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REVIEW

Revisiting the Clinical Phenomenology of "Cerebellar Tremor": Beyond the Intention Tremor

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Abstract

Tremor is an involuntary, rhythmic, oscillatory movement of a body part. It is a central feature of a range of diseases resulting from pathological changes in the cerebellum. Interestingly, in modern times, the terms "cerebellar tremor" and "intention tremor" are often used synonymously and interchangeably. However, "cerebellar tremor" (i.e., tremors of cerebellar origin) do not always present exclusively as intention tremor. In this article, we comprehensively revisit the clinical phenomenology of tremors observed in various diseases that are based in the cerebellum. By this, we mean diseases for which the cerebellum and its various connections are often seen as playing a central and defining role. These include spinocerebellar ataxias, essential tremor, orthostatic tremor, dystonia, acute cerebellitis, cerebellar tumors, paraneoplastic cerebellar degeneration, and cerebellar strokes. The theme of this article is to highlight, through published data available in the current literature, that the clinical phenomenology of tremor of cerebellar origin is heterogeneous, and it extends beyond that of intention tremor to include postural tremors, kinetic tremor, rest tremor, and orthostatic tremor. This heterogeneity is consistent with the seminal work of Gordon Holmes, in which he described a variety of tremors aside from intention tremor in the setting of cerebellar lesions. In the end, it would seem that the notion that intention tremor is the sole signature of cerebellar lesions is an over-simplification and is not correct. Future studies are warranted to identify and further characterize the heterogeneity of tremors arising from the various cerebellar etiologies.

Keywords Tremor · Cerebellar tremor · Intention tremor · Postural tremor · Kinetic tremor · Rest tremor

Introduction

Tremor is an involuntary, rhythmic, oscillatory movement of a body part [1]. It is among the most common movement disorders in adults. Knowledge of the etiology, pathophysiology, and clinical phenomenology of tremor has increased considerably over the past several decades. The task force on tremor of the International Parkinson and Movement Disorders Society recently proposed a revised classification of tremor [1]. As such, tremor is divided into two broad categories, i.e., rest tremor and action tremor. Under the umbrella of action tremor are kinetic, postural, and isometric tremors. Kinetic tremor is further divided into simple kinetic tremor, intention tremor, and task-specific kinetic tremor [1]. Intention tremor usually occurs during goal-directed movements (e.g., finger-to-nose maneuver) and has a low frequency (< 5 Hz).

Tremor is a central feature of various diseases that are the result of pathological changes in the cerebellum [2]. The terms "cerebellar tremor" and "intention tremor" are often used synonymously and interchangeably. However, tremors of cerebellar origin do not always present as intention tremor. Indeed, it is of historical interest that Gordon Holmes, in his seminal papers on cerebellar disease, described a variety of tremors in the setting of

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cerebellar lesions [3, 4]. Thus, Holmes wrote, "…all tremors occurring in cerebellar disease are not of the same nature [3]." In addition to describing *intention tremor*, he also described *static tremor* (equivalent to postural tremor) and *kinetic tremor*, which were secondary to cerebellar insults [4]. The kinetic tremor described by Holmes was different from intention tremor, as the tremor occurred at the commencement of movement.

As another example of a tremor disorder that is increasingly being linked to dysfunction of the cerebellar system, but that does not present primarily as intention tremor, we may look to essential tremor (ET), one of the most common tremor disorders. Recent understanding about the neurobiology of ET, and its links to the cerebellum, further suggests a need to revisit the phenomenology of what we broadly refer to as "cerebellar tremors." A number of studies, including clinical [5], physiological [6], neuroimaging [7, 8], and postmortem [9] strongly implicate a central role of the cerebellum and its connections in the pathogenesis of ET. However, the intention tremor that has been equated with "cerebellar tremors" is not the sine qua non of ET; rather, kinetic tremor of the upper limbs is the most common manifestation of ET [10].

Our aim in this article is to comprehensively revisit the clinical phenomenology of tremors observed in diseases that are based in the cerebellum. By this, we mean diseases for which the cerebellum and its various connections are often seen as playing a central and defining role. These include the spinocerebellar ataxias (SCAs), ET, orthostatic tremor, dystonia, acute cerebellitis, cerebellar tumors, paraneoplastic cerebellar degeneration, and cerebellar strokes. The theme of this article is to highlight, through evidence available in the current literature, that the clinical phenomenology of tremor of cerebellar origin is heterogeneous, and it extends beyond that of intention tremor.

Methods

In November 2018, the authors utilized PubMed to search the relevant literature, using several keywords and their combinations listed in Table 1. This yielded 583 articles (Table 1, Fig. 1). During the initial screening of the abstracts/full texts, publications that were not relevant to this review, duplicates, and those that were published in languages other than English were removed (total 542), leaving 41 remaining articles. The references from these articles as well as full-text articles/abstracts from authors' personal collections were also thoroughly searched for any additional articles, yielding 65. In total, 106 articles pertinent to this topic were included for this review (Table 1, Fig. 1).

Tremor in Disorders of Cerebellar Neurodegeneration

SCAs

SCAs are familial neurodegenerative disorders, which primarily involve the cerebellum, although they also typically involve other brain regions. Although gait ataxia is the most common sign of most of the SCAs, patients may also exhibit tremor as their presenting, dominant, or isolated disease feature [11]. Although the cerebellum is clearly central to the pathogenesis of SCAs, aside from intention tremor, other tremors are commonly observed. Thus, postural tremor is commonly observed in a number of the SCAs (e.g., SCA1, 2, 3, 6, 10, 12, 15, 17, and 27) [12–14]. In a recently published multi-center study in the USA, the authors reported a prevalence of postural tremor of 5.8% in SCA1 patients, 27.5% in SCA2 patients, 12.4% in SCA3 patients, and 16.9% in SCA6 patients [15]. Another study, in India, of 85 patients with SCA 1, 2, and 3, reported a prevalence of postural tremor in 10% of SCA1 patients, 20.9% of SCA2 patients, and 17.6% SCA3 patients [16].

Bonnet et.al. [17] studied the spectrum of tremor in 72 patients with SCA3 and documented tremor in 6 patients. The authors described two different tremor types: (1) a fast (6.5–8 Hz) action, postural upper limb tremor, and orthostatic tremor at an early stage in younger patients vs. (2) a slow (3–4 Hz) rest, action, and intentional tremor in older patients, at a later stage of the disease. It is interesting to note that orthostatic tremor was the presenting sign and the sole manifestation of SCA3 for 2 years in one of the patients described by Bonnet and colleagues [17]. Sarva et al. also reported a patient with SCA2 whose predominant tremor was an orthostatic tremor [18].

SCA12, which is commonly observed in north-Indians, is one of the SCAs in which tremor may be the presenting symptom, long before the onset of ataxia. A recently published abstract noted that tremor in SCA12 has strong clinical, phenomenological, and electrophysiological overlap with the tremor observed in patients with ET [19]. In fact, because of the marked clinical similarity between SCA12 and ET, SCA12 patients are often initially diagnosed with ET [11]. In a recently published series of 21 SCA12 patients, tremor was the most common initial presenting symptom (90%); intention tremor was observed in 57%, postural tremor in 81%, and rest tremor in 86% [20].

The aforementioned discussion emphasizes the fact that in disorders such as the SCAs in which cerebellar involvement is a central-defining pathological feature, aside from intention tremor, postural tremor is commonly observed and, in some cases, rest and orthostatic tremors as well.

Table 1 Results of search for articles from PubMed using various keywords and their combinations

Keywords and combinations	Number of publications		
	Total	Included	Excluded
"Cerebellar tremor"	104	0	0 (not in English: 12, not relevant:92)
"Cerebellum" AND "Postural tremor"	67	4	63 (not in English: 9, not relevant: 54)
"Cerebellum" AND "Rest tremor"	11	0	11 (not in English: 0, not relevant: 11)
"Cerebellum" AND "Head tremor"	46	4	42 (not in English: 4, not relevant: 38)
"Cerebellum" AND "Palatal tremor"	20	3	17 (not in English: 2, not relevant: 15)
"Cerebellum" AND "Orthostatic tremor"	28	3	25 (not in English: 2, not relevant: 23)
"Cerebellum" AND "Dystonic tremor"	10	1	9 (not in English: 0, not relevant: 9)
"Cerebellum" AND "Tremor" AND "Dystonia"	74	5	69 (not in English: 9, not relevant: 60)
"Cerebellar tremor" AND "Neurodegeneration"	0	0	0 (not in English: 0, not relevant:0)
"Cerebellar tremor" AND "Infection"	1	0	1(not in English: 0, not relevant:1)
"Cerebellar tremor" AND "Cerebellitis"	0	0	0 (not in English:0, not relevant: 0)
"Tremor" AND "Cerebellitis"	8	4	4 (not in English:1, not relevant: 3)
"Cerebellar tremor" AND "Tumor"	1	0	1 (not in English: 0, not relevant: 1)
"Cerebellar tremor" AND "Vascular"	1	0	1 (not in English: 0, not relevant: 1)
"Cerebellar tremor" AND "Autoimmune"	0	0	0 (not in English: 0, not relevant: 0)
"Cerebellar tremor" AND "Trauma"	2	0	2 (not in English: 0, not relevant: 2)
"Tremor" AND "Cerebellar trauma"	1	0	1 (not in English: 0, not relevant: 0)
"Cerebellar tremor" AND "Injury"	4	0	4 (not in English: 0, not relevant:4)
"Cerebellum" AND "Tremor" AND "Neurodegeneration"	43	6	37 (not in English: 2, not relevant:35)
"Cerebellum" AND "Tremor" AND "Infection"	28	0	28 (not in English:1, not relevant: 27)
"Cerebellum" AND "Tremor" AND "Tumor"	16	2	14 (not in English: 2, not relevant:12)
"Cerebellum" AND "Tremor" AND "Vascular"	17	2	15 (not in English:4, not relevant: 11)
"Cerebellum" AND "Tremor" AND "Autoimmune"	3	0	3 (not in English:1, not relevant: 2)
"Cerebellum" AND "Tremor" AND "Trauma"	11	1	10 (not in English:1, not relevant: 9)
"Cerebellum" AND "Tremor" AND "Injury"	25	1	24 (not in English:0, not relevant: 24)
"Cerebellum" AND "Shaking" AND "Neurodegeneration"	0	0	0 (not in English: 0, not relevant: 0)
"Cerebellum" AND "Shaking" AND "Infection"	4	0	4 (not in English:0, not relevant: 4)
"Cerebellum" AND "Shaking" AND "Tumor"	1	0	1 (not in English:0, not relevant: 1)
"Cerebellum" AND "Shaking" AND "Vascular"	1	0	1 (not in English:0, not relevant: 1)
"Cerebellum" AND "Shaking" AND "Autoimmune"	0	0	0 (not in English:0, not relevant: 0)
"Cerebellum" AND "Shaking" AND "Trauma"	1	0	1 (not in English:0, not relevant: 1)
"Cerebellum" AND "Shaking" AND "Injury"	2	0	2 (not in English:0, not relevant: 2)
"Cerebellitis" AND "Shaking"	0	0	0 (not in English:0, not relevant: 0)
"Cerebellum" AND "Tremor" AND "Paraneoplastic"	5	1	4 (not in English: 2, not relevant: 2)
"Cerebellar tremor" AND "Paraneoplastic"	0	0	0 (not in English: 0, not relevant: 0)
"Cerebellum" AND "Tremor" AND "Stroke"	43	4	39 (not in English: 4, not relevant: 35)
"Cerebellar tremor" AND "Stroke"	5	0	5 (not in English: 0, not relevant: 5)
Total number of articles included for review after removing the duplicates			41
Total number of articles from authors' personal collection and from the reference sections of the shortlisted articles			65
Final total number of articles included for review			106

Fragile X-Associated Tremor/Ataxia Syndrome

Fragile X syndrome (FXS) and fragile X-associated tremor/ataxia syndrome (FXTAS) are two separate disorders having distinct molecular pathologies. While "full mutation" CGG expansions (> 200 repeats) and subsequent epigenetic silencing of the fragile X mental retardation 1 (FMR1) gene on the X chromosome results in fragile X syndrome (FXS), FXTAS is associated with premutation alleles (50–200 repeats) in FMR1 that are associated with an up to eight-fold increase

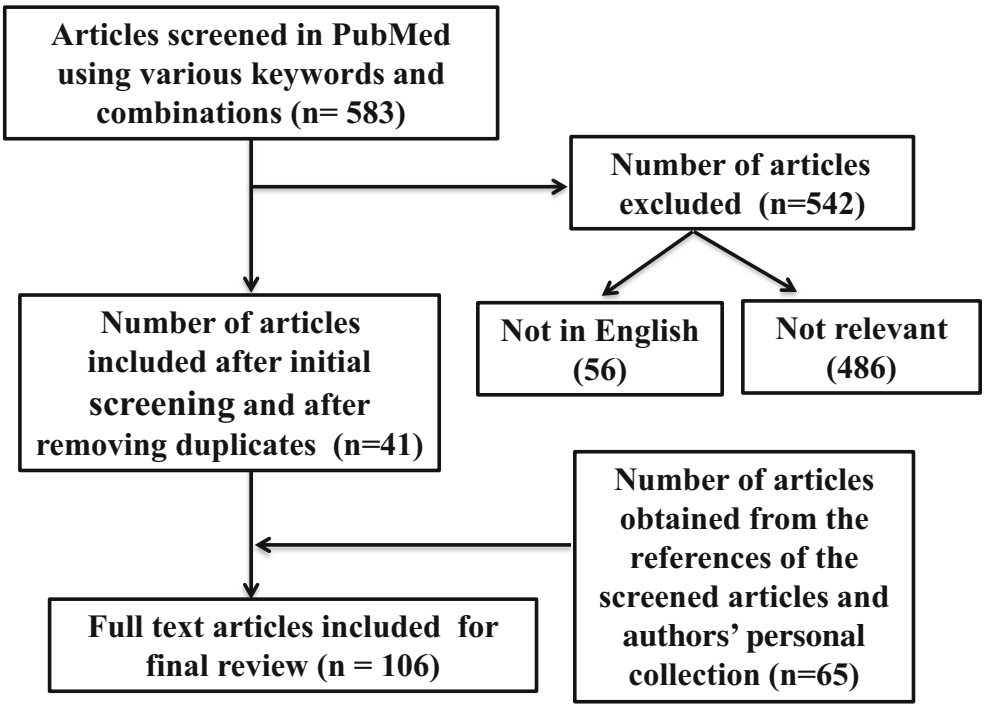

Fig. 1 Summary of the steps of literature search for the article

in mRNA production, leading in turn to RNA gain-of-function toxicity and the phenotypic features of disorders associated with the premutation, the most severe of which is FXTAS [21]. Although significant postmortem changes (e.g., white matter disease, associated astrocytic pathology, intranuclear inclusions) are also present throughout the central nervous system (i.e., cerebral cortex and spinal cord), prominent among the brain regions involved in FXTAS is the cerebellum [22, 23]. Further underscoring the important involvement of the cerebellum and its connections is that one of the sentinel clues for diagnosing FXTAS is hyperintensity on T2-weighted magnetic resonance (MR) images of the cerebellar white matter and the middle cerebellar peduncles (MCP sign) [24].

As evident from the name of the disease, the core signs of FXTAS are tremor and ataxia. Aside from intention tremor (noted in 70% of patients in a series of 20) [25], kinetic and postural tremors are reported to be common findings in patients with FXTAS [26–28], and these have variable severity; unfortunately, their relative prevalence has not been well-documented. What is apparent, though, is that the tremor phenomenology in FXTAS includes a variety of types of tremor (i.e., postural, kinetic) aside from intention tremor.

It deserves mention that aside from these action tremors, there is rest tremor in these patients as well. In one of the initial papers on FXTAS, Jaquemont and colleagues described the clinical spectrum of 20 patients and they documented the presence of rest tremor (10% of patients) in addition to the commonly observed intention tremor (70% of patients) [25]. It is not clear, however, whether the rest tremor in FXTAS is primarily due to cerebellar involvement or parkinsonism in the setting of lesions in basal ganglia-associated white matter tracts.

ET

ET is among the most prevalent movement disorders of adults; the diagnosis is based on the presence of action tremor of the upper limbs [1]. The traditional concept that the inferior olivary nucleus is the primary site of pathology in ET has largely fallen out of favor, in part due to a lack of convincing evidence [29–33]. In parallel, there has been a surge of evidence suggesting that the cerebellum and its connections are more central to the pathophysiology of ET [34]. A number of neuroimaging studies have reported abnormalities in the cerebellum and its connections in patients with ET [8, 35–37] and postmortem studies have revealed numerous structural changes in the ET compared to control cerebellum; a number of these changes are consistent with neurodegeneration [9, 38–41].

Patients with ET often have intention tremor. Thus, intention tremor of the upper limbs is present in approximately 44% of ET cases [42], in the lower limbs in approximately 27% of ET cases [43], and in the neck (i.e., head) in approximately 9% of ET cases [44]. However, the phenomenology of tremor in ET is not limited to intention tremor. In fact, the sine qua non of ET is the presence of kinetic tremor in the upper limbs [10]. In addition, although in the vast bulk of cases it is less severe than that of kinetic tremor, many patients (e.g., 305 [82.7%] of 369 in one large series) also have postural tremor of the upper limbs [10]. Patients may also have rest tremor in addition to postural and kinetic tremor of the upper limbs, with the prevalence of

rest tremor ranging from only 1.9% in population-based studies to 46.4% in brain bank studies [45–47].

ET is a disorder in which the cerebellum and its connections are increasingly viewed as central to the pathophysiology. The aforementioned data provide abundant evidence that tremor in such a disorder is not restricted solely to intention tremor; indeed, kinetic tremor is the defining feature. Further underscoring specific links between cerebellar pathology and kinetic tremor in ET is that in one study, the limb with the more severe kinetic tremor was ipsilateral to the cerebellar hemisphere with the more severe degenerative changes, providing a clinical-pathological link between the cerebellar pathology and kinetic tremor [48].

Orthostatic Tremor

Orthostatic tremor is a rare movement disorder that is usually seen in the sixth decade of life; it has a preponderance towards the female gender [49, 50]. On visual inspection, orthostatic tremor is characterized by rapid tremor of the legs, and palpation and auscultation may reveal the presence of a thrill and a thumping sound (helicopter sign), respectively [50]. Orthostatic tremor may manifest as a primary disorder (i.e., primary orthostatic tremor) or may occur secondary to several other medical conditions (i.e., secondary orthostatic tremor). The pathogenesis of primary orthostatic tremor is not fully understood; however, there is considerable evidence that structural and functional abnormalities in the cerebellum and its connections play a central role [50]. Interestingly, Setta and colleagues described three patients with orthostatic tremor and cerebellar ataxia in the background cerebellar cortical atrophy [51]. An extensive diagnostic workup was performed on all three patients and the only notable abnormality was the cerebellar cortical atrophy. A study using magnetic resonance spectroscopy (MRS) in patients with primary orthostatic tremor had revealed a significant reduction in the absolute concentration of *N*-acetyl aspartate (NAA) in the cerebellar vermis, cerebellar white matter, and in the mid-parietal gray matter [52]. A reduction in NAA indicates greater neuronal dysfunction or increased neuronal loss and suggests a possible underlying neurodegenerative process in primary orthostatic tremor. The reports of orthostatic tremor in SCA2 [18], SCA3 [17], and in patients with cerebellar cortical atrophy [51] further endorse the possibility that cerebellum plays a pivotal role in the pathogenesis of primary orthostatic tremor and this rare entity would therefore seem to expand the spectrum of "cerebellar tremor."

Tremor in Patients with Dystonia

Dystonia, a commonly observed movement disorder, is characterized by sustained muscle contractions, frequently resulting in twisting and repetitive movements or abnormal postures [53]. Although dystonia was originally viewed as a disorder of the basal ganglia, recent evidence also suggests a role of the cerebellum in the pathogenesis of dystonia [54–56]. In these patients, tremor may occur in body parts that also exhibit dystonic postures and movements (i.e., dystonic tremor) as well as body parts that do not (i.e., tremor associated with dystonia). In a study in India of 90 patients with adult-onset dystonia, tremor was present in 41 (45.6%), with the upper limb being the most commonly observed location, followed by the neck [57]. The limb tremor was postural or kinetic in 24/41 (58.5%), postural or kinetic and at rest in 5/41 (12.2%), only at rest in 4/41 (9.8%), and isometric in 8/41 (19.5%) [57]. In a larger series in London, tremor was present in 262 of 473 (55.4%) patients with adult-onset primary dystonia [58]. Of the 140 patients with arm tremor, 100% had postural tremor, 103 (73.6%) also had kinetic tremor, and 57 patients (40.7%) also had rest tremor [58]. A study in Poland of 123 patients with focal and segmental dystonia similarly reported that tremor was present in 60 (48.8%) patients; postural tremor was the most commonly observed tremor (41/60 or 68.3%), followed by kinetic tremor (13/60 or 21.7%) and rest tremor (6/60 or 10.0%) [59]. While the above studies reported a prevalence of tremor that was in the range of 45.6–58.5% [60–62], a study in Italy of 429 adult-onset dystonia patients reported a lower prevalence—72 (16.7%) [63]. None of the studies noted whether intention tremor was present or absent.

In summary, approximately one half of patients with dystonia exhibit tremor, with postural tremor being the most common but kinetic tremor also occurring in a large percentage of cases. Rest tremor occurs, but to a lesser degree. The presence of intention tremor has not been noted.

Tremor in Patients with Acute Cerebellitis

Acute cerebellitis is a cerebellar disorder that was first described by Westphal and Batten in 1872 [64]. It is an inflammatory syndrome resulting in acute cerebellar dysfunction; it is more commonly seen in children than adults [64, 65]. It may be the result of primary infections or post-infectious immune-mediated processes [66]. While the etiology remains unknown in a majority of the cases, viral infections, including varicella zoster virus [67], rota virus [60], Epstein-Barr virus [68], human immunodeficiency virus (HIV) [68], and herpes simplex virus [69], remain among the commonly implicated causes. Rarely, bacterial infections [70, 71] and toxic medication reactions (e.g., isoniazid) [72, 73] have been reported as causative.

Although acute cerebellitis results in acute cerebellar dysfunction, and the predominant clinical features are headache and cerebellar ataxia [64, 65], some patients with cerebellitis may also present with tremor. Both intention tremor [61, 74]

and postural tremor [62] of the upper limbs, and truncal titubation [75] have been reported in patients with acute cerebellitis. In a case of acute cerebellitis secondary to varicella zoster infection, Shilo and colleagues [62] reported the presence of postural and intentional tremors of both upper limbs. Gökçe et.al. [75] noted the presence of truncal titubation and cerebellar ataxia in a 6-year-old girl with influenza-associated acute cerebellitis. A long-term follow-up study of 11 children with cerebellitis revealed the presence of upper limb tremor in 5 children and all of the 5 had intentional tremor during the onset of the illness [74]. Although several other published studies have reported tremor in patients with cerebellitis, the phenomenology of the tremor is not described [60, 67].

Although the literature on tremor in acute cerebellitis is not robust, what we do know from available literature is that aside from intention tremor, postural tremor [62] and truncal titubation [75] have been reported. It is clear that more studies of the phenomenology of tremor in patients with acute cerebellitis are warranted.

Tremor in the Setting of Cerebellar Trauma and Tumors

As discussed above, Gordon Holmes' observations in the early twentieth century suggest that tremor in the setting of cerebellar pathology is not exclusively intention tremor. Most of Holmes' observations were based on individuals with cerebellar trauma (especially gunshot injuries) or cerebellar tumors [76, 77]. In his seminal paper on clinical features of cerebellar gunshot injuries, Holmes described two types of tremors; while the majority of patients had coarse tremor when reaching towards a target (i.e., intention tremor), several had tremor that he described as "static tremor". The "static tremor" appears to have been what in modern dialect we would refer to as "postural arm tremor"; however, this tremor set in after sustaining the affected limb in an outstretched position for some time. Although many case reports over the years have documented intention tremor in patients with cerebellar masses [78–81], there are indeed a number of case reports that have noted postural tremor of upper limbs in patients with cerebellar lesions, including a patient with a cerebellar arachnoid cyst [82] and another with cortical cerebellar dysplasia [83].

Other types of postural tremor have also been reported in patients with cerebellar lesions. Thus, Kobylecki et.al. [84] later reported a 37-year-old patient who at age 6 had undergone resection of an astrocytoma of the cerebellar vermis, without adjuvant chemoradiotherapy; the patient now had a 3-year history of episodic postural tremor of the neck, shoulder, and trunk. This case falls under the umbrella of the entity known as cerebellar axial postural tremor (CPAT) and further adds to the spectrum of cerebellar tremors. Brown et.al. described CPAT in three patients with cerebellar pathologies [85]. The patients had tremor of the head and shoulders while sitting and while walking. In addition, they had postural tremor of the arms that disappeared during voluntary movements [85].

Rest tremors have also been reported in the setting of cerebellar lesions. Thus, Griffith reported his observations of several patients with primary cerebellar structural lesions [86]. Among the important observations was coarse resting tremor in patients with intracranial hemorrhages involving the cerebellar hemisphere and in those with metastasis to the cerebellar hemisphere [86]. In a patient with a large meningioma originating from the right tentorium cerebelli, the right dentate nucleus was completely atrophied and the patient had developed episodes of coarse rest tremors of the right arm [86]. Thus, it is of interest that a structural cerebellar lesion would result in episodic rest tremor. It is of further interest that in animal studies of cerebellar injury, especially involving the regions of the dentate nucleus and the interpositus nuclei, rest tremor was reported [87].

In summary, patients with cerebellar trauma or tumors provide evidence suggesting that the phenomenology of cerebellar tremor is not limited to intention tremor. In addition to the observations of Holmes and Griffith, several case reports as discussed above reveal that cerebellar trauma or tumors may result in postural as well as rest tremors of arms, and axial tremors involving neck and shoulders.

Tremor in Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is an uncommon autoimmune disorder characterized pathologically by destruction of cerebellar Purkinje cells, with variable loss of other cell populations, and clinically by signs and symptoms suggestive of progressive cerebellar dysfunction [88]. PCD is commonly associated with gynecological carcinomas involving the ovary and breast, small-cell carcinoma of the lungs, and Hodgkin's lymphoma [89].

In addition to progressive gait ataxia, which is observed in all patients with PCD, tremor has also been reported. Although case reports have documented the presence of intention tremor in patients with PCD [90–92], there are several reports of PCD which indicate that tremor in PCD is not limited to intention tremor [93–96]. Although rare, patients with PCD, and especially those with anti-Yo antibodies, present with Holmes tremor [93–95]. Holmes tremor was first described in 1904 by Gordon Holmes as a coarse 3–4-Hz tremor of the arms, which is present at rest, exacerbated with posture and additionally intensified with action [97, 98]. Rydz et.al. [93] reported Holmes tremor along with head tremor in a

patient with PCD due to an anti-Yo antibody. Postmortem examination revealed cerebellar atrophy (vermis > cerebellar hemispheres), subtotal loss of Purkinje cells and severe Bergmann gliosis, and moderate neuronal loss in the dentate nucleus with reactive gliosis. However, pathological changes were also observed in the red nucleus and inferior olivary nucleus [93]. Considering the fact that anti-Yo is an antibody against Purkinje cells (also known as Purkinje cell cytoplasmic antibody type-1), it is possible that the pathological changes in the red nucleus and in the inferior olivary nucleus in the aforementioned patient were age-related or were secondary to the cerebellar pathology. These reports seem to expand the spectrum of cerebellar tremors by providing postmortem evidence of cerebellar pathology in a PCD patient who presented with Holmes tremor. Similar to the report by Rydz et.al. [93], Kiriyama and colleagues [94] reported rubral tremor of both upper limbs and head tremor in a 66-year-old woman (anti-Yo positive) in whom the severity of tremor diminished significantly with chemotherapy. Interestingly, rubral tremor has also been reported in patients with seronegative (i.e., absence of anti-Purkinje cell antibody or anti-Yo) paraneoplastic cerebellar degeneration [95].

In addition to Holmes tremor, patients with PCD may also rarely manifest postural tremor of the arms as well as legs. Klein et.al. [96] reported a case of PCD secondary to small-cell lung carcinoma in which the patient was initially diagnosed with ET because of the presence of postural tremors. In this case, the patient with PCD which was secondary to anti-Zic4 antibodies had postural tremor of all extremities. The Zic family of proteins plays a role in the development of the cerebellum, and anti-Zic4 has been identified in cases of small-cell lung cancer with PCD [99].

In summary, "cerebellar tremor" among patients with PCD is not limited to intention tremor, and it would seem that patients may exhibit a variety of other forms of tremor (i.e., Holmes, postural), as noted above. However, the literature on the phenomenology of tremor in PCD is sparse; hence, future studies exploring this topic would provide better insights.

Tremor Secondary to Cerebellar Strokes

Movement disorders after stroke are uncommon and usually resolve over time [100]. Ghika-Schmid et.al. [101] noted hyperkinetic movement disorders in 1% of patients in a registry of 2500 patients with stroke; hemiballismus/hemichorea was the most common post-stroke movement disorder, present in 40% of such cases with movement disorders. Cerebellar strokes are uncommon and comprise fewer than 10% of all stroke cases [102]. As abnormalities in the cerebello-thalamo-cortical pathway are associated with tremor, certain cerebellar strokes may result in tremor or may inhibit the pre-existing tremor. Several reports have described mid-line tremors such as palatal tremor and head tremor after cerebellar stroke. While Alnaimat et.al. [103] had reported palatal tremor in a patient with hemorrhagic stroke in both cerebellar hemispheres, Walsh et.al. [104] reported palatal tremor as well dysphonia in a patient with bilateral cerebellar ischemia. It is possible that in these two cases of cerebellar stroke, the palatal tremor was due to the involvement of the dentate nucleus, which is a part of the Guillain-Mollaret triangle. Ueno et al. [105] reported antero-posterior head titubation (frequency 2–3 Hz) in a patient with an infarct in the territory of the right superior cerebellar artery; the patient also had an old infarct in the territory of the left superior cerebellar artery. Finsterer et.al. [106] reported yes-yes head tremor (frequency 2–3 Hz) in a patient with bilateral cerebellar infarctions. It is important to note that these post-stroke mid-line tremors such as palatal tremor and head tremor occurred in the background of bilateral cerebellar involvement. These tremors, which are not intentional in nature, certainly widen the spectrum of "cerebellar tremor."

Conclusion

Our aim in this article was to comprehensively revisit the clinical phenomenology of tremors observed in diseases that are based in the cerebellum (i.e., diseases for which the cerebellum and its various connections are often seen as playing a central and defining role). These include the SCAs, ET, orthostatic tremor, acute cerebellitis, cerebellar tumors, paraneoplastic cerebellar degeneration, and cerebellar strokes. We can see from SCAs, FXTAS, and ET that "cerebellar tremor" is heterogeneous and is not limited to intention tremor. Thus, while postural tremor is the early and often the dominant symptom of SCA 12, it has also been reported in SCA1, 2, 3, 6, 10, 15, 17, and 27. Similarly, patients with FXTAS may have postural tremor in addition to the commonly observed intention tremor. ET is a disorder in which the cerebellum and its connections are increasingly viewed as central to the pathophysiology, and kinetic tremor of the arms is the most common manifestation of ET. In addition, the presence of rest tremor of the arms, postural tremor, head tremor, and voice tremor in a subset of ET patients seem to further expand the spectrum of cerebellar tremor. Orthostatic tremor may also have its underpinnings in the cerebellum and has been reported in patients with SCAs. Although the literature on tremor phenomenology in acute cerebellitis is sparse, there is some reported postural tremor of the arms. The bulk of the evidence from patients with cerebellar trauma and tremors is from the direct observations of Holmes and Griffith as they reported the presence of postural tremor as well as rest tremor in a few of their patients with gunshot injuries to the cerebellum as well as those with cerebellar tumors. The observations from PCD

highlight that Holmes tremor and postural tremor may be included as the clinical spectrum of these cerebellar tremors. Moreover, cerebellar tremor may not be confined only to the arms as there are reports of mid-line tremors involving the palate and neck in patients with bilateral cerebellar strokes. This further underscores the fact that the type of tremor seen in cerebellar pathologies depends on the site and the extent of the pathologies.

Hence, in summary, it would seem that the notion that intention tremor is the sole signature of cerebellar lesions represents somewhat of an over-simplification. From a nomenclatural standpoint, the term "cerebellar tremor" has the potential to confuse. Preferable would be the terms "intention tremor," "postural tremor," "kinetic tremor," and so on, as these are more descriptive of and specific to the clinical phenomenology that is being observed. Future studies are warranted to identify and characterize the heterogeneity of tremors arising from the cerebellar etiologies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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