Diagnosis of Rapid Eye Movement Sleep Disorder With Electroencephalography and Treatment With Tricyclic Antidepressants in a Dog

A 9-month-old, female Labrador retriever mix was presented for two types of seizure-like episodes, one of which occurred only during sleep. The two types of episodes were morphologically distinct. An electroencephalogram (EEG) demonstrated that the sleep-associated episodes occurred during rapid eye movement (REM) sleep, supporting a diagnosis of a REM behavior disorder. Based on their morphology and response to antiseizure medications, the waking episodes were diagnosed as seizures. The animal was also diagnosed with an obsessive-compulsive and generalized anxiety disorder. The REM behavior disorder and anxiety-related behaviors improved with tricyclic antidepressant therapy. **J Am Anim Hosp Assoc 2004;40:495-500.**

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Introduction

Three dogs diagnosed with rapid eye movement (REM) behavior disorder have been previously reported in the veterinary literature.[1,2] Each of these dogs had an adult-onset disorder and a concurrent disease. Congenital hydrocephalus, spinal cord trauma, and a thyroid tumor were associated with the diagnosis of REM behavior disorder in these cases.[1,2] The dog with hydrocephalus also had partial seizure activity that secondarily became generalized.[1] There are no current reports of congenital-onset REM behavior disorders in dogs with associated anxiety disorders, and there are no reports of successful treatments of such conditions.

In previous reports in cats, a cyst in the piriform lobe and idiopathic conditions have been associated with REM behavior disorders.[1] In humans, REM behavior disorder is often an idiopathic condition, typically seen in males late in life, and it commonly precedes a neurodegenerative disease, such as Parkinson's disease.[3] Other associated conditions in humans include narcolepsy, prior encephalitis, brain-stem infarcts, drug abuse, tricyclic antidepressant withdrawal, multiple sclerosis, post-traumatic stress disorder, and depression.[4-6] The purpose of this paper was to describe a dog diagnosed with a REM behavior disorder accompanied by an anxiety disorder and recurrent seizures of unknown origin, and the therapies attempted in this case.

Case Report

Clinical Presentation

A 9-month-old, 27-kg, female Labrador retriever mix was presented to the Veterinary Hospital of the University of Pennsylvania (VHUP) for seizure-like episodes that occurred during sleep. Historically, the dog was first presented to the VHUP Emergency Service at 3 days of age for vomiting immediately after nursing. She was also evaluated by the Medical Genetics Service at that time, but only a small stature and a flattened sternum were noted. At 4 weeks of age, the dog was presented to the local veterinarian for seizure-like episodes that occurred during sleep. A

complete blood count (CBC), serum biochemical profile, and pre- and postprandial bile acid assays were unremarkable at that time.

Initially, the seizure-like episodes occurred only during sleep and mainly at night. At 10 weeks of age, the dog had a similar episode while awake. Phenobarbital (2 mg/kg per os [PO] *q* 12 hours) was initiated by the referring veterinarian and was continued until 9 months of age. During this 6-month period, no more seizure-like episodes were observed, but the sleep-associated events continued. From the age of 6 to 8 months, potassium bromide (20 mg/kg PO *q* 24 hours) was added to the therapeutic regimen. Neither treatment had any effect on the frequency, severity, duration, or start time of the sleep-associated events once the dog fell asleep. Persistent nocturnal symptoms prompted referral to the VHUP Neurology Service.

The sleep-associated events were observed every night. Twenty to 30 minutes after the onset of sleep, with the dog in lateral recumbency, the distal limbs began twitching and the dog began to vocalize and move her jaw rhythmically. After 30 seconds, all four limbs became fully extended, and vigorous running movements began that lasted for approximately 20 seconds. The dog would then assume a sternal position and begin swaying her head and neck from side to side. The third eyelids were always prolapsed, and the dog could not be awakened from this state. The dog would then suddenly return to lateral recumbency and resume the running motion. The limb movement was so vigorous that the dog would often propel herself across the surface on which she was lying, displacing objects in her path. After another 1 to 2 minutes of running movements, the animal would awaken, either spontaneously or in response to the owner's coaxing.

The dog had between 10 and 20 such episodes during the night, each lasting between 2 and 3 minutes. During one of the episodes, the dog appeared to be acting out a dream sequence, tugging at the pads of the cage. This episode occurred after the dog had spent much of her time that day pulling a play toy against resistance offered by the owner. In addition to the sleep-associated events, the owners reported excessive daytime somnolence. The dog also engaged in tail chasing and licking the walls, people, the dorsal surfaces of both antebrachia, and the medial aspects of the stifles.

Examination Findings

Neurological examination revealed a bright and responsive dog with normal cranial nerve function and normal ocular fundi. The animal was moderately hypermetric in the thoracic limbs, circumducted the left thoracic limb, and, while sitting, would intermittently and rhythmically lift the right thoracic limb approximately 10 cm off of the ground. The dog was mildly slow at hopping on the thoracic limbs. All segmental reflexes were substantially increased, and a crossed-extensor response was noted in all four limbs. The neurological findings suggested a lesion in the brain stem or the first five segments of the cervical spinal cord. Results of a CBC, serum biochemical profile, urinalysis, and urine metabolic screen[a] were unremarkable.

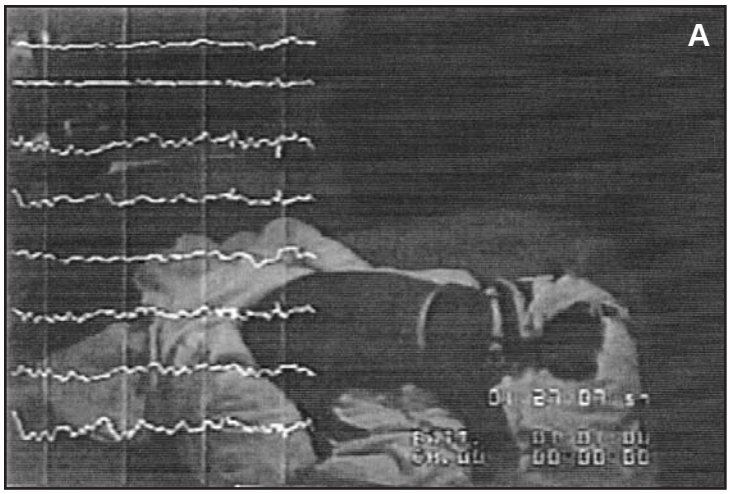
An examination by the behaviorist (Overall) revealed narrowing of the dog's palpebral fissures, and the dog struggled to stay awake while the owner was interviewed. Areas of alopecia and broken hair shafts were present along the dorsal aspects of the antebrachia and the medial surfaces of the thighs, immediately proximal to the stifles. Attention-seeking behaviors and behaviors associated with nonspecific or generalized anxiety, such as panting, pacing, shifting weight in the thoracic limbs, yawning, licking at walls and people, licking and biting at the flanks, and rhythmic motion of the right thoracic limb also occurred.[7,8] A lack of stimulation caused the dog to bite or lick at her stifles, all four paws, flanks, people, and objects (e.g., blankets, wall) for periods lasting from 30 seconds to 5 minutes. These behaviors were interrupted when the dog's attention was directed elsewhere. The self-play and oral behaviors reported in this animal met the criteria for obsessive-compulsive disorder (OCD), while the licking, yawning, scanning, and locomotor behaviors met the criteria for generalized anxiety disorder.[9,10]

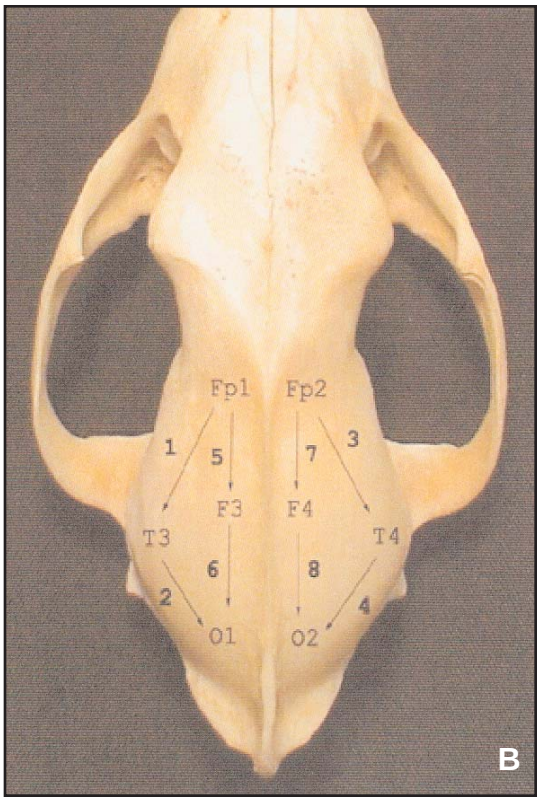
Diagnostic Testing

In order to better understand the sleep-associated events and effects of the phenobarbital, the dog was weaned off of the phenobarbital over 4 weeks. During this weaning period, therapy for the sleep-associated events was initiated with clonazepam[b] (1 mg/kg PO *q* 12 hours), a benzodiazepine used in the treatment of both seizure and sleep disorders. Clonazepam had no effect on the sleep-associated events and induced several side effects, including mild pelvic-limb ataxia, a voracious appetite, irritability, and aggression. Decreasing the dosage of clonazepam (to 0.7 mg/kg PO *q* 8 hours) affected neither the episodes or the side effects. Diazepam[c] (0.3 mg/kg via rectal suppository) was used three times at 10-minute intervals for one night, but it failed to attenuate the nocturnal signs.

Two days after the phenobarbital was discontinued, the seizure-like episodes resumed. The dog ran up the stairs, stopped suddenly, fell into lateral recumbency, and began rhythmically opening and closing her jaw. Then for about 2 minutes, the dog rhythmically flexed and extended all four limbs while taking deep and frequent breaths. When these episodes occurred, the dog was unresponsive to stimuli, and, once the motor activity had ceased, she frenetically paced around the room for 30 seconds before returning to normal. These episodes continued on a weekly basis and were only observed during the day. The episodes often occurred immediately after the dog was awakened and released from her crate. Based on the description of these events and their recurrence after the phenobarbital therapy was discontinued, seizure activity was suspected.

Once drug therapy was discontinued, an electroencephalogram (EEG)[d] and simultaneous video [Figure 1A] were recorded. Gold-cup scalp electrodes, held in place with collodion, were placed in a manner similar to the 10 to 20 system used in humans [Figure 1B].[11] A video[e]-EEG recording system was used to record activity during waking,





***Figures 1A, 1B*—Methodology for the electroencephalogram (EEG). (A)** Still frame from the simultaneous videotape and EEG recording. A picture from the videotape generated by the Telefactor video-EEG recording system, showing both the eight-channel EEG and the animal with REM behavior disorder. The EEG was also recorded on paper [see Figure 2]. **(B)** Skull showing electrode placement for the recording of the eight-channel, longitudinal bipolar EEG. Fp1=left frontal pole; Fp2=right frontal pole; T3=left temporal; T4=right temporal; F3=left central; F4=right central; O1=left occipital; O2=right occipital. The numbers 1-8 represent the channels. Channel 1 (Fp1-T3) and channel 2 (T3-O1) are the left parasagittal channels; channel 3 (Fp2-T4) and channel 4 (T4-O2) are the right parasagittal channels; channel 5 (Fp1-F3) and channel 6 (F3-O1) are the left sagittal channels; and channel 7 (Fp2-F4) and channel 8 (F4-O2) are the right sagittal channels.

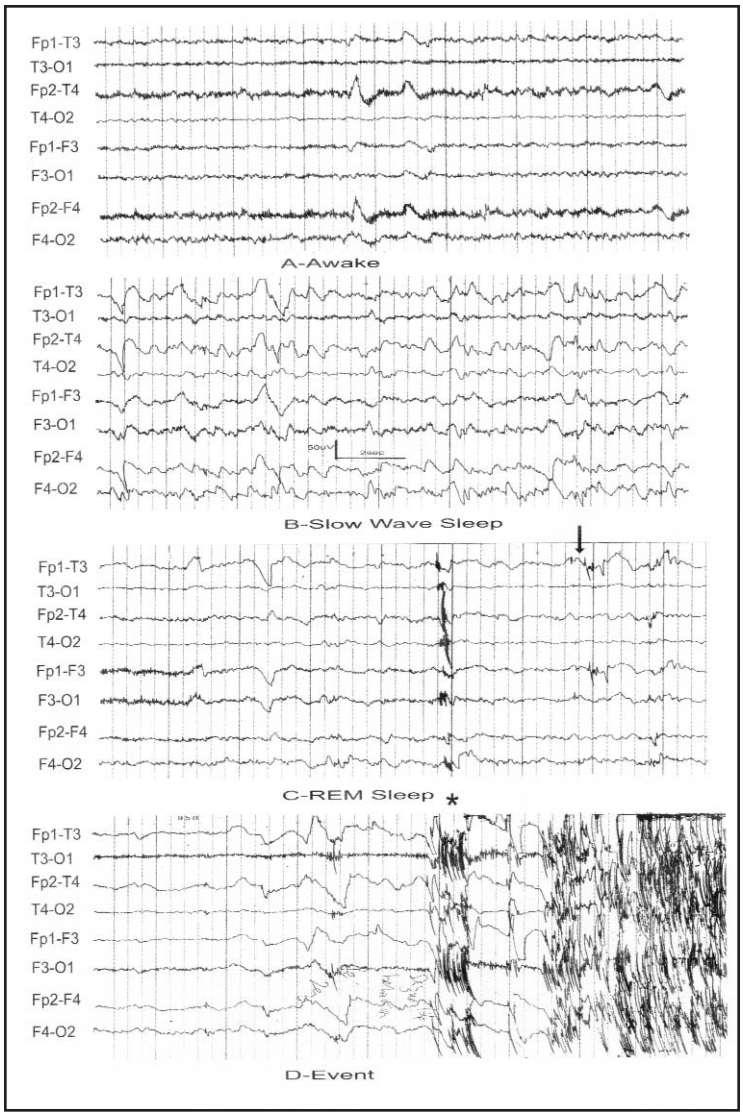
sleeping, and several sleep events. A longitudinal, bipolar, eight-channel montage was used for recording (high-frequency filter=75 KHz, low-frequency filter=2 Hz, paper speed=30 mm per second).

During the first 80 minutes of continuous recording, the animal showed low-amplitude, high-frequency activity and muscle activity suggesting wakefulness [Figure 2]. After 80 minutes, higher amplitude, lower frequency activity (characteristic of slow-wave sleep) was recorded. Twelve minutes after the onset of slow-wave sleep, there was a sudden decrease in the amplitude with a concomitant increase in the frequency of the electrical activity and lateral REM. Within 2 minutes of the onset of REM sleep, the first sleep-associated event was observed. At 4 to 6 minutes after the first episode, two additional events were recorded on the EEG. Between these episodes, high-frequency, low-amplitude potentials (suggestive of REM sleep) were recorded. No epileptiform activity or postevent slow-wave activity was observed during the EEG. The video-EEG and recorded-EEG were also evaluated by an expert in the field of REM behavior disorder (Morrison) and a neurologist specializing in human electroencephalography (Stecker), who confirmed that the episodes were not seizures and that their onset coincided with the onset of REM sleep.

A diagnostic effort was then made to find a cause for the seizures, REM behavior disorder, and abnormal neurological findings. Radiographs of the cervical spine were unremarkable. Magnetic resonance images (MRI)[f] of the brain were obtained and included axial T2-weighted images, sagittal and axial T1-weighted images, before and after the administration of gadolinium[g] (0.4 mL/kg intravenously [IV]). All images were unremarkable. A brain-stem auditory-evoked response was also normal. A cerebrospinal fluid (CSF) analysis, taken from the cerebellomedullary cistern while the dog was under anesthesia, revealed a normal white cell count (0 nucleated cell count/µL; reference range <5 cells/µL), a scant number of red blood cells (RBC; 1 RBC/µL), and a normal protein concentration (15 mg/dL; reference range <25 mg/dL). Cytopathology revealed only rare, small lymphocytes. Because the CSF and MRI were normal and the dog's signs were not progressive, infectious disease testing was not pursued. No cause was established for the seizure activity, REM behavior disorder, or the abnormal neurological findings.

Treatment and Outcome

The dog continued to have two to four seizures per month for the next 4 months, at which point the potassium bromide



***Figures 2A-2D*—An electroencephalogram (EEG) during the awake state, slow-wave sleep, rapid eye movement (REM) sleep, and during an abnormal event. (A)** During the awake state, the dog was responsive to external stimuli, and the EEG showed low-amplitude high-frequency potentials. **(B)** During the sleep state, the dog was not responsive to external stimuli, and the EEG showed high-amplitude low-frequency potentials. **(C)** During REM sleep, the dog was not responsive and had fine twitching of the distal limbs, and the EEG showed higher frequency, low-amplitude potentials similar to those of the waking state. The black arrow represents typical rapid horizontal eye movements that are seen during REM sleep. **(D)** During the event, the dog was not responsive, and while in lateral recumbency she had rapid paddling movements similar to running (onset marked by asterisk). The high-amplitude activity seen at this point is generated during muscle contractions.

therapy was resumed (150 mg/kg PO *q* 24 hours for 6 days, then 50 mg/kg PO *q* 24 hours). Potassium bromide was preferred over phenobarbital, as it does not cause hepatotoxicity or affect the metabolism of other drugs. A serum bromide concentration after 3 months of treatment was within the therapeutic range (2300 parts per million [ppm]; reference range 1500 to 3000 ppm). The potassium bromide was effective in controlling the seizure episodes but had no effect on the nocturnal symptoms.

In addition to the potassium bromide, the dog was also treated for the REM behavior disorder and signs of anxiety with the short-acting tricyclic antidepressant, amitriptyline[h] (2.5 mg/kg PO *q* 12 hours). The owners noted substantial, transient improvement in the REM behavior disorder in the first week of amitriptyline therapy. However, after the first week, the sleep behavior was similar to that seen prior to therapy. The dog was subsequently started on imipramine[i] (1 mg/kg PO *q* 24 hours) before being placed in the crate at night, and the dose was increased by 1 mg/kg increments until a dosage of 4 mg/kg PO *q* 24 hours. The drug was only moderately efficacious for 1 week after each dosage adjustment. Treatment with these tricyclic antidepressants did not alter the frequency or appearance of the anxiety-related behaviors. The imipramine dose was tapered and then discontinued. An ovariohysterectomy was performed because of the demonstrated role of gonadal steroids in both behavior and neuromodulation, but it had no effect on the animal's clinical signs.[12]

Clomipramine,[j] a tricyclic antidepressant with increased specificity and duration of action relative to imipramine and amitriptyline, has been commonly used for the treatment of obsessive-compulsive behaviors in both animals and people.[7,13,14] Clomipramine (1 mg/kg PO *q* 12 hours for 2 weeks; then 1.5 mg/kg PO *q* 12 hours for 2 weeks, 2 mg/kg PO *q* 12 hours for 6 weeks, 3 mg/kg PO *q* 12 hours for 2 weeks, then 4 mg/kg PO *q* 12 hours) was initiated in this dog 3 months after discontinuing the imipramine. A serum metabolite concentration 6 hours after a 2 mg/kg dose of clomipramine was within the therapeutic range (270 ng/mL; reference range 176 to 627 ng/mL).[15]

To evaluate the efficacy of clomipramine therapy, the owners were asked to observe and videotape the dog during the night. The REM behavior disorder episodes ceased during the first week of therapy. Despite this improvement, a significant amount of twitching of the distal limbs, digits, and jaw commenced 45 minutes in to sleep and persisted throughout the night. After the first week, the twitching would begin at the same time and continue for approximately 4 hours, at which point the dog would have two or three REM behavior disorder episodes interspersed with the twitching. The REM behavior disorder episodes were less severe, as the running movement was less intense, and the dog awakened quickly from these episodes. Progressive increases in the drug, as described above, consistently decreased the frequency and intensity of the REM behavior disorder episodes, but the effects lasted for only 1 week.

In addition to improvement of the REM behavior disorder, the owners noted fewer anxiety-related behaviors. Specifically, a decrease in shifting of weight on the thoracic limbs, less biting and licking at the limbs, less anxiety and restlessness, and resolution of the alopecia occurred. No difference in the dog's frequency of yawning or in the degree of somnolence was noted. It should be noted that somnolence is a manufacturer-reported side effect of clomipramine treatment in people.

The animal remained on clomipramine for about 6 months; however, the drug was tapered and discontinued by the owners because of the cost of drug therapy and monitoring. The REM behavior disorder episodes have not changed in frequency or severity since discontinuing the clomipramine.

Discussion

The behaviors observed during REM in the dog in this report (i.e., running in lateral recumbency, shifting into sternal recumbency, lifting and swaying the head, third eyelid prolapse, arousability without confusion) are similar to those observed in cats with experimentally-induced lesions in the pons and to congenital REM behavior disorders.[16] Moreover, these behaviors are typical of REM behavior disorder in humans.[3,17] The incident described by the dog's owners, during which the dog appeared to be acting out a dream sequence, is reminiscent of accounts in the human literature.[3,17] Abnormal dream mentation is a common clinical sign in humans with REM behavior disorder.[3,17]

Although the precise mechanism is not fully understood, the pons is integral to the inhibition of motor activity during REM sleep.[18] The dorsal pontine tegmentum indirectly inhibits the alpha motor neuron in the spinal cord through multiple pathways that project to the medulla. Sleep causes release of gamma-aminobutyric acid (GABA) in the pons, inhibiting serotonergic and noradrenergic transmission in the raphe nuclei and locus ceruleus, respectively. Gamma-aminobutyric acid disinhibits cholinergic neurons in the pons. These cholinergic neurons then excite glutaminergic neurons, which project to spinal cord glycinergic inhibitory interneurons, hyperpolarizing motor neurons and resulting in the atonia observed during REM sleep.[19]

Traditional therapy for REM behavior disorder in humans involves the use of clonazepam.[3] Clonazepam therapy is effective in approximately 90% of humans diagnosed with REM behavior disorder, and the drug has also been efficacious in cats, presumably by increasing GABA-mediated inhibition of serotonin and noradrenaline release in the pons.[3,14,16] In the dog reported here, however, clonazepam therapy failed to ameliorate the clinical signs, and the drug was ultimately discontinued when the dog developed aggression, irritability, pelvic-limb ataxia, and polyphagia. These side effects were likely attributed to benzodiazepine-associated disinhibition of the centers of satiety and behavior.[7]

The mesopontine area receives many afferents, and many different neurotransmitters act at this level of the brain stem. Norepinephrine and serotonin are released from the locus ceruleus and dorsal raphe nuclei, respectively.[19,20] During REM sleep, however, they are inactive.[18] Diminution in serotonin and norepinephrine neurotransmission in the pontine tegmentum is thought to be an important signal for induction of REM and also plays a role in REM-associated muscle relaxation.[19] Tricyclic antidepressants generally increase synaptic levels of serotonin and norepinephrine, although there is variability in the relative transmission of each neurotransmitter among the drugs in this class.[21] Generally, an increase in motor movement during REM sleep would be anticipated; however, the increases in synaptic levels of serotonin and norepinephrine also inhibit REM sleep.[22,23] Early in treatment, both serotonin and norepinephrine reuptake inhibitors substantially decrease the amount of REM sleep in cats, but there is an attenuation of this effect with chronicity of treatment, possibly from a receptor or postreceptor effect.[22] It is also possible that serotonergic projections to other areas of the brain (e.g., spinal cord, frontal cortex, cerebellum) are similarly affected by the drug therapy and help to reduce the severity of the clinical signs.

This dog's REM behavior disorder and signs of anxiety improved with tricyclic antidepressant therapy. The effectiveness of serotonin reuptake inhibitors in people with depressed mood and REM behavior disorder has also been reported.[6] Tricyclic antidepressant therapy has been effective in treating many canine behavioral disorders, including separation anxiety, generalized anxiety, anxiety-associated elimination, and aggressive behaviors, as well as sleep disorders such as narcolepsy.[7]

Other neurotransmitters released in the pons include dopamine and acetylcholine. Inhibitors of L-dopa and acetylcholinesterase have been used successfully in treating REM behavior disorder in people.[22,23] Recently, the role of melatonin in REM sleep suppression has been demonstrated in animal models.[24] In the treatment of humans with REM behavior disorder, melatonin alleviates symptoms and produces increased wakefulness during the day.[25]

Conclusion

This report documented a case of congenital-onset REM behavior disorder in a dog with an associated behavioral disorder. Video-EEG was used to definitively diagnose a REM sleep disorder, and treatment with tricyclic antidepressants was partially successful.

[a] University of Pennsylvania Laboratory of Medical Genetics, Philadelphia, PA 19104
[b] Clonazepam; Roche Pharmaceuticals, Nutley, NJ 07110
[c] Diazepam; Purepac Pharmaceutical Company, Elizabeth, NJ 07202
[d] Grass Model 8 Electroencephalograph; Grass-Astromed, West Warwick, RI 02893
[e] Telefactor Model W/TV-16 B; Grass-Astromed, West Warwick, RI 02893
[f] Signa General Electric Corporation, Milwaukee, WI 53201
[g] Gadolinium; Mallinckrodt, St. Louis, MO 63042
[h] Amitriptyline; Mutual Pharmaceutical Company, Inc., Philadelphia, PA 19104
[i] Imipramine; Novartis Animal Health U.K. Ltd., Whittlesford, Cambridge, England
[j] Clomipramine; Novartis Animal Health U.K. Ltd., Whittlesford, Cambridge, England

Acknowledgments

The authors thank Drs. Sheldon Steinberg and Deena Ticheson for their suggestions and guidance in preparing this manuscript.

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