

# Cerebellar Tremor – Definition and Treatment

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*One of the most difficult movement disorders to diagnose and treat is cerebellar tremor. This review serves to familiarize the clinician with basic definitions and treatment options for this tremor type.*

Definition. Cerebellar tremor is defined as a proximal 3 to 5 Hertz action tremor in the extremity ipsilateral to lesions of the deep cerebellar nuclei or the outflow tracts of these nuclei in the superior cerebellar peduncle. Most commonly, cerebellar tremor is a low frequency tremor, that is, below 4 Hertz. Although, there is some confusion regarding the nosology of the types of tremor, it is generally accepted that one calls the action tremor during movement a “kinetic tremor”, the increase in kinetic tremor amplitude at endpoint “intention tremor” and the action tremor during posture holding a “postural tremor”.<sup>1</sup> Classically, the tremor amplitude of cerebellar tremor increases as the limb is visually guided to the target thus termed “intention tremor.” It can be elicited by performing finger-to-nose testing, finger-chase testing or heel-knee-shin testing. There may be a postural component of the tremor. One must differentiate tremor from the incoordinated ataxic movements of the limb also seen with cerebellar dysfunction. Limb ataxia is a general term that refers to the gross irregular decomposition of movements of the limb. Specifically, poor performance in smooth, fluent, rapid alternating movements is called dysdiadochokinesis. Dyssynergia is the loss of muscle coordination leading to breakdown of ‘en mass’ movements into

individual parts and dysmetria is the inability to measure properly range in motion with hypometria (undershooting target) as well as hypermetria (overshooting target). Cerebellar tremor is usually perpendicular to the direction of movement and variable in amplitude. The dominant feature of tremor should be its rhythmic nature. The diagnosis of cerebellar tremor may be made only when there is a pure or predominant intention tremor (unilateral or bilateral) of low frequency (usually below 5 Hz) without the presence of a resting tremor.<sup>1</sup>

### Pathophysiology of Cerebellar Tremor.

There are 3 theories about how the normal cerebellum guides and controls movement.<sup>2</sup> The first is that the cerebellum acts through a feedback system. This system uses constant feedback to the cerebellum from the peripheral receptors to adjust ongoing movement. A lesion study in cats supports the role of cerebellar outflow neurons in correcting ongoing movement initiated by the motor cortex.<sup>3</sup> The second theory is that the cerebellum uses feedforward control. In this theory, the cerebellum has planned motor sequences that are sent to the motor cortex in anticipation of movement. This enables movements to be accomplished more quickly especially for learned movements. Evidence shows that there is



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activation of the dentate nucleus that proceeds intended movement.<sup>2</sup> Lastly, there is the idea of efferent copy in which the motor cortex provides the cerebellum with a 'copy' of the motor plan that is being sent to effector muscles prior to movement. The cerebellum can then make short loop corrections back to the motor cortex even before movement is completed. It stands to reason that the development of pathologic tremor must involve dysfunction of one or more of these control systems allowing oscillation to occur. The most important cerebellar pathways for movement control involve the cerebello-dentato-rubro-thalamic circuit. Cerebellar tremor is caused by a lesion of these deep lateral cerebellar nuclei or their outflow paths in the superior cerebellar peduncle up to but not beyond the red nucleus.<sup>4</sup> Injury to the cerebellar cortex itself does not initiate tremor. Electrophysiologic studies of tremor frequency may be helpful in diagnosis of cerebellar tremor as few types of tremor have such low frequency.<sup>5</sup>

*Etiology of Cerebellar Tremor.* There are many causes of cerebellar tremor. The most common causes are multiple sclerosis (MS), trauma, and degenerative diseases of the cerebellum. Tremor and other cerebellar signs are often seen in MS, especially with disease progression. After severe closed head injury, tremor emerged between 2 weeks and 6 months in 19 percent of survivors in one study with 58 percent of those experiencing tremor of less than one year duration.<sup>6</sup> The cerebellar degenerative diseases may be inherited or spontaneous (*Table 1*). Rarely do any of these disorders present with tremor as an isolated feature nor does the tremor distinguish the etiology of cerebellar disease. This tremor, like most others, is

never a sign of normal aging. As a general rule, degenerative or toxic cerebellar dysfunction cause bilateral tremor and a focal unilateral disease process, such as a mass, infarction, or plaque, causes unilateral tremor. But there are a variety of other signs of cerebellar dysfunction depending on the areas of the cerebellum or outflow tracts that are affected. The tremor in context with history, neurological exam and evaluation should lead the clinician to a working diagnosis in most cases. Magnetic resonance imaging (MRI) is very helpful to assess the cerebellum for degeneration, white matter disease and to show the plaques of multiple sclerosis. MRI brain scanning can also define traumatic injury, tumor formation or cerebrovascular accident and is recommended in any case of new onset cerebellar tremor. Toxic causes of intention tremor include: chronic alcoholism, lithium, heavy metal intoxication, and some medications<sup>7</sup> of the anticonvulsant, antidepressant and neuroleptic classes. Other causes of cerebellar tremor: neoplasm and paraneoplastic syndromes, Wilson's disease and other inherited metabolic diseases, endocrinopathies, and infections.<sup>8</sup>

*Treatment of Cerebellar Tremor.* As our understanding of the pathophysiologic basis of cerebellar tremor grows it is hoped that better treatments for these potentially disabling tremors will be developed. Open label studies and case reports have suggested several medications that may have some benefit including propranolol, primidone, glutethimide, carbamazepine, isoniazid, clonazepam, buspirone and topiramate. However, there have been few randomized double-blind (DB) trials. Many of the medications tried for cerebellar tremor have been used to treat essential tremor. Braham

Table 1. Causes of Cerebellar Tremor

CAUSE	GENETIC TEST AVAILABLE
<i>Trauma</i>	
Closed head injury, Hypoxia, Stroke, Cerebellar neoplasm, Hyperthermia	
<i>Inherited</i>	
Spinocerebellar ataxias	SA1-SCA 17 SCA-12, SCA-16, SCA19
FXTAS	Fragile X DNA
<i>Diseases</i>	
Multiple Sclerosis, OPCA/MSA, Wilson's Disease Paraneoplastic syndrome	Hu, Yo, CV2, TaTa, Ri, CAR, LEMS
Creutzfeldt-Jacob disease Guillain-Barre' Syndrome Endocrinopathy Hyperthyroid Hypoparathyroid Hypoglycemia (insulinoma) Cerebellar Neoplasm	
<i>Infections</i>	
Rubella, H. Influenzae, Rabies, Varicella infection or vaccination	
<i>Drug effects</i>	
EtOH, Lithium, Heavy metal, Anticonvulsants, Antidepressants, Neuroleptics, Chemotherapeutic agents	

FXTAS, Fragile X associated tremor and ataxia; OPCA, olivopontocerebellar atrophy; MSA, multiple system atrophy

et al.<sup>19</sup> noted beneficial effects on ataxia and intention tremor in 2 brothers with familial ataxia treated with propranolol 120 mg/day. However, in a crossover treatment trial of 6 patients, propranolol was not found to benefit cerebellar tremor.<sup>18</sup> In another report, 2 patients with MS-related tremor given primidone experienced tremor reduction and better hand control.<sup>14</sup>

In a 10 patient single-blind study, carbamazepine significantly reduced cerebellar tremor amplitude and clinical tremor scores at 15 days (400 mg/day) and 30 days (600 mg/day). Improvement

correlated with mean carbamazepine plasma levels.<sup>12</sup> Seven of the 10 patients chose to stay on long-term treatment and attempts to lower the carbamazepine dose were associated with worsening of tremor. An open-label study of 3 patients with cerebellar tremor following stroke noted marked efficacy of carbamazepine at 600 mg/day (serum levels between 5.8 - 9.6 micrograms/ml) with return of tremor severity upon cessation of the agent.<sup>11</sup> It has been postulated that the mechanism by which carbamazepine ameliorates cerebellar tremor is through reduction of

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repetitive neuronal firing in the VIM nucleus of the thalamus.<sup>10</sup>

Evidence as to whether isoniazid can reduce cerebellar tremor has been mixed. Limited improvement from isoniazid up to 1000 mg/day was reported by Duquette in 13 MS patients with 10 patients showing slight change on one or more assessments.<sup>20</sup> However, other trials with isoniazid reported better success with doses up to 1200 milligrams per day. Isoniazid inhibits  $\gamma$ -aminobutyric acid-aminotransferase, the first step in the enzymatic breakdown of GABA, and therefore increases GABA concentration. GABA is the major inhibitory neurotransmitter of the efferent pathways of the cerebellum and CSF levels of GABA are known to be reduced in some degenerative cerebellar ataxias.<sup>21</sup> Isoniazid has many adverse effects including the potential for hepatic toxicity and liver function testing should be done regularly.

Other treatments to enhance GABA have been tried. Weiss et al, reported marked improvement in upper extremity cerebellar tremor in one case after an intrathecal baclofen pump was placed for bilateral lower extremity spasticity.<sup>22</sup> In addition, benzodiazepines have been reported shown to improve some cases of cerebellar tremor<sup>10, 23</sup> by facilitating GABAergic transmission. In a study by Sechi et al, the GABA agonist, topiramate was employed in doses up to 200 mg per day (average 122 mg/day) in 9 patients (5 with MS, 2 with inherited degenerative disease, 1 with paraneoplastic syndrome, and 1 CVA) with 7 taking it as monotherapy and 2 in combination with carbamazepine.<sup>15</sup> There were significant reductions in both postural and intention tremor in the treated group but 3 of 9 patients terminated early due to side effects.

These results suggest that a placebo-controlled trial of topiramate using a slower titration in an effort to lessen side effects is warranted.

Buspirone hydrochloride, a serotonin agonist, has been evaluated in one open-label and one double-blind trial for cerebellar ataxia. The open label trial of buspirone 60 mg/day found significant overall benefit in clinical rating of ataxia in the mild-moderate group, particularly for those with lower extremity dysfunction.<sup>13</sup> Similarly, a double-blind study of buspirone<sup>16</sup> for cerebellar ataxia demonstrated improvement in kinetic scores. Neither of these studies specifically evaluated tremor, but overall functional improvement may be more important than isolated tremor reduction. The therapeutic mechanism of action of buspirone in this setting is unknown but is independent of any anxiolytic or anti-depressant effect.

The intravenous and oral forms of ondansetron, a 5-HT 3 receptor antagonist, have been studied as possible treatments for cerebellar tremor. A recent double-blind trial evaluating oral ondansetron, 16 mg/day versus placebo, for tremor in 45 patients with various cerebellar disorders showed no significant improvement in upper extremity tremor in any group.<sup>17</sup>

*Surgical Interventions.* A wide variety of tremor types improve after ventral intermediate nucleus (Vim) thalamotomy, reflecting this area's role as a common pathway for rhythmic activity in the brain. Narabayashi described rhythmic, large-spiked burst discharges in the Vim synchronous with contralateral body tremor and proposed that lesions of this nucleus would disrupt the tremor circuit.<sup>24</sup> He considered intention tremor to be one of the movements most

successfully improved by thalamotomy based on his many years of performing the surgery.

*Thalamotomy.* Thalamotomy has been used to treat cerebellar tremor arising from various causes, including trauma, multiple sclerosis, stroke, and unknown. In a series of 7 mostly pediatric trauma-induced cases of intention tremor, Marks reported improvement in tremor and function in 6 of 7 patients who underwent thalamotomy.<sup>25</sup> However, it should be noted there were no specific measures of function or tremor assessment reported and 2 of the seven experienced transient hemiparesis following surgery. Similarly, in 8 head trauma patients with mixed tremor undergoing thalamotomy, Andrew et al, described marked improvement in all 8 due to resolution of postural tremor and reduction of kinetic tremor but temporary worsening of dysarthria, ataxia and weakness.<sup>9</sup> Again, there were no measures of tremor or function used to quantify these results. Because post-traumatic movements can spontaneously improve within the first year after injury, patients should generally not be referred for surgery within this time.<sup>9,25</sup>

A larger study of thalamotomy for cerebellar tremor of various etiologies (22 ET, 46 MS, 11 posttraumatic, 9 post stroke, and 7 idiopathic) found that most patients experienced improvement in several domains including tremor severity, motor dexterity and ability to drink from a cup without spilling.<sup>27</sup> MS patients had a significant number of post-operative complications (44 events in 53 surgeries including persistent cognitive dysfunction, hemiparesis, dysarthria, gait ataxia, arm ataxia and numbness) and worsening of MS was observed in 8.7 percent despite peri-operative steroid treatment. The majority of MS

patients were evaluated for one year or less with more than half exhibiting recurrence of some tremor within the first year after surgery. The risks of lack of sustained improvement in tremor and possible relapse of MS symptoms must be explained to potential surgical candidates along with possible benefits. Of the 25 patients who underwent thalamotomy for other types of cerebellar tremor in this series the best improvement was observed for post-stroke tremor. Bilateral thalamotomy is usually avoided because of the high risk of dysarthria and dysphagia.

*Deep Brain Stimulation.* Deep brain stimulation (DBS) of the Vim nucleus has now been used to treat cerebellar tremor. DBS does not improve the associated signs of dyssynergia and dysmetria which may be the most disabling aspects of the cerebellar dysfunction. Therefore, candidates for DBS must be carefully selected and reasonable expectations for outcomes set. Deep brain stimulation has gained favor because of the decline in tremor suppression with thalamotomy over time. The advantages of DBS include no permanent lesion, the potential for bilateral placement in patients with bilateral tremor, and adjustability of stimulation settings if tremor control wanes. In a study by Geny et al, 69.2 percent of 13 patients with MS related tremor undergoing DBS had reduction in tremor amplitude (mostly proximal), although none had complete resolution of tremor.<sup>28</sup> In 2 studies of DBS for different tremor types, including some individuals with MS-related tremor, dysarthria was reported in about 30 percent of those having bilateral DBS or a unilateral DBS placed contralateral to a thalamotomy lesions.<sup>30,31</sup> Change in stimulation parameters was reported to help the dysarthria but

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resulted in less tremor control. Recently, a long term (mean of 32 months) study of DBS in 9 medically refractory multiple sclerosis patients demonstrated a reduction of tremor in all, though improvement was greatest at the outset.<sup>29</sup> Extended Disability Status Scale (EDSS) scores worsened over time and were on average, 6.7 before surgery, 6.8 at 6 months and 7.8 at late follow-up. Improvement in tremor scores persisted despite the fact that disability scores worsened. This is consistent with continued benefit for tremor despite progression of the underlying disease. Within one month of surgery, one-third had exacerbations of MS symptoms, requiring steroid therapy. However, one-third, had long term restitution of their ability to feed themselves and maintain independent personal hygiene when stimulated. The authors conclude after reviewing other published accounts of DBS for MS-related tremor that the surgery is safe and effective for reducing tremor. In addition, some patients may have sustained benefit but the progressive nature of MS makes it difficult to assess functional outcomes from surgery over time. This finding is likely to hold true for any neurodegenerative cause of cerebellar tremor. Better outcome tools are required to truly determine functional outcome, disability, and quality of life following DBS so these concerns should be addressed in future trials of surgical treatment for cerebellar tremor. Although there are limitations in functional improvement as currently measured, the resistance to medical treatment and debilitating aspects of this tremor along with the low morbidity and mortality rate of DBS make the surgery an acceptable option for those appropriately selected patients with moderately to severely disabling cerebellar tremor.

*Conclusion.* Cerebellar tremor is remarkable in its presentation, can be disabling for the patient, and is very difficult to treat. Although the underlying cause is usually able to be determined, the treatment is based on amelioration of symptoms of tremor rather than by change in tremor expected by treatment of the disease. Over the years many medications have been tried for cerebellar tremor with mixed success. New surgical techniques may be of benefit in some patients who have failed attempts at medical therapies.

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