

Case Report

What is It? Difficult to Pigeon Hole Tremor: a Clinical–Pathological Study of a Man with Jaw Tremor

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Abstract

Background: The phenomenology of tremor is broad and its classification is complicated. Furthermore, the full range of tremor phenomenology with respect to specific neurological and neurodegenerative diseases has not been fully elaborated.

Case Report: This right-handed man had a chief complaint of jaw tremor, which began approximately 20 years prior to death at age 101 years. He had been diagnosed with essential tremor (ET) by a local doctor. His examination at age 100 years was notable for marked jaw tremor at rest in the absence of other clear features of parkinsonism, mild kinetic tremor of the hands and, in the last year of life, a score of 22/41 on a cognitive screen. A senior movement disorder neurologist raised doubt about the “ET” diagnosis. The history and videotaped examination were reviewed by three additional senior tremor experts, who raised a number of diagnostic possibilities. A complete postmortem examination was performed by a senior neuropathologist, and was notable for the presence of tufted astrocytes, AT8-labeled glial cytoplasmic inclusions, and globose neuronal tangles. These changes were widespread and definitive. A neuropathological diagnosis of progressive supranuclear palsy was assigned.

Discussion: This case presents with mixed and difficult to clinically classify tremor phenomenology and other neurological findings. The postmortem diagnosis was not predicted based on the clinical features, and it is possible that it does not account for all of the features. The case raises many interesting issues and provides a window into the complexity of the interpretation, nosology, and classification of tremor phenomenology.

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Introduction

The phenomenology of tremor is broad and classification schemes are complex.^{1–3} Furthermore, the full range of tremor phenomenology with respect to specific neurological and neurodegenerative diseases has not been fully elaborated. The current case presents with mixed and difficult to clinically classify tremor phenomenology, as well as other neurological findings. The postmortem diagnosis was not predicted based on the clinical features. The case provides an interesting and instructive discussion, and provides a window into the complexity of the interpretation, nosology, and classification of tremor phenomenology.

Case report

This right-handed man enrolled as a brain donor in the Essential Tremor Centralized Brain Repository (ETCBR) at age 100 years, and had an in-person home assessment by a trained tester who administered questionnaires and performed a videotaped neurological examination. He signed an informed consent form approved by Columbia University Medical Center Internal Review Board. The donor had a high school education. He had never smoked cigarettes and reported drinking less than one alcoholic beverage per week. On a tremor screening questionnaire, he complained of tremor and indicated that he had been diagnosed as “essential tremor” (ET) by



Video 1. Videotaped Examination. The videotaped tremor examination (initially 10 minutes in length) is edited here to show the most salient features. The current clip is 2 minutes in length. There is no tremor at rest. While pouring, mild and very intermittent tremor is present only on the left. There is no tremor while drinking from a cup or during the finger–nose–finger maneuver. Rapid alternating movements in the arms and legs are normal for age. A tremor is present in the jaw while the patient’s mouth is closed. It lessens while the mouth is wide open (during sustained phonation). The tremor resumes after sustained phonation.

his general doctor many years previously. His main complaint was his “chin tremor” rather than hand tremor. The precise age of onset was unclear, but he estimated it began when he was in his late 70s or early 80s. Hence, it had probably been present for approximately 20 years.

His family history was notable for a daughter with head tremor, which began at age 45 years and had continued for the past 20 years; it was diagnosed as ET by a neurologist. His past medical history was notable for an enlarged prostate, bilateral cataracts, and bladder cancer. He wore dentures. He used a walker after a fall at home at age 97 or 98 years, and prior to that had used a cane for a couple of years; the reasons were not clear, and the history was limited and further confounded by his advanced age and frailty. He had not seen a neurologist for his tremor and had not taken any medications or had surgery for his tremor. There was no brain imaging. He had never been exposed to chemotherapeutic agents, lithium, levosulpride, metoclopramide, or anticonvulsant medications. He had no history of neuroleptic exposure. His current medications were esomeprazole for acid reflux and metoprolol ER 50 mg prescribed as a cardiac medication. On a brief nine-item screening questionnaire, modified from the Telephone Interview for Cognitive Status, he scored a 9/9 (no errors). A videotaped neurological examination was performed (see Video 1, Figures 1 and 2). Based upon this evaluation, the senior ETCBR neurologist (E.D.L.) raised considerable doubt about the diagnosis of ET; nevertheless, the decision was made to continue to follow the patient as a brain donor with a clinically undefined tremor. A follow-up telephone call approximately 1 year later (9–10 months prior to death at age 101 years and 10 months), he noted no changes other than the addition of levothyroxine to his medications. He also noted recent problems with “short-term memory”. On a telephone interview for cognitive status, he scored a 22/41, with disorientation

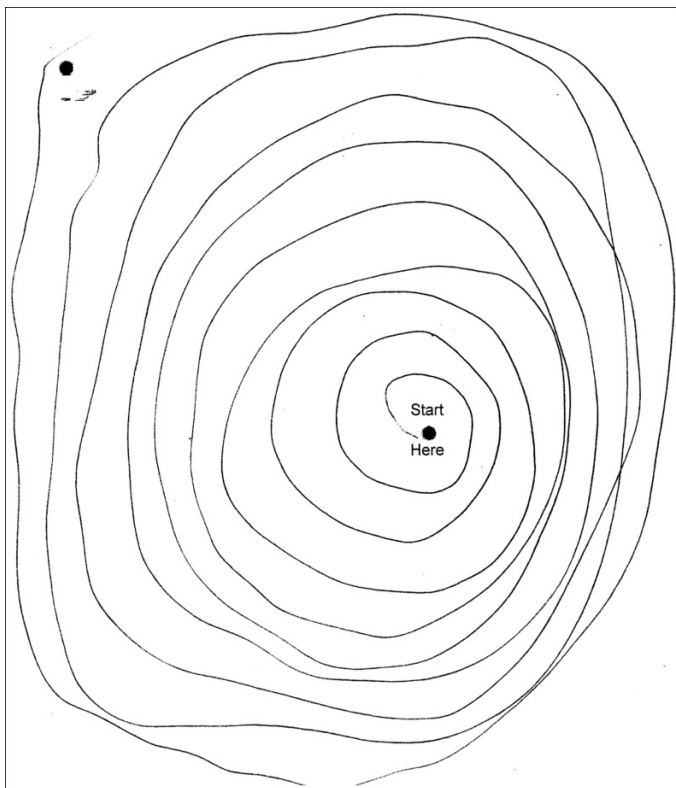


Figure 1. Spiral Drawn with Right Hand During the Videotaped Neurological Examination at Age 100. Mild tremor is evident in the upper left quadrant.

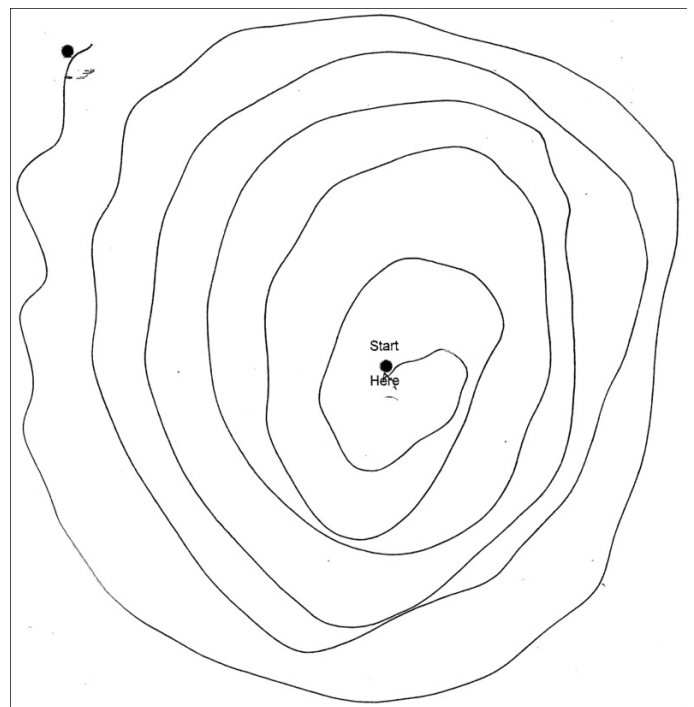


Figure 2. Spiral Drawn with Left Hand During the Videotaped Neurological Examination at Age 100. Tremor is evident in the upper left quadrant.

about the day of the week and year, errors in word recall (he recalled 3/10 words after 5 minutes), and two errors in serial 7s. Four Archimedes spirals (two right and two left) were unchanged compared with those seen on his videotaped examination. He died of natural causes at home at age 101 years.

Expert commentary

Dr. Bain

This 100-year-old man has suffered from tremor for 20–30 years that affects his jaw and hands, the former (unusually) being more intrusive. His daughter has, apparently, head tremor. He does not appear to have taken any tremorigenic medication. He has had prostatic hypertrophy, bladder cancer, a “cardiac condition” and cataracts. He has required a walking aid for at least 5 years, presumably for a gait disturbance, although other factors, namely poor vision, loss of confidence after falling, and general frailty may be relevant. One year later his cognitive function is impaired with disorientation in time, dyscalculia, and poor word recall, and he has commenced levothyroxine, probably for hypothyroidism.

The videotapes indicate that he cannot stand unaided. There is facial impassivity and he has a low-volume voice. There is a slight tremor in his voice and an intermittent quite marked jaw tremor. His voluntary arm movements are quite good, but there is a paucity of spontaneous movement. There is no rest tremor but there is a mild action tremor of the hands, although it does not interfere significantly with drinking or using a spoon. There is no dysdiadokinesia in the right hand but there are one or two interruptions of alternating movements on the left and no dysmetria. There appears to be slight wasting of the first dorsal interosseous muscles and evidence of osteoarthritis in some of his proximal interphalangeal joints. Opening and closing his hands is of slightly reduced amplitude on the right, but with no fatiguing, and normal on the left. His spiral drawings are of good size and show a mild action tremor, which is slightly worse on the left. The spirals drawn with his right hand are a little cramped on the right.

The history suggests that he has had a tremor for two or three decades before either another condition developed that caused gait and cognitive dysfunction or the (single) illness may have been very slowly evolving over the preceding two or three decades. The presence of head tremor in his daughter suggests that the tremor could be hereditary.

The jaw appears to have been differentially affected more than the hands, which is very unusual for ET and perhaps a little more in keeping with a dystonic tremor. Hereditary geniospasm should be considered, but this rare entity is usually paroxysmal and is reported to have a much younger onset. The absence of rest tremor and the presence of an action tremor in the hands is uncommon in Parkinson's disease (PD) but jaw tremor is frequently encountered. The spiral drawings are quite large, which is more indicative of an action tremor than PD but there is some cramping on the right-hand side of the spiral drawn with the right hand.

The cause of gait deterioration is unclear. One can speculate that it may be multifactorial, as he is elderly, may have poor vision, has signs

of osteoarthritis, and neuropathy (ulnar) as well as a tremor. The fact he is taking metoprolol could indicate that he has hypertension, angina, or an arrhythmia, raising the possibility of co-existent small-vessel cerebrovascular disease. The gait might have been Parkinsonian or ataxic, although the fact that he cannot stand up without aid suggests a degree of proximal leg weakness.

The declining cognitive profile might reflect small-vessel cerebrovascular disease or Alzheimer's pathology but does not have a “frontal” or visuospatial flavor.

I would consider longstanding dystonic tremor and co-existent small-vessel cerebrovascular disease to be the most likely sequential diagnoses. However, Alzheimer's pathology might also be present and gait deterioration and cognitive decline might reflect hydrocephalus but there is no accompanying bladder disturbance.

However, if the whole illness were the result of one condition, fragile X tremor ataxia syndrome (FXTAS) should be seriously considered and, although less likely, a spinocerebellar ataxia or Kennedy's syndrome enter the differential diagnosis.

Dr. Hallett

The patient is examined at age 100 years with a chief complaint of isolated jaw tremor, although the diagnosis may have been previously made of ET (which is why he is being evaluated). The tremor has been present for about 20 years. Additionally, we are told that the patient cannot stand or walk without a walker, and that this has been the case for about 3 years, but the explanation of this is not made clear. The neurological examination is limited and we do not have information about strength, tone, sensation, reflexes, or anything about stance and gait. We have to presume that his balance was poor. Cognitively he was normal at the time of the examination, but apparently became demented over the next few years, prior to death and his postmortem examination. Another bit of information is that his daughter is reported to have head tremor. The videotapes show predominantly a jaw tremor at about 3 Hz that waxes and wanes in amplitude and seems to largely go away when he talks or vocalizes. There is also a little dyskinesia of the jaw, lips, and tongue when the tremor is less. There is a very slight voice tremor. There is no rest or action tremor of the limbs. Movements are slightly slow and slightly uncoordinated, but are likely within normal range for someone of his age.

The best diagnosis is the Movement Disorder Society consensus category of “monosymptomatic tremor at rest”. This is a descriptive diagnosis, but recognizes the limited experience with this clinical syndrome and the possibility of several underlying pathologies. Deuschl⁴ notes the possibility of tremor-dominant PD (or benign tremulous PD), ET with rest tremor, dystonic tremor, Holmes tremor, and other. In relation to ET, jaw tremor can certainly occur, but in the series of Louis et al⁵ jaw tremor was most common when the disorder was more severe. The small amount of voice tremor might be consistent with that (and the history of his daughter's head tremor), but the important jaw tremor largely goes away with action but should continue for an ET diagnosis. The possibility of isolated rest tremor for many years in PD has been noted for many years, and in the series of

251 patients of Leventoglu and Baysal,⁶ three had isolated jaw tremor for a long period. In the new series of 21 autopsied patients from Selikhova et al,⁷ 16 had nigral degeneration with Lewy bodies, and, relevantly, some of these patients developed dementia as well as more “complete” parkinsonism prior to death. Parkinsonism might also explain his difficulty in walking at the time of the examination. In my view, the most likely pathology will be that of PD.

Dr. Jankovic

This is a brief case report of a man who was examined at the age of 100 years, about 2 years before his death of “natural causes”. The 13 video segments (without sound) show a man with an intermittent jaw tremor of about 4–5 Hz frequency while seated in a chair. In addition to the prominent jaw tremor, which he apparently has had for over 20 years, one video segment indicated a transient, intermittent, anterior–posterior oscillation of the head and coordinated stereotypic orolingual movement. The very slight head tremor, coupled with the family history of head tremor, suggests the possibility of ET. The mild orofacial stereotypy may be partly explained by edentulous dyskinesia, unrelated to the jaw tremor. Except for slight hypomimia and hand and foot bradykinesia he had no other apparent parkinsonian features. Furthermore, he had no kinetic or postural tremor except for a very slight left-hand tremor when drawing a spiral.

Although the patient is reported to have “chin tremor”, which usually implies predominant involvement of the mentalis muscle, he actually has jaw tremor, probably produced by rhythmical contractions of the masseter and submental muscles. In 2007 we described an interesting case of a 74-year-old man with familial, childhood-onset chin tremor that became more prominent when he developed symptoms of classic PD about 3 years before our evaluation. That patient thus had PD with presumably coincidental co-existent hereditary chin tremor, sometimes referred to as hereditary geniopsasm.⁸ The latter is a benign autosomal-dominant disorder with a gene locus mapped to chromosome 9q13–q21. Although jaw tremor can be seen in up to 18% of, particularly elderly, patients with ET,⁵ it is usually accompanied by prominent hand, arm, head, and voice tremor. Thus isolated jaw tremor, as manifested in this case, is relatively uncommon. Besides PD and ET, jaw tremor can be also seen as a manifestation of oromandibular dystonia.⁹ Other causes of jaw tremor include palatal or branchial myoclonus (tremor), drug-induced tremor (tardive tremor secondary to dopamine receptor blocking drugs or due to drugs such as lithium or donepezil), and myorhythmia.^{10,11}

Although this patient appears to have only minimal parkinsonian features, it is possible that he has jaw tremor associated with benign tremulous parkinsonism, present in three of 16 pathologically proven cases in a recently reported series.⁷ Whether he also has an underlying ET, as suggested by the head tremor in him and in his daughter, is difficult to ascertain without additional clinical information, but the presence of an ET–PD subtype with longstanding ET followed by PD phenotype has now been well documented.¹²

Postmortem brain examination

The patient’s brain was removed and transported to the ETCBR at the New York Brain Bank, which operates under the approval of the Columbia University Medical Center Internal Review Board. The brain underwent a comprehensive neuropathological assessment and determination of detectable pathological findings (see nybb.hs.columbia.edu).

Blocks were taken from standardized brain regions and embedded in paraffin; 7- μ m-thick sections were stained with Luxol fast blue counterstained with hematoxylin–eosin (LH&E).^{13–15} Additional sections from selected blocks were stained with modified Bielschowsky silver stain, and others with antibodies directed against alpha-synuclein (1:40, Leica, Buffalo Grove, IL, USA) (including cerebral cortex, hippocampal formation, globus pallidum, putamen, amygdala, mid-brain with substantia nigra, pons with the locus ceruleus, medulla with the dorsal vagal nucleus, and olfactory bulbs), beta-amyloid (1:400, Biocare Medical, Concord, CA, USA) (including cerebral cortex, hippocampal formation, globus pallidum and putamen, amygdala, and thalamus), hyperphosphorylated tau (AT8) (1:200, ThermoScientific, Rockford IL, USA) (hippocampus, globus pallidum, putamen, amygdala, thalamus, subthalamic nucleus, mesencephalon with red nucleus, pons, medulla oblongata, cerebellum with dentate nucleus, and cerebral cortex), and glial fibrillary acidic protein (Ventana, Tucson, AZ, USA) proteins.¹⁵

A standard 3 × 20 × 25 mm parasagittal, formalin-fixed, tissue block was also harvested from the neocerebellum;¹³ the block included the cerebellar cortex, white matter, and dentate nucleus. A senior neuropathologist who was blinded to all clinical information counted torpedoes throughout one entire LH&E 7- μ m-thick section and, when available, one entire Bielschowsky stained 7- μ m-thick section, and counted and averaged Purkinje cells in 15 100 × fields (LH&E).¹³ As described,¹⁶ a semiquantitative (0–3) rating of the appearance of the basket cell plexus surrounding Purkinje cell bodies throughout Bielschowsky preparations was carried out by the same neuropathologist.

The fresh brain was weighed (1,060 g). On external examination, the dura and brain appeared to be normal. There was a moderate amount of athero-arteriosclerosis. Cut surfaces of the brainstem revealed a well-pigmented substantia nigra and locus ceruleus. On microscopic examination, the amyloid burden was minimal and confined to the prefrontal region and consisted of rare diffuse plaques. Definite neuritic plaques were not found. Lewy bodies and Lewy neurites were not detected. The neuropathological diagnosis of progressive supranuclear palsy (PSP) was assigned based on the presence of tufted astrocytes, AT8-labeled glial cytoplasmic inclusions, and the presence of globose neuronal tangles. Furthermore, globose neuronal tangles had to be documented within at least seven of the nine following sites: cerebral cortex, neostriatum (caudate nucleus and putamen), globus pallidus, subthalamic nucleus, red nucleus, pars compacta of the substantia nigra, pontine nuclei, inferior olivary nucleus, and dentate nucleus of the cerebellum. They were also present in the third cranial nerve nucleus. These changes were widespread and

definitive (Figure 3A–D). A semiquantitative assessment of the density of tufted astrocytes, neuronal tangles, and glial cytoplasmic inclusions was performed (Table 1).^{15,17–19} Neuronal loss was mild in the locus ceruleus but normal elsewhere. In the cerebellum, the basket process rating was 1 and the torpedo counts were 5 (LH&E) and 6 (Bielschowsky). The Purkinje cell count was 12.3 (averaged Purkinje cells in 15 100× fields, LH&E).

Discussion

This present case is a complicated one. We are confronting an unusual tremor and a possible combination of comorbidities, some of which are motor, and some of which are non-motor.

The patient was referred to us with a diagnosis of ET. Studies have repeatedly demonstrated that as many as 30–50% of ET diagnoses are

incorrect, with the condition being overdiagnosed.^{20,21} In some portions of the spiral (Figures 1 and especially Figure 2), there is a considerable amount of tremor and there is a family history of tremor; yet the tremor is overall mild, and does not meet Washington Heights Inwood Genetic Study of Essential Tremor criteria for ET²² or Movement Disorder Society Consensus Criteria for ET.²³ The jaw appears to have been differentially affected more than the hands, which is very unusual for ET.⁵ Also, as noted, the jaw tremor largely goes away with action, whereas it should continue for an ET diagnosis.⁵ While the limb tremor is above and beyond what is normally exhibited even with advanced aging,²⁴ suggesting that it is related to some underlying pathology, the diagnosis of ET was not made definitely by any of the experts, and this diagnosis is unlikely. The relatively high number of Purkinje cells, the only modest number

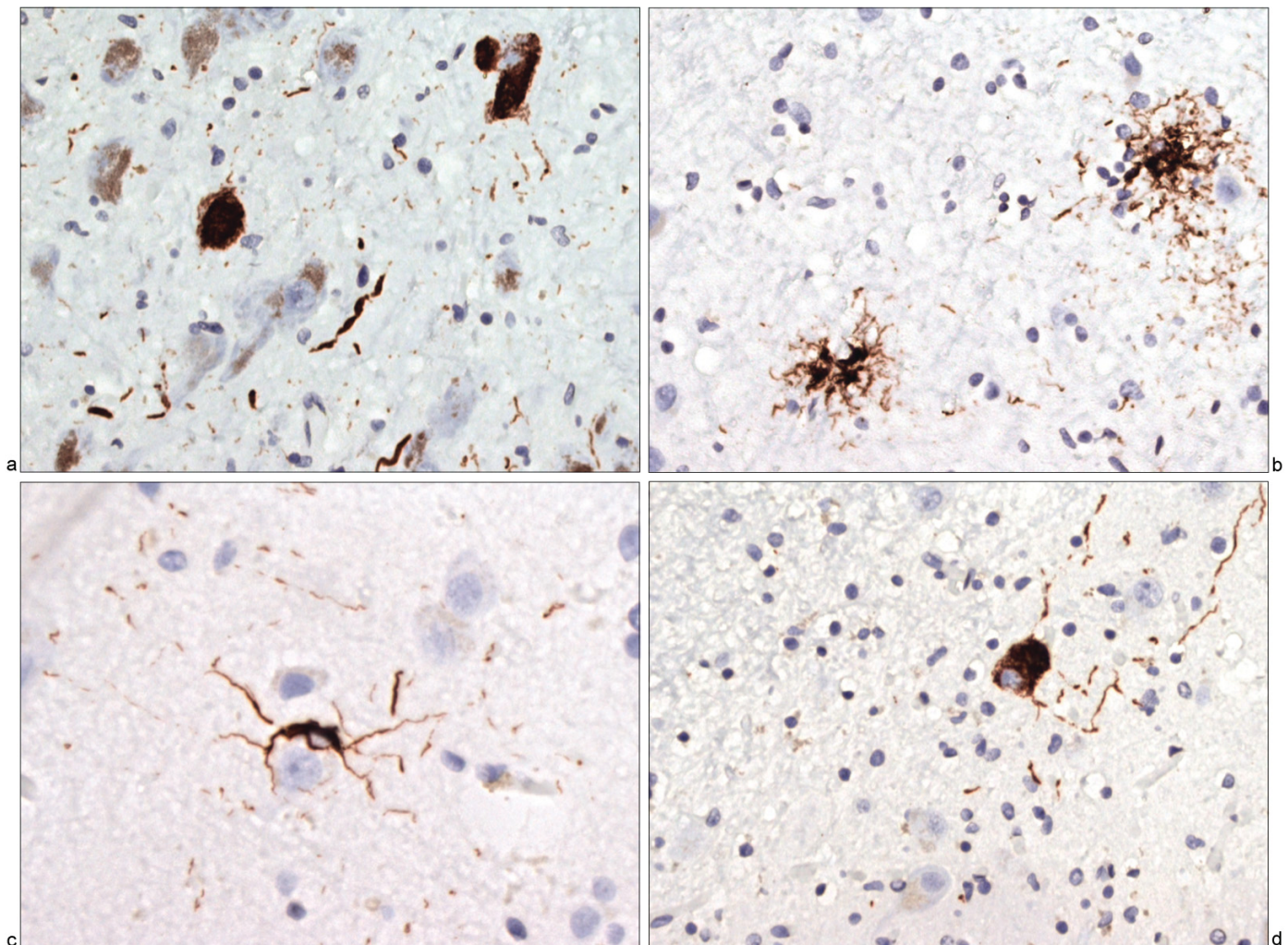


Figure 3. Postmortem Findings. (A) Microphotograph of the pars compacta of the substantia nigra at the level of the red nucleus. Two neurons and neuropil threads are labeled with AT8 antibodies and are among 11 normal appearing pigmented neurons (original magnification 400×). (B) Microphotograph of the sixth layer of the motor cortex showing two AT8-labeled tufted astrocytes (original magnification 400×). (C) Microphotograph of the fifth cortical layer of the superior parietal lobule (BA7) depicting an AT8-labeled glial cytoplasmic inclusion (original magnification 630×). (D) Microphotograph of the ventral arm of the dentate nucleus of the cerebellum depicting an AT8-labeled neuron and neuropil threads (original magnification 400×).

Table 1. Postmortem Findings

	Globose Neuronal Tangles	Tufted Astrocytes	Glial Cytoplasmic Inclusions
Cerebral cortex	+I	+I	+I
Cerebral white matter	0	0	+I
Neostriatum (caudate and putamen)	+I	+I	+I
Globus pallidus	+I	0	0
Clastrum	+I	+I	0
Subthalamic nucleus	+I	0	0
Red nucleus	+I	0	0
Substantia nigra pars compacta	+I	0	0
Pontine nuclei	+I	0	0
Inferior olivary nucleus	0	0	0
Cerebellar dentate nucleus	+I	0	0

I+ (1 per 100 × microscopic field), 2+ (up to 3 per 100 × microscopic field) 3+ (>3 per 100 × microscopic field).

of torpedoes, and absence of basket cell changes further contrasts with the findings that we have reported in ET patients in the New York Brain Bank.¹³

Monosymptomatic rest tremor is a category proposed by the Movement Disorder Society consensus statement.²³ These are patients with pure or predominant rest tremor for at least two years without an abnormal degree of bradykinesia. The underlying pathological basis is unclear, but some of these patients have evidence of dopaminergic deficits on neuroimaging.²³ In the series of 251 patients of Leventoglu and Baysal,⁶ three had isolated jaw tremor for a long period, but the entity is obviously rare. Hence, while a benign form of PD is a possibility, one would be dealing with a rare entity (jaw-predominant benign tremulous parkinsonism).

Dystonic tremor was raised as another possibility. Schneider et al⁹ reported seven women with jaw tremor and dystonia. Unlike our patient, however, these cases had other obvious evidence of dystonia (e.g., cervical dystonia, blepharospasm, writer's cramp), and often had clear jaw deviation, which accompanied their jaw tremor. Frucht et al²⁵ described 13 patients with embouchure dystonia, which is a task-specific dystonia that affects musicians; however, isolated jaw tremor was absent when these patients were not playing their wind instruments. A recent report of 429 patients with primary adult-onset dystonia did not report jaw tremor as a feature of any of the cases with oromandibular dystonia.²⁶

Given the combination of mild action tremor in the limbs, parkinsonian-like jaw tremor, and cognitive features, FXTAS is another interesting possibility. Classically, FXTAS patients tend to be men in their 60s who develop parkinsonism and cognitive decline, intention tremor, and cerebellar ataxia.²⁷ Tremor is one of the earliest

signs.²⁸ The tremor phenomenology in FXTAS has variably been described as “action” or “intention” tremor,^{27,29–31} although many patients likely have mixed phenomenology (i.e., a kinetic tremor with an intentional component).²⁹ The tremor has also been reported as a postural tremor,^{29,30,32} indicating what is likely a mixed tremor that varies with position. To our knowledge, however, this particular constellation of findings (jaw tremor without other clear signs of parkinsonism in the absence of clear ataxia or intention tremor) has not been reported in FXTAS.

Given the tremor and gait difficulty, spinocerebellar ataxia is raised as a possibility but, as noted, this is low on the differential given the nature of the tremor and the absence of clear signs of ataxia, dysarthria, or other problems with the force and timing of motion.

Hereditary geniospasm is another condition that can produce jaw tremor. However, the tremor is often clearly familial and generally begins early in life; furthermore, the tremor is episodic and primarily affects the mentalis rather than the jaw muscles.^{33,34}

An interesting possibility is edentulous dyskinesia.^{35–37} These are stereotyped movements of the jaw, lips, and tongue that occur in edentulous patients and even among those who wear dentures (especially ill-fitting dentures). The movements are observed as smacking and pursing of the lips, lateral deviation and protrusion of the tongue, and chewing/repetitive movements of the jaw, which often involve lateral deviation of the jaw.^{35–37} In this sense, they differ somewhat from the movements observed in our patient. The movements of edentulous dyskinesia differ from those of tardive dyskinesia because they are confined to the oral region and there are no dystonic movements of the tongue.

The postmortem diagnosis was PSP. Based on the clinical history and videotaped examination, none of the four experts raised this as a possibility. Could the PSP have been incidental? The prevalence of “incidental” PSP is difficult to estimate but is likely to be low, making this an unlikely possibility: the Harvard Brain Tissue Center reported incidental PSP in only one of 39 (2.6%) normal controls,³⁸ and in another series, two of 76 (2.6%) autopsies of clinically normal subjects had mild pathological changes of PSP.¹⁸ Furthermore, “incidental” suggests the absence of associated clinical features, and our patient had a prominent, longstanding, and clearly abnormal movement disorder, which resembled that seen in patients with extrapyramidal diseases.

Louis et al¹⁵ recently reported 11 ET cases who subsequently developed PSP. The current case differs from those because all 11 had typical and obvious ET.

Most autopsy series of PSP are inherently biased, as it is the more typical PSP case, with parkinsonism or dementia, that typically comes to autopsy, rather than individuals with atypical cranial tremors. Thus, the wider clinical spectrum of PSP, as well as other tauopathies, has not been catalogued.³⁹

A clinical-pathological diagnosis of PSP would account for nearly all of the patient’s clinical features, including cognitive difficulties (though there was a clear amnesic component, amnesic features may occur even in PSP⁴⁰), mild limb tremor, parkinsonian-like jaw tremor, and possibly some of his gait difficulty.⁴¹ The 20-year history of jaw tremor is curious and it raises two possibilities: 1) There is a benign tremulous form of PSP that can span at least two decades. The 20-year history of jaw tremor is curious, and raises the possibility that some cases of “monosymptomatic rest tremor” may be due to a more benign form of PSP rather than a more benign form of PD; 2) The patient had two illnesses, a predominant and marked jaw tremor beginning in his late 70s (which may not have had obvious pathological hallmarks) followed by PSP arising in his mid-90s.

In summary, this case presents with a mixed and difficult to clinically classify form of tremor as well as other neurological symptoms and signs. Whether the case represents in its entirety a benign tremulous form of PSP or a combination of several diagnoses, including PSP, is not fully clear. The case raises many interesting issues and provides a window into the complexity of the interpretation, nosology, and classification of tremor phenomenology.

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