

# Headache and Tremor: Co-occurrences and Possible Associations

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## Abstract

**Background:** Tremor and headache are two of the most prevalent neurological conditions. This review addresses possible associations between various types of tremor and headache, and provides a differential diagnosis for patients presenting with both tremor and headache.

**Methods:** Data were identified by searching MEDLINE in February 2015, with the terms “tremor” and terms representing the primary headache syndromes.

**Results:** Evidence for an association between migraine and essential tremor is conflicting. Other primary headaches are not associated with tremor. Conditions that may present with both tremor and headache include cervical dystonia, infectious diseases, hydrocephalus, spontaneous cerebrospinal fluid leaks, space-occupying lesions, and metabolic disease. Furthermore, both can be seen as a side effect of medication and in the use of recreational drugs.

**Discussion:** No clear association between primary headaches and tremor has been found. Many conditions may feature both headache and tremor, but rarely as core clinical symptoms at presentation.

**Keywords:** Headache, migraine, tremor

**Citation:** Kuiper M, Hendriks S, Koehler PJ. Headache and tremor: Co-occurrences and possible associations. *Tremor Other Hyperkinet Mov* 2015; 5. doi: 10.7916/D8P55MKX

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**Editor:** Elan D. Louis, Yale University, USA

**Received:** November 7, 2014 **Accepted:** May 12, 2015 **Published:** June 17, 2015

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**Funding:** None

**Financial Disclosures:** None

**Conflict of Interest:** The authors report no conflict of interest.

## Introduction

Headache and tremor are two common neurological conditions. The prevalence of tension-type headache in the general population has been found to be 63% in males and 86% in females.<sup>1</sup> Although less common, migraine prevalence is also high: 11.7% in individuals aged 12 years and older, peaking in middle life.<sup>2</sup> Essential tremor (ET), the most common tremor type, has a prevalence of 0.4% in the general population and of 4.6% in people  $\geq 65$  years.<sup>3</sup> In some patients, a short time interval between the debut of headache and tremor will suggest that their co-occurrence is more than just coincidence. An association between migraine headache and ET has been debated since the early 1990s. Studies examining co-occurrence of other primary headache syndromes and tremor are sparse. In view of the diverse pathophysiological mechanisms behind different types of headache and tremor, an association between migraine and ET, if present, would not suggest that similar associations between other types of headache and tremor are to be expected. However, most headache and tremor syndromes are incompletely understood and

identifying associations is helpful in generating new theories regarding their pathophysiology. Therefore, the possibility that other tremor and headache syndromes are associated should not be dismissed beforehand. This review aims to identify evidence for association of tremor and the primary headache disorders, which include tension-type headache, migraine, and the trigeminal autonomic cephalalgias. To provide clinicians with a differential diagnosis when faced with a patient presenting with both tremor and headache, various conditions in which tremor and secondary headaches occur are reviewed as well.

## Review criteria

Data were identified by searching MEDLINE with the term “tremor” added to the following terms: “primary headache syndrome”, “headache”, “migraine”, “cluster headache”, “trigeminal autonomic cephalalgia”, “SUNCT” (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), “SUNA” (short-lasting unilateral neuralgiform headache attacks with autonomic symptoms), “primary stabbing headache”, “primary cough

headache”, primary exertional headache”, primary headache associated with sexual activity”, “hypnic headache”, “primary thunderclap headache”, hemicrania continua” and “new daily-persistent headache”. The search was performed on February 28, 2015. It generated 478 articles. An additional 91 articles were identified by scanning references. Articles were deemed relevant if they described patients and/or conditions in which tremor and headache co-occurred. If tremor was reported without specification of tremor type, the article was not included. A total of 79 articles were identified in this manner, of which nine were generated by the primary search and 70 by scanning references.

### Migraine and essential tremor

#### Epidemiological studies

In the early 1990s, case-control studies showed a correlation between ET and migraine headaches. Biary et al.<sup>4</sup> compared 74 ET patients with 102 controls and found that ET patients were significantly more likely than controls to suffer migraine headaches: 36% vs. 18% ( $p=0.005$ ). In the same study, 58 patients with migraine headaches were found to be significantly more likely than 85 controls to suffer ET: 17% vs. 1% ( $p=0.001$ ). Bain et al.<sup>5</sup> studied 20 index patients with hereditary ET and 131 relatives. Classical migraine occurred in 26% of cases. It co-segregated with tremor. Biary’s study suffered from suboptimal age matching of cases and controls. Two more recent publications report on studies in sex- and age-matched cases and controls. Barbanti et al.<sup>6</sup> found no significant difference in reported lifetime migraine occurrence between 110 ET patients and 110 controls. Hu et al.<sup>7</sup> performed a similar study in 150 ET patients and 150 controls of Han Chinese origin and did find a significantly higher lifetime migraine prevalence in ET: 22.0% vs. 12.7%,  $p=0.035$ . The two studies were similar in design. Aside from the different ethnic background of the populations they studied, the only major difference in patient characteristics was age. The mean age of patients and controls in Barbanti’s study was 15.3 years higher than in Hu’s study (69.6 vs. 54.3 years).

#### Pathophysiology and genetics

A pathophysiological association between migraine and ET is suggested by clinical observations, for example their shared responsiveness to beta-blockers.<sup>4</sup> Furthermore, migraine and ET show similar bilateral activation of the red nucleus on blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI).<sup>8–11</sup> So far, however, no common pathophysiology or genetics has been identified. A co-inheritance of migraine, vertigo, and ET was reported in one family.<sup>12</sup> Further evidence for a shared pathophysiology of migraine and ET in this family might be found in the fact that both conditions reacted favorably to treatment with acetazolamide. The syndrome was presumed to be a variant of familial hemiplegic migraine (FHM) and a linkage analysis was done to markers on a region of chromosome 19p (since then identified as the CACNA1a gene) known to be linked to syndromes of hemiplegic migraine and periodic ataxia. No linkage was found. Another gene of interest is the DRD3 gene, which encodes for

the dopamine D3 receptor. The “rs6280” single nucleotide polymorphism (SNP) was found to be associated with risk and age of onset of ET. In migraineurs, an increased density of lymphocytic DRD3 receptors has been reported. Hu et al.<sup>7</sup> studied the prevalence of the “rs6280” SNP in the DRD3 gene in ET patients with and without migraine and found no significant difference. Duval and Norton<sup>13</sup> argued that if ET and migraine shared a common pathophysiology, a subclinical ET should be found in migraineurs without overt ET. No difference was found between physiological tremor in patients with and without migraine. This suggests that a correlation between migraine and ET, if there is one, would not be caused by a shared pathophysiology. Duval suggested that otherwise asymptomatic microvascular insults, for which migraine patients have a higher risk than controls, might be implicated.

### Tremor in hemiplegic migraine

In a population-based clinical description of 147 FHM patients, a head tremor was found in one patient.<sup>14</sup> Geerlings et al.<sup>15</sup> report on two adult patients suffering from migraine headaches and a permanent 3–5 Hz “no-no” tremor of the head; one of them also had a tremor of the hands. These patients did not fulfill the diagnostic criteria for hemiplegic migraine because of lack of clear motor symptoms. However, mutations in the CACNA1A gene associated with familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6 were found in both. Dichgans et al.<sup>16</sup> reported two patients with CACNA1A mutations who suffered from an intention tremor without head tremor. Zifkin et al.<sup>17</sup> describe a mother and son with childhood onset hemiplegic migraine, who both featured an asymmetrical tremor with the characteristics of an ET.

### Cervical dystonia, dystonic tremor, and headache

Although a dystonic “no-no” head tremor is frequently observed in cervical dystonia and headache in craniocervical dystonia is listed as a separate headache type in the International Classification of Headache Disorders (ICHD),<sup>18</sup> we did not find any articles addressing their co-occurrence. Nevertheless, in a patient with a head tremor and an unexplained headache, cervical dystonia should be considered.

### Headache and tremor in infectious disease

Headache in infectious disease can be a non-specific sign of malaise. Less often, it will be a symptom of inflammation of the paranasal sinuses, focal or generalized inflammation of the meninges, or of increased intracranial pressure (ICP). Many infectious diseases will occasionally produce headache and tremor, but only as a clinical rarity or against a background of other, more prominent symptoms. In some these are more typical signs. West Nile virus (WNV) is an example of an infectious disease with the co-occurrence of headache and tremor. Postural, kinetic, and intention tremors appear to be a frequent and early feature of WNV meningitis and encephalitis, with a prevalence of 12–94%. Tremor occurred in 15 out of 16 consecutive WNV patients described by Sevjar et al.,<sup>19</sup> making it the third most prevalent symptom after fever and headache. Tremor in WNV usually, but not

invariably, disappears within several months. The high incidence of tremor in WNV may reflect the predilection of the virus for the basal ganglia, thalamus, substantia nigra, and brainstem.<sup>20,21</sup> Tremor has also been described in the acute phase of Japanese encephalitis<sup>22</sup> and Murray Valley encephalitis,<sup>23</sup> both closely related to WNV.

In bacterial meningitis headache is almost uniformly present but tremor is uncommon, with the possible exception of *Listeria* infections of the central nervous system.<sup>24,25</sup> Lorber<sup>24</sup> reports that movement disorders including tremor are present in 15–20% of patients. Whether tremor in these patients is related to subcortical abscesses in the thalamus, pons and medulla, which can be found in *Listeria*, but are rare in other bacterial central nervous system infections, is not specified.

In (para)infectious disease affecting the cerebellum and brainstem such as acute cerebellar ataxia, acute cerebellitis and rhombencephalitis, onset with tremor and headache appears to be exceptional.

Tremor, usually Holmes tremor, is one of the most frequently encountered movement disorders in human immunodeficiency virus infection, usually in patients with established acquired immune deficiency syndrome.<sup>26</sup> In the majority of cases it is secondary to *Toxoplasma* abscesses in the mesencephalon of thalamus.<sup>27</sup> Holmes tremor usually is a late feature. Lekoubou et al.<sup>27</sup> describe a patient with a relatively short latency between onset of neurological signs and Holmes tremor, and even in this patient the tremor did not become apparent until 8 days after he first came to medical attention.

There are case reports of other neuroinfections presenting with headache and tremor. Jin et al.<sup>28</sup> describe a 52-year-old male in whom brucellosis caused a headache, partial seizures, and bilateral parkinsonian tremor affecting both arms. Roselli et al.<sup>29</sup> describe a 56-year-old male with a fever, headache, and unilateral Holmes tremor caused by HSV-1 cerebral pedunculitis. Neurosyphilis is often accompanied by headache and can feature rest tremor, rubral tremor,<sup>30</sup> and tongue tremor.<sup>31</sup>

## Headache and tremor in hydrocephalus

### Epidemiological studies

Parkinsonism and other movement disorders, including tremor are frequent symptoms of hydrocephalus. In a case series describing 118 adult patients with hydrocephalus, Krauss et al.<sup>32</sup> found 35% to have a tremor; tremor characteristics varied. The majority of patients in this study were diagnosed with normal pressure hydrocephalus, in which headache is not a prominent symptom. Of five patients with obstructive (non-communicating) hydrocephalus, more likely to feature headache, none had tremor. Parkinsonism indeed appears to be rare in obstructive hydrocephalus. When it does occur, often accompanied by symptoms of Parinaud's syndrome, it is most often late in the course of the disease, and tremor is usually overshadowed by other symptoms.<sup>33</sup> Keane,<sup>34</sup> however, describes four patients in whom a 4–5 Hz resting and postural tremor of head, jaw, and extremities (most often the right arm) was an important, and sometimes presenting feature, of shunt failure. The cause of hydrocephalus in all patients was cysticercosis. Tremor resembling ET has been noted in obstructive hydrocephalus.

Halterman et al.<sup>35</sup> describe an 18-year-old African American male who developed action tremor in his dominant right hand and his right leg at the age of 9 years. At presentation, his academic performance had declined and he experienced frequent headaches. Examination showed mild cognitive deficits and predominantly right-sided 4 Hz action tremor when performing the finger-to-nose test. MRI demonstrated a triventricular non-communicating hydrocephalus secondary to aqueductal stenosis. The patient was initially diagnosed with ET, which was recognized to be atypical in its presentation because of a young age at onset, a negative family history, and because symptoms were not limited to the upper limb. Tremor markedly improved after an endoscopic third ventriculostomy. Hertel et al.<sup>36</sup> describe a typical Holmes tremor with 4–5 Hz rest, posture, and intention components affecting the right arm and leg in a 58-year-old male who also suffered from headaches and dizziness. Imaging showed signs of a chronic communicating hydrocephalus, but also a small, older ischemic midbrain lesion caudal and slightly dorsal to the red nucleus on the left side. Tremor repeatedly responded favorably to CSF removal via lumbar puncture, and initially to subsequent placement of a VP shunt, but the patient ultimately required stereotactic electrode implantation in the motor thalamus.

### Pathophysiology

The cause of tremor in hydrocephalus is unknown. Hypotheses include mechanical compression due to ventriculomegaly and reduced periventricular blood flow. Headache in hydrocephalus is caused by stretching of intracranial pain-sensitive structures such as the meninges. Raised ICP is also implicated, as headache is the most prominent feature of idiopathic intracranial hypertension, in which ICP is raised but very little anatomical disturbance occurs.

## Headache and tremor in spontaneous CSF leaks

There are several case reports describing patients with a, usually orthostatic, headache due to spontaneous CSF leaks who also featured a tremor. In a case described by Pakiam et al.<sup>37</sup> a 54-year-old female presented with a unilateral resting tremor and other parkinsonian features; in this patient, a mild headache occurred late in the disease. Turgut et al.<sup>38</sup> report a 57-year-old male with a postural bilateral hand tremor. Mokri<sup>39</sup> describes a 52-year-old female with a mixed static and kinetic tremor of the upper limbs. She also suffered from tinnitus, altered hearing, vertigo, and gait unsteadiness. All three patients showed a good response with respect to the tremor to an epidural blood patch, although the beneficial effect was temporary in one. The underlying cause for tremor to occur in spontaneous CSF leaks is presumed to be sinking of the brain resulting in compressing, stretching, and distorting the deep brain and brainstem structures.

## Cysts, vascular malformations, and tumors

Holmes tremor, also known as rubral or midbrain tremor, is an irregular rest and action tremor. Lesions causing interruption of the dentate–thalamic or nigrostriatal pathways can cause both headache and Holmes tremor. Menon et al.<sup>40</sup> present a 35-year old female,

presenting with headache and tremor due to a giant middle fossa epidermoid cyst, which compromised the midbrain tegmentum.

Akhaddar et al.<sup>41</sup> present a 50-year-old female with progressive headache and a tremor of the head and the right hand due to a dermoid cyst in the Sylvian fissure, and suggested that compression of the basal ganglia and tumor infiltration might be the pathophysiological mechanism of hemiparkinsonism in this patient. In pineal cysts, headache and other symptoms of raised ICP are common. Morgan et al.<sup>42</sup> present a young female with new-onset resting tremor secondary to a pineal cyst. A possible explanation for the tremor could be the disturbance of the microvasculature surrounding the nigro-striatal-pallidal system.

Although brain tumors are a rare cause of hemiparkinsonism, they have been reported in astrocytoma,<sup>43,44</sup> meningioma,<sup>45</sup> hemangiopericytomas,<sup>46</sup> oligodendroglioma,<sup>47</sup> and glioblastoma.<sup>48</sup> Other space-occupying lesions, such as cavernomas, can also cause hemiparkinsonism.<sup>49</sup>

### Headache and tremor in cerebrovascular disease

Headache and tremor can both be symptoms of stroke. However, we found no reports on stroke patients presenting with both, presumably because headache is usually an early feature, while tremor occurs after the acute phase.

### Headache and tremor in metabolic disease

Tremor is one of the most common neurologic manifestations of hyperthyroidism, seen in up to 70–76% of patients.<sup>50,51</sup> It is a kinetic and postural tremor that can involve the extremities, face, and head. Its responsiveness to propranolol suggests that it is mediated by a heightened beta-adrenergic state.<sup>52</sup> Headache can be a symptom of hyperthyroidism,<sup>53</sup> but symptoms and signs such as tremor, diarrhea, tachycardia, and heat intolerance usually predominate. In rare instances, however, headache can be the presenting feature. Stone et al.<sup>54</sup> describe three patients encountered in a single year in a neurological service in whom thyrotoxicosis due to Graves' disease presented with new-onset headache. The headache was unremitting in quality. None of the patients reported photo- or phonophobia. On examination, a tremor was found in all three; it was a prominent sign in one. Headache subsided in all three patients following treatment of their hyperthyroidism. It is not known how hyperthyroidism causes headache. Raised ICP and an altered threshold to migraine have been proposed.<sup>54,55</sup> There are several case reports on patients with symptoms of increased ICP that appear to be caused by hyperthyroidism.<sup>56–59</sup> Next to tremor and other features attributable to hyperthyroidism, patients experienced headache and vomiting and showed signs of raised ICP, such as papilledema. In three patients, an increased ICP was confirmed by a lumbar puncture. In one, ICP was within the normal range.<sup>57</sup> Two of these patients were also diagnosed with communicating hydrocephalus,<sup>56,57</sup> and in a third slight dilation of ventricles was noted.<sup>58</sup> It is possible that raised ICP in these patients was caused by decompensation of pre-existent CSF circulation

abnormalities, as proposed by Herwig. The mechanism by which hyperthyroidism causes raised ICP, however, is still open to debate.

Other metabolic conditions are less likely to feature both headache and tremor as prominent features. Both can be seen in the dialysis disequilibrium syndrome that can follow initial hemodialysis in patients with end-stage renal failure.<sup>60</sup>

In addition to the classical triad of episodic headache, sweating, and tachycardia, tremor is also seen in pheochromocytomas.<sup>61</sup>

## Medication

In patients suffering from headache and tremor, the use of medication always has to be considered as a cause. Instruction leaflets of numerous drugs mention headache and tremor among their side effects. In this section we mention only some of the most relevant associations.

### Antidepressants and mood stabilizers

Both tricyclic and non-tricyclic antidepressants may be useful in the treatment of neuropathic pain and headaches. However, tremor and headaches are reported as side effects of these medications. Amitriptyline, a tricyclic antidepressant, is an effective compound in the treatment of headaches.<sup>62</sup> It has been associated with enhancement of physiological tremor.<sup>63</sup> Selective serotonin re-uptake inhibitors (SSRIs) have yet to prove their efficacy in the treatment of migraine and tension-type headaches, but are well established in the treatment of adult depression. Common side effects of SSRIs and serotonin and norepinephrine reuptake inhibitors include headache.<sup>64</sup> Furthermore, postural and action tremor are well-known side effects of these groups of drugs. For example, fluoxetine side effects include headaches and tremor.<sup>65</sup> A rare, but potentially fatal condition in the use of SSRI is the serotonin syndrome, caused by excess central serotonergic tone. Serotonin syndrome may occur in the use of SSRIs alone, or in combination with MAO inhibitor.<sup>66</sup> Although neither tremor nor headache is part of the typical triad of symptoms in serotonin syndrome, this clinical condition may present with tremor and headache.<sup>67</sup>

Lithium is used as a mood stabilizer and as a prophylactic treatment for cluster headaches as well as the rare hypnic headache.<sup>68,69</sup> Lithium is the most important contributor to drug-induced tremors found in clinical practice, causing an enhanced physiological tremor of 8–12 Hz. The mechanism by which lithium causes tremor is unknown and the tremor can improve over time.<sup>70</sup>

### Anti-epileptic drugs

An updated Cochrane review shows the efficacy of a number of anti-epileptic drugs (AEDs) in the treatment of episodic migraine and chronic daily headache in adults. Important side effects of some anti-epileptic drugs include tremor as well as headache. Valproate (VPA) induces postural tremor in 6–45% of patients.<sup>71</sup> There are also a few reports on drug-related tremor in other AEDs such as tiagabine, gabapentin, and lamotrigine.<sup>70,72</sup> Several AEDs are reported to have

improved ET, e.g. tiagabine, valproate, gabapentin, and possibly levetiracetam.<sup>73</sup>

### Anti-emetics

Several anti-emetics are used in the treatment of migraine in adults. Metoclopramide is a dopamine receptor antagonist used in several gastrointestinal diseases, but also in the acute treatment of migraine-induced nausea and vomiting.<sup>74</sup> Metoclopramide has been known to cause several movement disorders such as parkinsonism, akathisia, and dystonia.<sup>75</sup> Tardive tremor due to metoclopramide appears to be rare. Tarsy and Indorf described a 68-year old female with a disabling resting and postural tremor due to metoclopramide. She also suffered a tremor of the jaw, perioral muscles, and tongue.<sup>76</sup>

### Substance abuse

Clinicians need to consider substance abuse in patients with unexplained tremor and headache. Alcohol-withdrawal tremor is probably the most common tremor associated with substance abuse. It is an irregular and high-frequency tremor, and as such differs from ET, which usually does not exceed 8 Hz. Alcohol withdrawal is frequently accompanied by headache. Alcohol may reduce ET. Both cocaine and amphetamine abuse are associated with tremor and with headache.<sup>77</sup> Caffeine, nicotine, and  $\beta$ -agonist inhalers worsen physiological tremor. Tremor and headache are observed as withdrawal symptoms in patients trying to quit smoking.<sup>78</sup> Nicotine increases tremor amplitudes in all frequencies. Party pills including benzylpiperazine and trifluoromethylphenylpiperazine have been associated with a number of toxic effects, including tremor and headache.<sup>79</sup> Ecstasy (3,4-methylenedioxymethamphetamine) has been associated with headache<sup>80</sup> and with tremor in abstinent users.<sup>81</sup>

### Headache and tremor in toxicology

Headache and tremor are among the effects of spider bite envenomation, particularly in latrodectism, which is related to neurotoxins present in the venom of widow spiders.<sup>82</sup> Furthermore, headache and tremor have been observed in metal poisoning, including lead,<sup>83</sup> manganese,<sup>84</sup> methyl bromide,<sup>85</sup> and carbon disulfide.<sup>86</sup>

## Discussion

Co-occurrence of ET and migraine has been studied for over two decades. Early reports<sup>4,5</sup> suggested an association; however, more recent studies<sup>6,7</sup> of better quality present conflicting data. A possible explanation can be found in the 15.3-year difference in mean age of the ET patients between the two studies. An association between ET and migraine might be more difficult to detect in older ET populations, because the prevalence of migraine decreases in older age. In both Barbanti's study and Hu's study, this was accounted for by determining lifetime migraine prevalence instead of current prevalence. Nevertheless, Biary showed a stronger association of ET with migraine in ET patients below the age of 55 years than in patients at or above this age. A possible explanation might be found in the bimodal age of ET onset found in tertiary referral settings.<sup>87</sup> This could result in

a relative overrepresentation of hereditary ET cases in younger study populations. There are, however, no studies indicating that any association between ET and migraine would be exclusively attributable to hereditary ET cases. Moreover, both Barbanti and Hu report a similar prevalence of a positive family history for ET in ET patients with and without migraine.

In conclusion, there is no clear association between migraine and ET. Moreover, no evidence was found for associations of other primary headaches with tremor syndromes.

Conditions in which both tremor and secondary headache are features were identified. They include cervical dystonia, flaviviral and other infectious diseases, hydrocephalus, space-occupying lesions, and treatment with several classes of medication and recreational drugs. All may present with headache and tremor; however, in most this is either unusual or against a background of more prominent symptoms and signs.

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