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Tremor and Other Hyperkinetic Movements

Reviews

Neuroimaging Studies of Essential Tremor: How Well Do These Studies Support/Refute the Neurodegenerative Hypothesis?

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Abstract

Background: Tissue-based research has recently led to a new patho-mechanistic model of essential tremor (ET)—the cerebellar degenerative model. We are not aware of a study that has reviewed the current neuroimaging evidence, focusing on whether the studies support or refute the neurodegenerative hypothesis of ET. This was our aim.

Methods: References for this review were identified by searches of PubMed (1966 to February 2014).

Results: Several neuroimaging methods have been used to study ET, most of them based on magnetic resonance imaging (MRI). The methods most specific to address the question of neurodegeneration are MRI-based volumetry, magnetic resonance spectroscopy, and diffusion-weighted imaging. Studies using each of these methods provide support for the presence of cerebellar degeneration in ET, finding reduced cerebellar brain volumes, consistent decreases in cerebellar *N*-acetylaspartate, and increased mean diffusivity. Other neuroimaging techniques, such as functional MRI and positron emission tomography (PET) are less specific, but still sensitive to potential neurodegeneration. These techniques are used for measuring a variety of brain functions and their impairment. Studies using these modalities also largely support cerebellar neuronal impairment. In particular, changes in ^{11}C-flumazenil binding in PET studies and changes in iron deposition in an MRI study provide evidence along these lines. The composite data point to neuronal impairment and likely neuronal degeneration in ET.

Discussion: Recent years have seen a marked increase in the number of imaging studies of ET. As a whole, the combined data provide support for the presence of cerebellar neuronal degeneration in this disease.

Keywords: Essential tremor, neurodegeneration, cerebellum, neuroimaging, magnetic resonance imaging

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Introduction

Essential tremor (ET) is one of the most prevalent neurological diseases. [1,2] Its most recognizable clinical feature is an 8–12 Hz action tremor of the arms (i.e., a tremor that occurs during volitional movement); however, head tremor and other cranial tremors may also occur,[3,4] as well as limb and gait ataxia and subtle eye motion abnormalities.[5–7] ET is a progressive disease,[8,9] and the tremor is often disabling.[10,11] The one prospective population-based study that attempted to estimate risk of mortality indicated a modest yet significant increased risk of mortality in ET cases compared with age-matched controls.[12]

Aside from being among the most prevalent neurological diseases, ET is also the most common tremor disorder. The disease is present in 4.0% of individuals aged ⩾40 years of age,[1] and the incidence[13] and

prevalence[1] increase with age, so that as many as 22%–23% of individuals aged >90 years have ET.[14] The condition is global, affecting human beings of all ethnicities, ranging from the remote Okapa sub-district of Papua New Guinea to the densely populated, urban community of Washington Heights–Inwood in Manhattan, New York.[14,15]

Recent tissue-based research has led to a new patho-mechanistic model of ET, namely the cerebellar degenerative model. This model posits that ET begins with an as-yet unidentified molecular event that stresses the Purkinje cell population, and this stress is evidenced by structural changes in that population, including cell death.[16–18] The model offers an alternative to the older olivary model, which posited that tremor in ET originates in the inferior olivary nucleus; that model suffers from a number of important problems, and is consequently falling out of favor.[17] As with all new models, the cerebellar degenerative model has engendered discussion and controversy.[19–21]

Clinically, ET shares a number of important features with neurodegenerative diseases. It has an insidious onset[22,23] and then follows a gradual yet progressive clinical course.[8,9] With time, there is a spread of tremor somatotopically across body regions (from arms to cranial structures), and the development of a more extensive tremor diathesis, with the onset of rest tremor and intention tremor with disease progression.[24,25] Furthermore, both the incidence and the prevalence of ET increase with age and aging, with an exponential increase in prevalence in advanced age.[1,13,14] Additionally, carefully controlled prospective studies indicate that prevalent ET is associated with an increased risk of several degenerative disorders, including Parkinson's disease and Alzheimer's disease.[26–28]

A growing number of neuroimaging studies have been performed in ET patients,[29,30] and the question one may ask is how these studies have contributed to our understanding of the underlying disease mechanisms. To our knowledge, there is no study that has reviewed the cumulative neuroimaging evidence, focusing on whether the studies support or refute the neurodegenerative hypothesis of ET. Hence, the aim of this paper was to review the neuroimaging studies of ET with this specific question in mind: Do the studies support or refute the notion that ET is a neurodegenerative disease (i.e., do they show evidence of regional brain atrophy and/or a metabolic signature consistent with regional neuronal loss)?

Methods

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 until February 2014. The terms "essential tremor", "magnetic resonance imaging", "functional magnetic resonance imaging", "positron emission tomography", "single-photon emission computed tomography", magnetic resonance spectroscopy", "diffusion tensor imaging", "voxel-based morphometry", "atrophy", "brain", and "GABA" were crossed together in the search engine. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed (Tables 1 and 2).

Results

Magnetic resonance volumetry

Magnetic resonance (MR) volumetry uses high-resolution anatomical images to calculate total and region-specific brain volumes, and thus allows for the comparison of regional patterns of brain volume between groups of subjects. It thereby allows investigators to specifically assess regional gray and white matter atrophy.[31,32] Therefore, of all neuroimaging modalities, it most directly addresses the issue of neurodegeneration.

Three studies used 1.5-tesla magnetic resonance imaging (MRI) to study ET.[33–35] First, in 2006, Daniels and colleagues[33] used voxel-based morphometry (VBM) to study 27 ET patients, comparing them with 27 controls. Fourteen of these patients had only postural tremor; thus, there is some diagnostic ambiguity, as kinetic tremor rather than

Table 1. Imaging Studies in ET with Respect to Their Support or Refutation of the Neurodegenerative Hypothesis of ET

Imaging Method	Supports the Neurodegenerative Hypothesis	Refutes the Neurodegenerative Hypothesis	Method Does Not Specifically Assess the Neurodegenerative Hypothesis
MRI volumetry	√		
Magnetic resonance spectroscopy	√		
Diffusion-weighted imaging and diffusion tensor imaging	√		
Functional magnetic resonance imaging			√
Other magnetic resonance imaging	√		
Positron emission tomography	√ (^{11}C-flumazenil PET studies)		√ (other PET studies)

ET, Essential Tremor; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography.

Table 2. Enumeration of Imaging Studies in ET that are Relevant to the Question of the Neurodegenerative Hypothesis of ET

Authors (year)	Imaging Method	Number of Subjects	Main Findings
Daniels et al. 2006[33]	MRI volumetry	27 ET, 27 controls	No regional decreases in gray and white matter volume in patients with ET
Quattrone et al. 2008[34]	MRI volumetry	50 ET (30 with arm tremor and 20 with both arm and head tremor), 32 Controls	Marked atrophy of the cerebellar vermis in the ET patients with arm and head tremor when compared with controls
Cerasa et al. 2009[35]	MRI volumetry	46 ET (27 with arm tremor and 19 with arm and head tremor), 28 controls	A reduction of cerebellar volume in ET patients with head tremor, with respect to healthy controls
Benito-León et al. 2009[38]	MRI volumetry	19 ET, 20 controls	In case–control comparisons, white matter changes were seen in several areas, including the right cerebellum, left medulla, right parietal lobe, and right limbic lobe; gray matter changes were seen in several areas as well, including the bilateral cerebellum, bilateral parietal lobes, right frontal lobe, and right insula
Bagepally et al. 2012[39]	MRI volumetry	20 ET, 17 controls	ET patients exhibited widespread areas of atrophy in both the cerebellum and cerebral gray matter
Lin et al. 2013[40]	MRI volumetry	10 ET, 10 Parkinson's disease, 13 controls	Compared to the control group, the ET group showed significantly smaller volumes of many brain regions, including the caudate body, middle temporal pole, insula, precuneus, and superior temporal gyrus, but not the cerebellum
Louis et al. 2002[47]	MRS	16 ET, 11 controls	Mean cerebellar cortical NAA/Cr was reduced in cases compared to controls
Pagan et al. 2003[48]	MRS	10 ET, 10 controls	Left and right cerebellar hemisphere NAA/Cr ratios were significantly smaller in the ET patients than controls
Kendi et al. 2005[49]	MRS	14 ET, 9 controls	The study focused exclusively on the thalamus. In the ET patients, the NAA/Cr ratio in the right thalamus was significantly higher than the NAA/Cr ratio of the left thalamus.
Martinelli et al. 2007[54]	DWI	10 ET, 10 controls	Diffusion coefficients were similar in all brain areas in ET patients and controls
Buijink et al. 2013[55]	DTI	8 ET, 5 controls	No significant decrease in FA values (cerebellum) in ET patients compared to controls

Table 2. Continued

Authors (year)	Imaging Method	Number of Subjects	Main Findings
Shin et al. 2008[52]	DTI	10 ET, 8 controls	ET patients exhibited significantly reduced FA in the bilateral cerebellum as well as other brain regions, including the anterolateral portion of the right pons, left midbrain, and bilateral deep white matter of the orbitofrontal, lateral frontal, parietal, and temporal white matter
Nicoletti et al. 2010[56]	DTI	25 ET, 15 controls	In ET, FA values were reduced in the region of the dentate nucleus and middle cerebellar peduncle, and mean diffusivity values were higher in the superior cerebellar peduncle
Klein et al. 2011[57]	DTI	14 ET, 20 controls	Reduced FA in the right inferior cerebellar peduncle and increased mean diffusivity bilaterally in the inferior cerebellar peduncles in ET. Increased mean diffusivity was distributed in both motor and non-motor white matter fibers of ET.
Jia et al. 2011[58]	DTI	15 ET, 15 controls	Diffusion values in the red nuclei were higher in ET cases than controls, but the authors only assessed a limited number of regions of interest, which did not include the cerebellum
Saini et al. 2012[59]	DTI	20 ET, 17 controls	ET patients showed significant increases in diffusivity in the bilateral cerebral hemispheres, cerebellar hemisphere white matter, thalamus, brainstem and right frontoparietal white matter. No significant change in FA of the white matter was seen. Region of interest analysis also revealed abnormalities in the anterior limb of the internal capsules and cerebellar peduncles.
Oliveira et al. 2012[65]	Other MRI	33 ET, 507 controls	Total white matter hyperintensity volume was greater in ET cases than controls. Cerebellar white matter hyperintensity volume was greater in ET cases than controls in adjusted analyses.
Novellino et al. 2013[66]	Other MRI	24 ET, 25 controls	Whole-brain voxel-based analyses showed significant differences, consistent with increased iron deposition, in the bilateral globus pallidus, substantia nigra, and in right dentate nucleus

Table 2. Continued

Authors (year)	Imaging Method	Number of Subjects	Main Findings
Boecker et al. 2010[74]	PET	8 ET, 11 controls	In the ET patients, there was a significant increase in binding of ^{11}C-flumazenil at the benzodiazepine receptor site of the $GABA_A$ receptor in the cerebellum (at the level of the dentate nucleus), the ventrolateral thalamus, and the lateral premotor cortex
Gironell et al. 2012[76]		10 ET, no controls	There was a significant correlation between cerebellar flumazenil uptake and tremor rating scale scores

DTI, Diffusion Tensor Imaging; DWI, Diffusion-Weighted Imaging; ET, Essential Tremor; FA, fractional anisotropy; fMRI, functional Magnetic Resonance Imaging; GABA, gamma-aminobutyric acid; MRI, Magnetic Resonance Imaging; MRS, Magnetic Resonance Spectroscopy; NAA/Cr, *N*-acetylaspartate/total creatine; PET, Positron Emission Tomography.

isolated postural tremor is the typical feature of ET.[36,37] In this study, VBM did not demonstrate regional decreases in gray and white matter volume in patients with ET. Patients with intention tremor showed a relative expansion of gray matter bilaterally in the region of the temporoparietal junction and the right middle occipital cortex, which the authors argued might represent a long-term result of adaptive reorganization compensating the higher demands on the visuospatial control of skilled movements in the setting of tremor.[33] Second, in 2008, Quattrone and colleagues[34] used VBM (1.5 tesla) to study 50 ET cases, comparing them with 32 controls. The ET cases were divided into those with arm tremor (n=30) vs. those with both arm and head tremor (n=20). There was marked atrophy of the cerebellar vermis in the ET patients with arm and head tremor when compared with controls. ET patients with arm tremor demonstrated a trend toward a vermal gray matter volume loss, although this difference did not reach statistical significance. Third, in 2009, Cerasa and colleagues,[35] using 1.5 tesla MRI, studied 46 ET patients, grouping them into those who had arm tremor (n=27) vs. those having arm and head tremor (n=19), and compared them with 28 healthy controls. Their results revealed a reduction of cerebellar volume in ET patients with head tremor, with respect to healthy controls. No significant difference was detected in any other subcortical area.

Three further studies used 3 tesla MRI, and thus made use of higher special resolution.[38–40] First, a study in 2009 by Benito-León and colleagues[38] assessed whether gray or white matter changes occurred in ET patients vs. controls. The authors studied 19 ET patients and 20 controls. In case—control comparisons, white matter changes were seen in several areas, including the right cerebellum, left medulla, right parietal lobe, and right limbic lobe; gray matter changes were seen in several areas as well, including the bilateral cerebellum, bilateral parietal lobes, right frontal lobe, and right insula. Second, in 2012, Bagepally et al.[39] used VBM (3 tesla) to image 20 ET patients and 17 controls. The ET patients exhibited widespread areas of atrophy in both the cerebellum and cerebral gray matter. Finally, Lin and colleagues,[40] used VBM to study 10 ET patients, comparing them with 10 Parkinson's disease patients and 13 controls. Problems with the study are the small sample of ET cases and the fact that the authors did not document the diagnostic criteria that were used to identify ET cases.[40] Given the high misdiagnosis rate of ET (30–50% in some studies),[41,42] this is problematic. The authors found that, compared with the control group, the ET group showed significantly smaller volumes of many brain regions, including the caudate body, middle temporal pole, insula, precuneus, and superior temporal gyrus, but not the cerebellum.[40]

Although the most reasonable interpretation of the observed reductions in brain volume in the above studies is that they are due to neuronal loss (i.e., neurodegeneration with atrophy), one other possibility is that ET patients are born with smaller volumes in certain brain regions. There is no empirical support for this interpretation; furthermore, while ET can begin in childhood,[43] in most cases it begins during later adulthood.[1,44]

In summary, the data from the VBM studies are somewhat mixed, yet the majority of studies (four of six) report a reduction in brain volume in cerebellum in ET and, in particular, especially among those ET patients with head tremor. On the whole, these data are most consistent with the interpretation of neuronal loss in ET, thereby providing supportive neuroimaging evidence of neurodegeneration in ET.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a technique that allows investigators to measure *in vivo* concentrations of certain neurochemicals. *N*-acetylaspartate (NAA) is the most prominent MRS peak in the mammalian brain. It is an amino acid that is present in the cytosol of neurons, and it is often expressed as a ratio to total creatine (Cr). NAA is known to be a marker of neuronal integrity, and thus a reduction in NAA is suggestive of neuronal damage and/or neuronal dysfunction and/or neuronal loss.[45] Neurodegeneration is always accompanied by

a reduction in NAA. One caveat, however, is that while a reduction in NAA is highly suggestive of neurodegeneration, it may also be an early marker of chronic energy impairment (with consequent neuronal dysfunction) preceding obvious neurodegeneration.[46] Several MRS studies have been conducted in ET.

In 2002, Louis and colleagues[47] studied 16 ET patients and 11 controls, and reported that the mean cerebellar cortical NAA/Cr was reduced in cases compared with controls, and, furthermore, that there was an inverse association between cerebellar cortical NAA/Cr and dominant arm tremor severity. Furthermore, the reductions in NAA/Cr were specific to this region of interest and were not detected in other regions of interest (e.g., thalamus, basal ganglia).[47] In 2003, Pagan and colleagues[48] studied 10 ET patients and 10 controls, and both the left and the right cerebellar hemisphere NAA/Cr ratios were significantly smaller in the ET patients than controls. Hence, the results confirmed those of the first study. A third MRS study focused exclusively on the thalamus.[49] The study noted similar NAA/Cr ratios in the 14 ET patients and nine controls, but also noted in the ET patients that the NAA/Cr ratio in the right thalamus was significantly higher than the NAA/Cr ratio of the left thalamus. Due to the focused anatomical coverage, the study does not address the cerebellar degenerative model of ET.

In summary, the published MRS data from two studies[47,48] provide a consistent body of evidence that there is, at a minimum, neuronal dysfunction in the cerebellum in patients with ET. While it is probable that the MRS changes are consistent with neuronal loss, it is also possible that they could be an early marker of pre-terminal neurons prior to a state of actual neurodegeneration.[46]

Diffusion-weighted imaging and diffusion tensor imaging

Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) are MRI techniques that assess the orientation and integrity of white matter tracts by measuring the diffusion of water molecules in neuronal fibers.[50] The method estimates both the degree of directionality using anisotropy and the overall movement or diffusivity of molecules.[51] Disruptions to microstructural tissue integrity, such as found in the neurodegeneration of parkinsonian and other neurodegenerative syndromes, may be associated with alterations in anisotropy and diffusivity measures.[51] More specific to ET, degeneration of gray matter in the cerebellum may be followed by consequent Wallerian degeneration of white matter fibers, and these white matter changes would be detectable using DTI.[52] One caveat regarding DTI is that a difference in fractional anisotropy (FA) simply means that some orientation-dependent aspect of the microstructure of the tissue is different. The difference does not necessarily indicate axonal loss or neurodegeneration, so one must avoid overinterpreting DTI results.[53]

Seven studies have used diffusion imaging to study ET patients, comparing them with normal controls. The studies have used a variety of approaches, including whole brain voxel-by-voxel comparison as well as a region of interest approach, targeting areas involved in the olivary–cerebellar–thalamic network. Two of the seven studies reported null findings. Thus, in 2007, Martinelli et al.[54] studied 10 ET patients and 10 controls using DWI, and reported that diffusion coefficients were similar in all brain areas in ET patients and controls. Although the authors concluded that their findings argue against major structural damage in the ET brain, they noted that "more subtle neurodegenerative changes could not be ruled out."[54] In 2013, Buijink et al.[55] studied cerebellar fiber density in eight ET patients and five controls. Post hoc analyses did not reveal a significant decrease in FA values in ET patients compared with controls.[55] The authors recognized that their small sample size, along with the heterogeneous nature of ET, and the fact that they only assessed mean FA of the whole cerebellum, did not allow them to exclude the existence of more subtle and/or regional neurodegenerative changes in the cerebellum in ET or subgroups of ET patients.[55]

There are five additional studies that compared ET patients with controls. In 2008, Shin et al.[52] studied 10 ET patients and eight controls, and reported that ET patients exhibited significantly reduced FA in the bilateral cerebellum as well as other brain regions, including the anterolateral portion of the right pons, left midbrain, and bilateral deep white matter of the orbitofrontal, lateral frontal, parietal, and temporal white matter. The authors concluded that the white matter abnormalities they detected 1) corresponded well to abnormalities in fibers of the cerebellar–thalamic–cortical loop (involved in tremorogenesis) and 2) were also suggestive of additional extensive structural changes in white matter in ET.[52] In 2010, Nicoletti et al.[56] studied 25 ET patients, comparing them with 15 controls. In ET, FA values were reduced in the region of the dentate nucleus and middle cerebellar peduncle, and mean diffusivity values were higher in the superior cerebellar peduncle.[56] ET patients with longer duration disease showed FA values in the dentate nucleus that were lower than those in ET patients with shorter duration disease, thereby providing clinical–pathological correlation.[56] Their conclusion was that neuroimaging evidence of microstructural changes consistent with neurodegeneration was found in the region of the dentate nucleus and superior cerebellar peduncle of patients with ET, suggesting that neurodegenerative pathology of cerebellar structures may play a role in ET. In 2011, Klein et al.[57] studied 14 ET patients and 20 controls, reporting reduced FA in the right inferior cerebellar peduncle and increased mean diffusivity bilaterally in the inferior cerebellar peduncles. Furthermore, increased mean diffusivity was distributed in both motor and non-motor white matter fibers of ET patients.[57] They concluded that the circumscript findings in the inferior cerebellar peduncles corroborates the patho-mechanistic concept of the cerebellum and its projections as key structures for tremor generation in ET.[57] Similar to Nicoletti et al,[56] they concluded that the more widespread changes in white matter structures of both hemispheres suggested widespread alterations of fiber integrity in motor and non-motor networks in ET patients.[57] In 2011, Jia et al.[58] studied 15 ET patients and 15 controls, but only assessed a limited number of regions of interest (basal ganglia, thalamus, red nucleus, and substantia nigra), which did not include the cerebellum, so the results are of limited value to address the question of cerebellar degeneration. Diffusion values in the red nuclei were higher in ET cases than controls, so that the authors concluded that there is

neuronal damage or loss in ET, suggesting that ET may be a neurodegenerative disease.[58] In 2012, Saini et al.[59] studied 20 ET patients and 17 controls. ET patients showed significant increases in diffusivity in the bilateral cerebral hemispheres, cerebellar hemisphere white matter, thalamus, brainstem, and right frontoparietal white matter.[59] No significant change in FA of the white matter was seen.[59] Region of interest analysis also revealed abnormalities in the anterior limb of the internal capsules and cerebellar peduncles.[59] There was no correlation between the severity of white matter changes and clinical tremor severity score as well as disease duration.[59] They concluded that their study provided *in vivo* evidence for axonal disintegration of the cerebral and cerebellar white matter fibers in patients with ET.[59]

In summary, five of seven diffusion imaging studies have demonstrated important and consistent differences between ET cases and controls, and the two studies with null results have important methodological limitations. Therefore, the weight of evidence from the DTI literature demonstrates that some orientation-dependent aspect of the microstructure of the tissue in ET is abnormal. One may conclude that this is consistent with neurodegeneration, but should avoid the temptation to overinterpret the results by concluding that this is indicative of neurodegeneration. The bulk of these studies show evidence of axonal changes in the cerebellum, although more widespread changes have been noted as well, and these plausibly suggest widespread alterations of fiber integrity in motor and non-motor networks in ET patients.

Functional magnetic resonance imaging

fMRI is a technique that is used to assess neuronal activity, as reflected by changes in regional blood flow. There have been five fMRI studies of ET.[60–64] The first of these studies was performed in 1997; Bucher and colleagues studied 12 ET patients and 15 controls.[61] A number of tasks were chosen to relate tremor with brain activation patterns. These included the resting condition, postural stretching, mimicking tremor (control group), and passive movement of the wrist. Involuntary tremor in the ET patients was associated with a significantly greater activation in the cerebellar hemispheres and the red nucleus than mimicked tremor in the controls. The study showed that ET is mainly associated with an additional contralateral cerebellar pathway activation and overactivity in the cerebellum, red nucleus, and globus pallidus, without significant intrinsic inferior olivary nucleus activation Thus, the study was able to infer which brain regions were involved in the propagation of tremor in ET. Several of the other fMRI studies have similarly shown changes in the cerebellar–thalamic network in ET,[60,64] yet, fMRI is designed to assess changes in neuronal activity and function rather than neuronal loss or neuronal degeneration.

Magnetic resonance imaging (other)

A number of other studies have used MRI to address specific questions and to study patients with ET.[65,66] At least one of these has aimed at addressing the neurodegenerative hypothesis.[66]

In 2012, a study by Oliveira and colleagues[65] studied 33 ET cases, comparing them with 507 controls. Total white matter hyperintensity volume and regional white matter hyperintensity volume, thought to reflect small vessel disease, were derived from T2-weighted fluid attenuated inverse recovery-weighted (FLAIR) MR images.[65] Total white matter hyperintensity volume was greater in ET cases than controls.[65] Cerebellar white matter hyperintensity volume was greater in ET cases than controls in adjusted analyses.[65] In addition, large strokes were significantly more common in ET cases than in controls, but the distribution of strokes did not differ by diagnosis.[65] The authors concluded that ET was associated with greater total white matter hyperintensity volume, greater cerebellar white matter hyperintensity volume, and possibly more strokes, and that cerebrovascular disease could play a role in the development of ET.[65] With its focus on white matter hyperintensities, however, the study was not relevant to the question of neurodegeneration.

A recent study by Novellino and colleagues[66] attempted to assess brain iron deposition in ET, as abnormal brain iron deposition may be a feature of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Twenty-four ET patients were compared with 25 controls. Whole-brain voxel-based analyses showed significant differences, consistent with increased iron deposition, in the bilateral globus pallidus, substantia nigra, and in the right dentate nucleus.[66] While the study clearly showed increased iron accumulation in the ET brain, this is not direct proof of neurodegeneration; rather, it provides additional indirect evidence that is supportive of neurodegeneration.

Positron emission tomography

PET is a method that may provide information on regional cerebral blood flow, regional glucose metabolism, or regional binding of a variety of radiopharmaceutical compounds.

There are a large number of such studies.[67–72] The most consistent finding is the localization of changes in blood flow to the cerebellum, although a number of other structures in the motor system (i.e., thalamus, red nucleus) are implicated in selected studies as well. These studies, however, reflect the functional integrity of these brain regions rather than their structural integrity, and while they show that these brain regions are involved in the generation and/or propagation of tremor in ET, they are not suited to address the question of neurodegeneration in ET.

Several recent studies have specifically assessed the integrity of the gamma-aminobutyric acid (GABA) system in the ET cerebellum, as there is considerable evidence of GABAergic dysfunction in that disease.[73] Thus, in 2010, Boecker et al.[74] performed an ^{11}C-flumazenil PET study to calculate the distribution volume, an index of availability of benzodiazepine receptor sites, of the $GABA_A$ complex, in eight ET patients vs. 11 controls. In the ET patients, there was a significant increase in binding of ^{11}C-flumazenil at the benzodiazepine receptor site of the $GABA_A$ receptor in the cerebellum (at the level of the dentate nucleus), the ventrolateral thalamus, and the lateral premotor cortex. The authors concluded that ET is associated with reduced

GABAergic function and increased availability of benzodiazepine receptor sites in brain regions implicated in tremor genesis. They posited that the observed pattern of localized increased ^{11}C-flumazenil binding in ET could reflect a reactive receptor upregulation, indicating the presence of a localized GABAergic deficit, and that this is likely related to the cerebellar Purkinje cell loss that has been identified in post-mortem studies. Indeed, Paris-Robidas and colleagues,[75] working with postmortem tissue, demonstrated a reduction in GABA receptor concentrations in the dentate nucleus of ET. Hence, the study findings were supportive of the notion of Purkinje cell degeneration in ET. More recently, Gironell and colleagues[76] performed ^{11}C-flumazenil PET studies in 10 ET patients at different stages of clinical severity. There was a significant correlation between cerebellar flumazenil uptake and tremor rating scale scores, again suggesting an abnormality at the level of $GABA_A$ receptors in ET.

Summary

Recent tissue-based research has led to a new patho-mechanistic model of ET—the cerebellar degenerative model. The model offers an alternative to the older olivary model.[17] The cerebellar degenerative model has engendered controversy and discussion. How do the neuroimaging data add to this particular discussion? The aim of our study was to review the cumulative neuroimaging evidence, focusing on whether the studies support or refute the neurodegenerative hypothesis of ET.

A review of the studies indicates that they may be classified as those that directly measure neurodegeneration (MRI volumetry, MRS) and those that are less specific, but still sensitive to neurodegeneration (DTI, PET, fMRI, and others) (Table 1). The MRI volumetry, MRS, and DTI literature consistently point to problems within the cerebellum as well as wider motor and possibly non-motor systems in ET, and each method has yielded results that are consistent with the presence of neurodegeneration. Of these, the volumetric measurement literature, by demonstrating atrophy, provides the strongest support for the presence of neurodegeneration. Changes in ^{11}C-flumazenil binding in PET studies in ET as well as changes in iron deposition in an MRI study provide further evidence along these lines. Hence, considerable neuroimaging data, which use a broad range of methods, provide support for the presence of neuronal degeneration in ET.

Future directions

Recent years have seen a marked increase in the number of imaging studies of ET, with these studies utilizing a broad array of techniques to study the disease. These studies continue to point consistently to a localization within the cerebellum and perhaps to a wider and related motor system.[30] A number of techniques have allowed investigators to assess the integrity of the cerebellar neurons themselves and these studies provide in different ways evidence that supports the presence of cerebellar neuronal degeneration in ET. The cerebellar neurodegenerative model should be reflected in decreases in cerebellar brain volume, associated with decreases in NAA and GABA and increased mean diffusivity in the same region. A recent combined effort by investigators at our centers is using MRS to estimate GABA concentration in the dentate nucleus, with the hypothesis being that, in the setting of Purkinje cell degeneration, this concentration would be reduced. These and other studies will hopefully continue to provide valuable insights about disease pathogenesis in the years to come.

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