CLINICAL/SCIENTIFIC NOTES


Late-Life Action Tremor in a Southern Sea Otter (Enhydra lutris nereis)

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Abstract: Although tremor is highly prevalent in human beings, there are few reports of tremor occurring in other mammals. Such tremor can further our insights into the mechanisms and anatomical basis of human tremor disorders. We report on a southern sea otter with a slowly progressive 6.5–8.5 Hz action tremor of late life that shared several clinical characteristics with essential tremor. The main pathologic finding was in the cerebellum, where there was extensive vacuolization of Purkinje cells. © 2004 Movement Disorder Society.

Key words: tremor; essential tremor; animal, scavulation; pathology, toxin

Action tremor is a highly prevalent condition in human beings, with the most common forms including enhanced physiological tremor and essential tremor (ET). 1-4 There are experimental models for action tremor, including the hantavirus and penicillin. A models, in which these chemicals are administered to laboratory animals, resulting in acute, reversible action tremors. 5-6 Also, action tremor has been observed in mutant strains of laboratory mice and inbred strains of domesticated mammals. 7-10 With these exceptions, we know of few reports of action tremor occurring in other mammals. This is surprising given the very high prevalence of action tremors in humans. We report on a case of a late-life action tremor in a female southern sea otter.

Sea Otters

Sea otters (Enhydra lutris) are carnivorous marine mammals that are active both above and under water. 11 They are one of thirteen otter species worldwide. Sea otters are found off the central California coast (southern sea otters, E. lutris nereis) and off Washington, Canada, Alaska, and the Aleutian islands (northern sea otters, E. lutris kenyoni). 12 They inhabit nearshore ecosystems and feed on benthos (i.e., bottom-dwelling) and midwater invertebrates, including clams and mussels. 13 They are an example of the transition of a terrestrial carnivore to an aquatic lifestyle. 14 The weaning of sea otter pups begins at 4 months of age and females reach sexual maturity between 3 and 5 years. The average life span of wild female sea otters is 6 to 8 years and is higher for animals in captivity, during which time they attain weights of approximately 50 lb and lengths of 4 feet. Sea otters are among the few animals known to use tools on a regular basis while feeding. They also have the dexterous use of any object. Having been explained for many years for commercial purposes, approximately 2,500 southern sea otters remain in the wild.

Case Report

Clinical

On February 22, 1944, “Guide,” an orphaned female sea otter pup, was found at Astoria State Beach, near Monterey, CA. Her age was estimated to be 5 weeks. There were no signs of trauma. She was transported to and raised in the Monterey Bay Aquarium in Monterey, CA. She died on June 27, 2002 at the aquarium at the age of 18.5 years. The cause of death was respiratory tract infection with necrosis. During most of her life at the aquarium, she shared living quarters with two other sea otters, a male and a female, neither whom developed neurologic or other neurological signs. For the remaining 3 months of her life, she shared living quarters with one other female sea otter, who remains healthy.

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While under observation at the aquarium, there was no history of trauma or toxin exposure. She was under the care of a veterinarian (M.J.M.) who conducted comprehensive medical checkups every 4 months. During these checkups, she was anesthetized, weighed, her teeth were examined, she had a full body examination, and routine blood tests were carried out including a complete blood count, a serum electrolyte panel, liver function tests, blood urea nitrogen and creatinine, and serum glucose, calcium and cholesterol. During her life, she was treated intermittently with short courses of antibiotics for dental problems or minor bite wounds, but had not been on any other medications. Later in life, she developed osteoarthritis of the lower limbs (coco-femoral and cranial joints), which was diagnosed radiographically.

Tremor was first noted by the veterinarian in the first few months of 1997, when she was 13 years of age. The tremor was a mild, rapid postural and kinetic (i.e., action) head tremor that occurred when she strained her neck to reach for food, when arching her neck to look around, or when stretching her neck to groom. It was not present when she lay with her head at rest. The history that her veterinarian gives is that the tremor worsened gradually over the ensuing 5 years, becoming less intermittent, of greater amplitude, and eventually involved her upper and lower limbs.

To document her tremor, her trainer video-taped her regularly, resulting in footage from twenty dates between March 1997 and May 2002. The videotapes include footage of her daily activities, including swimming, floating on her back, rolling in the water, walking on land, holding food between her forepaws, eating, and grooming. Review of this videotaped material confirmed that the head tremor became less intermittent over time and that the amplitude of the head tremor increased. One of the authors (S.L.P.) digitized and analyzed the VHS videotape recordings using Image and Final Cut Pro (Apple Computer) using a Macintosh computer. Frequencies of the head tremor were calculated from 8 randomly sampled 1-second epochs with video images proportioned to maintain inter-image physical consistency. Specific landmarks on the face or head provided reference points from which the analyses were obtained. This digitalization demonstrated that the average frequency of the head tremor in 1997 was 8.5 Hz. By 2002, this had decreased to 6.5 Hz. Her veterinarian reported observing tremor in the head and upper and lower limbs. Based on the videotape, a head tremor was identifiable in 1997, and an intermittent lower limb tremor by 1999. The tremor, which had postural and kinetic components (see Video), was very regular without any jerking or twisting movements or neck rotation. Her gait, swimming, rolling, floating holding food between her forepaws, and grooming were all normal, with no signs of spasticity, cluminess, loss of coordination, or ataxia. She remained healthy in other respects and remained bright, alert, and responsive. She had consistent normal moods, as noted above. In addition, her thyroid function tests (including T4) and serum cortisol, estradiol, and progesterone levels were normal, and her immunofluorescent antibody titers for the protozoan parasites Toxoplasma gondii and Sarcozystis neuronyoni were negative (<1:80 serum dilution). Her blood lead concentration in 1997 (<0.06 ppm) was well below toxic levels (>35 ppm). In 1999, blood lead was undetectable. Her tremor was never treated with ethanol, β-receptor blocking agents, or other medications. Neuroimaging was not carried out. When she died, a complete necropsy was undertaken.

Pathological

On gross examination, the brain seemed normal and there were no areas of softening or discoloration in the cerebellum, brainstem, or cerebrum. Hematoxylin and eosin (H & E) stained sections (400X magnification) from the cerebel-lum showed five adjacent Purkinje cells with extensive cytoplasmic vaculation. A cracked elongated vacuole is seen in the first Purkinje cell from the right. Multiple small vacuoles are seen in the first Purkinje cell from the left.

FIG. 1. Hematoxylin and eosin (H&E) stained sections (400X magnification) from the cerebel-lum shows five adjacent Purkinje cells with exten-sive cytoplasmic vaculation. A cracked elongated vacuole is seen in the first Purkinje cell from the right. Multiple small vacuoles are seen in the first Purkinje cell from the left.
stained sections from the cerebellum (2 oblique sections), neo-
cortex (hippocampus and CA1, 2), and spinal cord (2) were examined microscopically. These were extensive cytolas-
mics, often affecting the majority of neurons in the sublayer of both cerebellar sections (Fig. 1). Vacuoles were of varying sizes, with multiple (2–4) vacuoles in most cells, which along with the majority (80%) suggested a chronic process. One section including the neocortex and white matter showed a large, broad, curving area containing peripherally empty vac-
oules especially involving the white matter. This area contained macrophages with foamy cytoplasmic, reactive, mainly gemato-
cytic astrocytes, and venules suggestive of axonal swelling. Sections of the cerebellum and neocortex were stained further with periodic acid-schiff. Alcian blue, hematoxylin, and von Graefenstamm counterstained with Luxol fast blue, and in situ, which indicated that the vacuolar material was not glycoprotein (i.e., the vacuoles contained abundant stainable PAS-positive material), not acid mucopolysaccharide (Alcian blue negative), not mye-
lin-based (Luxol fast blue negative) and not ubiquilinophilic protein (ubiquitin negative). A modiolus Bodian stain demonstrated only occasional empty baskets, indicating relative preservation of Purkinje cells. There were two detectable neurochemical tangles or plaques. The hippocampus was normal, as were the caudate nucleus, putamen, globus pallidus and substantia nigra (pars compacta and pars reticulata). These were no Lewy bodies.
In the inferior olivary nuclei were normal, with no cell loss, gliosis, or vacuolation. The spinal cord was unremarkable, with normal motor neurons and nerve roots.

Discussion

Action tremor is highly prevalent in human beings15,16 and has not been reported commonly in animals. Evaluation of action tremor when observed in animals is of potential importance for several reasons. The final conclusions of these evaluations can be used to further our insight into mechanisms or the anatomy of human tremor disorders, which are poorly understood. Also, tremulous animals can be used, in some circumstances,15,18,19 as a model to test new pharmacologic interventions.

The prevalence of tremor among sea otters is not known. This behavior has not been noted during field studies of sea otters in California or Alaska over the past 33 years (Dr. J. Rices, personal communication). Little is known about the otter brain,10 although these animals seem particularly prone to develop lesions in several settings, including mild anoxia, hypoglycemia, and hypothermia.12

The cause of the tremor in this sea otter is not known, but the presence of pathological changes in the cerebellar Purkinje cells is compelling. The human condition ET, which results in an action tremor, is thought to involve the cerebellum and its outflow pathways, with much of the evidence coming from neuroimaging studies.14,15 Loss of cerebellar Purkinje cells has been reported in several postmortems, although the pathology-
ology of ET is poorly understood. Clinically, this sea otter’s tremor had several characteristics in common with ET. First, the tremor was an action tremor. In addition, the tremor began when the otter was swimming, which is an advanced age for a sea otter. Both the incidence and prevalence of ET therease with advancing age.2,7 Third, the tremor frequency, which was between 6.5 and 8.5 Hz, was in the range of that observed commonly in patients with ET. Also, the tremor was slowly progressive, worsening gradually over time, without other signs of nervous system involvement. Finally, the tremor spread somatotopically over time, beginning in the head and later spreading to the limbs. Spreads is observed commonly in many humans with ET, in whom the tremor begins typically in the arms and later spreads to the head.2,7,30 Despite these clinical similarities, vacuolation of Purkinje cells has not been reported as a pathological feature of ET.

Although the tremor shared many features with ET, another possibility is that the tremor was a dystonic tremor. Although the tremor was not dystonic, some movement features, such as dystonic tremor, these features do not always accompany dystonic tremor. The fact that the head tremor was more prom-
inent than was the limb tremor also raises the possibility that this could have been a form of dystonic tremor. Head tremor occurs in 35 to 53% of patients with ET.31 Isolated head tremor with minimal or no arm tremor, can occur in up to 9% of ET cases.24

Vacuolation is a cellular response to a variety of different injuries including metabolic defects (storage diseases),25,26 27 vascu-
lar and paroxysmal injuries,22,24,31 and several toxins, including lead.24,25 In terms of storage diseases, special stains indicated that the material in the vacuoles was not glycoprotein, acid muco-
poly saccharide, myelin-based, or ubiquilinophilic, so that the na-
ture of the material is not clear. In terms of pilon diseases, the vacuoles that we observed in the cerebellum were confined to the neurons. By contrast, in paroxysmal diseases, vacuolation is also found within the neuropil and glial cells. In addition, cerebellar involvement in pylon diseases is not confined typically to the Purkinje cell layer, but also involves the molecular layer. TOXIN, such as lead, can cause tremor. Sea otters require a high metabolic rate to maintain a constant body temperature in cold water. Therefore, they eat a huge quantity of shellfish (approx-
imately 16 lb or up to 30% of their body weight per day). Lead, which is present in offshore sediments, has also been detected in hussells and other sea life that live on the ocean floor.32 These life forms comprise a large part of the diet of sea otters. Chronic exposure of laboratory animals and humans to organic or inorganic lead may lead to acute and chronic progressive disorders in which action tremor is a prominent feature.24-27

Lead levels in contemporary southern sea otters have increased by 2 to 3-folds over their pre-industrial counterparts.28 Despite this, these otters are considered to have low lead burdens.48 Goldie had a blood lead level that was normal on two occa-
sions, arguing against lead as a specific etiology. Arguing against a role for other toxins is the fact that Goldie shared living quarters with other otters who did not develop tremors. Other than its presence in prey species in the diet and the setting of toxin exposure, vacuolation throughout the nervous system has also been reported to occur in several neurodegenerative dis-
ases of animals whose etiology has not been determined, including diseases of dogs, racoons, and cattle.28-30,48 These conditions are characterized by a broad range of neurofibrillogical findings including supranuclear neuron signs, axonitis, and vacuolation.

One consideration is that sections through the cerebellum were oriented in an oblique rather than a sagittal plane. There-
fore, we were unable to examine cerebellum sections for cell loss in sagittal strips, which is a finding that has been described in the B-carotene work.34,35 In summary, we report on an animal with an action tremor of late life, which shared several clinical features with ET. As it is thought to be the case in ET, the cerebellum was involved,
although the main pathological finding of extensive vacuolation of Parkin-positive cells has not been reported in ET.

Legend to the Video

Action tremor is illustrated.

1. Head tremor is visible while Gollie lies in the water on her back and forcibly pushes or head and neck forward.
2. It is not visible while she floats on her back in the water (she is the one on the viewer’s left).
3. Tremor is not present while she lies, awake and reclining, on her back on land.
4. Head tremor occurs while she reaches for food and is also visible in between the chewing motions while she eats.
5. The head tremor occurs while she moves about a play table (she is on the viewer’s left).
6. The head tremor is present while she is being fed.
7. Head tremor occurs while she walks, sniffing the ground in front of her.

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References

Hyperhomocysteinaemia in Treated Patients With Huntington's Disease

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Abstract: Significantly increased plasma total homocysteine levels (Hcy) appear in treated Huntington disease (HD) patients compared to controls and untreated HD subjects. Be-

cause the protein Huntingtin interacts with the homocysteine metabolism modulating enzyme cystatin C (Cyst/C), we hypothesize that homocysteine promotes neurodegeneration in HD. Movement Disorders 2004 Movement Disorders. Vol 20, No 8

Key words: homocysteine; Huntington’s disease; neurode-
generation

Increased plasma total homocysteine levels (Hcy) represent an independent single risk factor for atherosclerosis-related disorders and appear in neurodegenerative disorders, i.e., Par-
kinson’s disease (PD) and Alzheimer’s disease (AD), or cor-
relate to brain atrophy. 1–3 Hcy is associated with methyl-
enetetrahydrofolate reductase (MTHFR) enzyme activity. Homocysteinyz for a recessive mutation of the MTHFR gene reduces enzyme activity and consequently increases Hcy. 4 Follic acid or vitamin B 12 deficiency are additional causes for Hcy elevation in addition to onset of metabolic disorders, i.e., diabetes mellitus. 5 O-methylation of levodopa supports Hcy increase and, thus, hypothetically accelerates neurode-
genation, since neurotoxic, excitotoxic partially by means of N-methyl-D-aspartate (NMDA) agonists and mimicking property effects of homocysteine and in oxidation product homocysteic acid were shown in various types of cultured human neuronal cell lines. 6,7 Excitotoxicity also plays an im-
portant role in the pathophysiology of Huntington’s disease (HD). Statin inclusion bodies occurring at elevated levels in postmortem brain tissue of HD patients showed fragments of the apoptotic cell death-inducing, mutated protein Huntingtin (mutHtt), which interacts with the homocysteinyz-inducing en-
zyme cystathionine β-synthase (CBS). 8 This interaction could also influence Hcy in HD patients. Therefore, we determined Hcy in HD patients and compared them to a healthy control group.

Subjects and Methods

We obtained blood samples drawn from 34 treated (defined as long-term intake of centrally acting compounds, e.g., anti-
depressants, neuroleptics, benzodiazepines, triazolam, anxi-
chollients) HD patients, 19 previously untreated HD subjects and 77 healthy controls (Table 1). Only Unified Huntington’s Disease Rating Scale (UHDRS) scores and HD duration sig-
nificantly (P < 0.0001) differed between both HD groups. We excluded subjects with metabolic disturbances, i.e., diabetes mellitus, hypertension, nicotine abuse, hypothyroidism, re-
duced levels of vitamins, or increase of cholesterol and triglyceride.

Sample Collection

We took a blood specimen in the morning between 8 and 9 after 10 hours fasting from a peripheral vein, deep-inside in plastic vacuum ethylenediaminetetraacetic acid tubes for Hcy determination. Samples were centrifuged 15 minutes, 200 × g, at 10°C without break within 10 minutes. The resulting supernatant (plasma) was decanted and stored at ≤−80°C. The time period between freezing and workflow of the samples was no longer than 3 months. The 1-Hcy were mea-
sured by an automated high performance liquid chromatogra-
phy method with reverse phase separation and fluoren-2-carboxylic acid detection by NaıH4InBr reduction followed by monoho-
me thioredoxin deactivation. Additionally, we determined the MTHFR gene mutations.

References

38. Gething AS, Stewart RM. Organic lead encephalopathy: behav-
tional changes and movement disorder following gasoline inhala-
39. Smith SS, Ryan RR, Travis RG, Chow PY. The neurological manifesta-
41. Young RS, Gobf SE, Croyton L. Recent cerebellar dysfunc-
44. Smith DR, Niemeyer TV, Fogel AR. Lead exposure to Californian sea otters: industrial/spatial circadian natural lead bioavailability mecha-
47. Hartley AN, Heidt JR, Petrin R, Rappaport CE. Neuromuscular vol-
48. Hansi AN, Beubeker P, Jerney A, Butta D, Stodd MG, Chupi TM, Sando J. In vitro enzymatic assay with cystatin A and percent hoxelat-
49. O’Harr E, Muller ME. The sulfenic acid redox inorganic mediators: (re)duced and overreduced (de)generation of Parkinson disease. A model of indi-