of FXTAS, and (d) patients who present with tremor and ataxia of unknown etiology (66). The presence of MRI hyperintensities in the middle cerebellar peduncles or the splenium of the corpus callosum are independent indicators for FMR1 testing (64).

When patients present with action tremor, propranolol, primidone, and topiramate are variably successful in treating symptoms (63). A memantine trial failed to show benefit in tremor, balance, or executive function in FXTAS patients (67). Parkinsonism may improve with dopaminergic medications and anticholinergics (60). Alloprenanolone, a natural neurosteriod, may lessen mRNA toxicity and is a targeted agent for future treatment trials. Little is known about the possible role of deep brain stimulation. A case series of three patients who received placement of the leads into the ventral intermedius nucleus reported persistent benefit (68). Patients may also benefit from MRI-guided focused ultrasound thalamotomy (69).

Wilson's disease

Wilson's disease is a rare autosomal recessive disorder associated with liver dysfunction and neurologic manifestations. The peak incidence of disease onset is 17 years-old but Wilson's may present in childhood and rarely in the sixth or seventh decade of life. Mutations in the ATP7B gene cause abnormalities in copper metabolism. Copper deposits in the corneal limbus may be visible to the naked eye, and are called Kayser-Fleischer (KF) rings (Figure 8.3). Thought to be present in virtually all Wilson's patients who have neurologic manifestations, the rings are brown to brownish-green discolorations that are typically best visualized on the northern and southern corneal poles. Neurologic manifestations typically present in the 20s and 30s (70). The workup includes a screen for low serum ceruloplasmin. Serum copper levels, 24-hour urinary copper excretion, liver biopsy and genetic testing may be needed in some cases (71). Wilson's patients with extrapyramidal symptoms commonly have MRI abnormalities. The reported "face of the giant panda" sign is seen in less than 20% of those with MRI abnormalities. Common abnormalities include tectal plate hyperintensity, central pontine myelinolysis-like changes, and concurrent signal changes in the basal ganglia, thalamus, and brain stem (72). Wilson's can be a treatable, and at times fully reversible, condition, granted chelation therapy is promptly instated. Copper chelators and zinc salts are the primary form of treatment. Treatment is life-long. Approximately 10% of patients with neurological symptoms prior to treatment may have worsening of symptoms upon treatment initiation (73).

Main points regarding tremor and neurologic findings in Wilson's disease include the following:

I. The classic description of tremor in Wilson's disease is a wing-beating tremor. This is seen when the patient is asked to hold the arms in a "wing" position during which the arms are extended forward, the elbows are flexed and the palms are facing downward. The wing-beating tremor may also be elicited by asking the patient to extend the arms laterally. Once the patient is positioned, the examiner looks for a high amplitude, low-frequency tremor in the proximal muscles. The tremor may increase in amplitude as the patient sustains the posture (74). The presence of a wing-beating tremor alongside dysarthria is highly suggestive of Wilson's disease (70).

II. Tremor is present in 22-55% of patients. Many types of tremor are seen in Wilson's patients and the classic tremor described above is not the most common. Dystonic tremor is the most common tremor observed. Early in the disease course the tremor can mimic essential tremor. Unlike essential tremor, the tremor of Wilson's is often overtly asymmetric and voice is not involved.

III. The upper extremities are the most common body part associated with tremor. Lower extremity and head tremor are seen in some cases. Tremor can be positional and kinetic. The kinetic tremor is most commonly seen in the distal upper extremity and is a low-amplitude, medium-to-high frequency tremor. It is rare to see a unilateral isolated rest tremor in Wilson's disease. Rest tremor, when present, usually accompanies an action tremor which is greater in severity (75).

IV. Tremor in Wilson's disease is typically not an isolated neurological finding; rather, it a one component in a constellation of symptoms, including chorea and dystonia. (76). Dysarthria is the most common neurologic manifestation of Wilson disease, present in the majority of cases with neurologic manifestations. Cognitive impairment can be present and is often subtle. Patients may have impairment of executive dysfunction, attention, apathy, impulsive, and social impairment suggestive of a frontal lobe syndrome. Seizures occur in approximately 6% of Wilson's patients. Psychiatric impairment is common and patients may have subtle personality changes early in the disease course. Depression is the most common psychiatric manifestation.

Peripheral nerve tremor

Tremor can occur in disorders of the peripheral nervous system. It is most commonly seen in demyelinating neuropathies. Frequent associations include chronic inflammatory demyelination polyneuropathy (CIDP) and hereditary motor and sensory neuropathy (HMSN1). One study found tremor in 56% of cases with inflammatory neuropathy (77). Less commonly it is associated with diabetes mellitus, uremia, porphyria, and diseases of anterior horn cells (78). Tremor severity does not correlate with severity of neuropathy. The tremor can appear similar to essential tremor with components of posture and action. Often, the postural tremor is greater in amplitude and severity than the action tremor. Reports suggest that propranolol, primidone, baclofen, and pregabalin may all be helpful for treatment (79). However, a study of 27 patients with inflammatory neuropathy found minimal response to treatment trials (77).

Tremor in multiple sclerosis (MS)

Tremor is a common neurological manifestation of multiple sclerosis. Estimates of prevalence range from 25%-58% of MS patients (80, 81). Postural and intention tremor are the two most common tremors detected and the most common distribution of symptoms is bibrachial. Tremor can also involve the head, neck, vocal cords, and trunk (82). Dystonic tremor has been reported as well (83). Rest tremor has also been reported, although a rare occurrence. Agents reported to have some success include propranolol, levetiracetam, isoniazid, botulinum toxin injections and 4-aminopyridine, the latter which has recently been approved for the treatment of MS-related gait dysfunction. (84-86). Thalamotomy (including gamma knife thalamotomy) and ViM deep brain stimulation are surgical approaches reserved for select patients with multiple sclerosis (87, 88). The majority of patients have significant improvement after surgical intervention (89, 90).

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