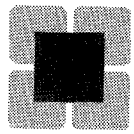

Startle disease (hyperekplexia): a hereditary disorder with abnormal startle, falling spells, and attacks of spontaneous clonus

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STARTLE is a basic alerting reaction common to all mammals. A rapid reflex not amenable to voluntary control, startle was studied extensively by Strauss in 1929,[1] and is the subject of a 1939 monograph by Landis and Hunt[2] and of a more recent study by Gogan.[3] In the human adult, except for minor interpersonal variations, a stereotyped motor pattern is seen consisting of eye blinking; facial grimacing; flexion of the head; elevation of the shoulders; and flexion of the elbows, trunk and knees. With repeated stimulation, the intensity of the surprise reaction decreases, but it never completely disappears. Tension, fatigue and heightened expectation of the stimulus enhance it. The intensity is greater in infancy, when the startle reflex appears at the same time as the Moro reflex (an extensor response to sudden stimuli). However, startle becomes more noticeable in time, while the Moro reflex disappears.[4]

This reflex, so basic to man, can be present in a pathologically exaggerated form which is always embarrassing, sometimes interfering with normal activities; occasionally, it may even be dangerous. The pathophysiology of startle was recently reviewed by Wilkins et al.[5]

Abnormal, excessive startle is a feature of three distinct conditions (*Table 1*): startle disease (hyperekplexia), jumping (the "jumping Frenchmen of Maine"), and startle epilepsy. The first of these disorders, hyperekplexia, is described here.

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CASE HISTORIES

Twenty years ago a mother brought her two daughters, who had been diagnosed and treated for epilepsy, complaining that the older girl was falling when startled. Both girls had a mechanical, broad-based gait which suggested cerebellar dysfunction, but they were not ataxic; they were hyperreflexic. Since extensive questioning did not solve the problem, a kidney basin was dropped to the stone floor and the older girl fell forward like a log, hit her head on the foot of the metal examining table, and began to cry. This response was far greater than anticipated. The patient, the family, and the examiner were quite mortified, and the girl has since always been wary in her neurologist's presence.

Kirstein and Silfverskiold first described startle disease in 1958.[6] Two sisters, their father, and the daughter of one of the sisters suffered from sudden violent falls precipitated by stress, fright or surprise. Three of these family members also had nocturnal myoclonus. The authors cautiously considered the disorder to represent an unusual, genetically determined form of drop seizures.

Minor and major forms of startle disease

In a letter to the *Lancet* in 1962, Kok and Bruyn[7] drew attention to a hereditary disease affecting 29 individuals in six generations of a German-Dutch family totaling 127 members. In 1966, Suhren (née Kok), Bruyn and Tuynman[8] described this family in greater detail. The affected individuals had a strikingly excessive response to startle elicited by visual, auditory and proprioceptive stimuli that failed to produce a

TABLE 1
STARTLE DISORDERS OF MAN

	Startle disease (hyperekplexia)	Jumping	Startle epilepsy
Onset	Birth, rarely later	Variable	Variable
Excessive startle	+	+	+
Stiffness	+	−	−
Generalized hyperreflexia	+	−	−
Attacks of spontaneous clonus	+	−	−
Falling	+	Rarely	With some attack patterns
Insecure gait	+	−	+
Echolalia	−	+	−
Echopraxia	−	+	−
Forced obedience	−	+	−
Crying out, swearing	−	+	−
Fighting stance	−	+	−
Epileptic seizures, nonstartle related	Rarely	−	Sometimes
Epileptogenic EEG abnormality	Rarely	−	Usually
Inheritance	Autosomal dominant or sporadic	Autosomal dominant with variable penetrance	Acquired
Treatment	Clonazepam, valproic acid	−	Antiepileptic drugs

startle response in most normal individuals. The disorder occurred in two forms, both of which usually, but not always, started in infancy: a *minor* form, in which the response was only quantitatively different from normal (ie, the startle response was more violent); and a *major* form, which included additional clinical symptoms. When startled, patients with the major form experienced momentary generalized muscular stiffness, with loss of voluntary postural control causing them to fall as if frozen with their arms at their sides, unable to carry out protective movements. As soon as they hit the ground, muscle tone and control of voluntary movements returned, and there was never evidence of loss of consciousness. (Although Kirstein and Silfverskiod[6] did describe, in 1958, brief loss of consciousness in association with these falls, it was probably related to concussion.) According to Suhren et al,[8] urinary incontinence may also occur in the major form of startle disease, probably due to increased intra-abdominal pressure associated with the extensor spasm. This abnormal response was almost always present, from the time the affected child first attempted to walk. It was increased by emotional tension, nervousness, fatigue, and the expectation of being frightened; alcohol, phenobarbital, and chlordiazepoxide lessened its intensity to some degree.

In the major form, there was also transient generalized hypertonia during infancy. As babies, when awakened or handled, affected individuals had an immediate increase in muscle tone in flexion, which disappeared during sleep. This abnormality diminished as spontaneous activity increased during the first year of life. Around the time of its disappearance, frequent violent and often repetitive jerks of the limbs were described as the child fell asleep. The jerks could lift the child off the bed.

Neonatal manifestations

The neonatal form of this condition was redescribed by Klein et al[9] as a "familial congenital disorder resembling Stiff-Man Syndrome" occurring in 10 individuals from three generations of a family. The family stressed the onset of stiffness within 4 or 5 hours after birth, the absence of crawling (with the children scooting about in a seated position, propelling themselves with their arms), and some delay in walking. Stiffness disappeared during sleep. Difficulty swallowing and frequent choking were also described. The infants had hard, tense shoulder-girdle muscles and their faces were set in a somewhat unhappy and inappropriate expression. Lingam, Wilson and Hart,[10] in a second report on the hereditary stiff baby syndrome, suggested the identity of this condition with startle disease. A third report, again not identifying the disorder with the manifestations of hyperekplexia early in life was published by Sander et al.[11]

Infants with startle disease have a high incidence of umbilical and other hernias, previously noted by Suhren et al,[8] probably related to their hypertonicity. Associated congenital dislocation of the hip has also been described by Morley et al.[12] A boy with a convincing history of hyperekplexia also had a thoracic meningomyelocele, Arnold-Chiari malformation, and hydrocephalus.[13] While these disorders may have been fortuitously associated, the intrauterine hypertonicity could perhaps be a factor in the development of the closure defect. Interestingly, the symptoms of hyperekplexia were relieved by surgical decompression of the cervicomedullary region. The association of startle disease with symphalangia has been described by Peter Camfield (personal communication). Apnea due to spasm of respiratory muscles may also occur; in a patient mentioned by Kurczynski,[14] the apnea led to

the child's death.

Phenotypic variations

Exceptionally, the symptoms of startle disease arise later in life. Dooley and Andermann[15] recently studied an adolescent boy with normal neonatal history who had developed generalized stiffness making it impossible for him to participate in sports, as well as falling attacks. Rare members of the family described by Suhren et al[8] also had onset of symptoms later than in the neonatal period.

The major and the minor forms of startle disease can occur in the same family, as illustrated in the large family reported by Suhren et al,[8] or in those reported by Andermann et al[16–18] and by Dooley and Andermann.[15] As already mentioned, the minor form of the disease consists only of excessive startle. A parent with the minor form can have children with the major form and vice versa; siblings, however, tend to be affected to the same degree. It is therefore likely, as Suhren et al[8] have suggested, that these two forms represent different phenotypic expressions of the same autosomal dominant gene.

A positive family history may be difficult to elicit in startle disease because of this phenotypic variation. In the first family we described, the disorder was obvious in the proband and her sister. Only the minor form was present in the proband's own children, and only when they were ill. For years, it was impossible to obtain a history of abnormal startle from either of the proband's parents. Eventually it became clear that, in the years leading up to the mother's divorce from her alcoholic husband, she too had startled excessively and literally jumped off her chair when the telephone rang. Thus, autosomal dominant inheritance with variable expressivity was again confirmed. In the second family reported by us,[16] however, no other member was found to be affected by either the major or the minor form, even on intensive questioning. This may be explained by a new mutation in the proband or by lack of penetrance of the gene in other family members. One sporadic patient with this disease was also described by Boudouresques et al in 1964,[19] and Saenz Lope et al[20] described 3 additional sporadic patients and 5 affected siblings.

Gastaut and Villeneuve[21] in 1967 presented in detail 12 patients with sporadic startle disease or disorder. The authors stressed the psychogenic precipitation of startle and falling. Eleven of their patients had falling attacks which, in at least one of these individuals, were—according to their description—identical to those occurring in familial cases. The incidence of mild retardation or low intelligence in these 12 patients was higher than in the general population and similar to that noticed by Andermann et al[16] and by Suhren et al.[8] Nine had nocturnal jerking of the legs. The authors felt that their patients differed from those described by Suhren et al,[8] though it seems likely that at least a few had the same disorder but without an obvious family history. It is also possible that some of these patients had excessive startle, as seen in the jumping Frenchmen of Maine or in related disorders such as latah, myriachit or "goosey". The junior author of that report, currently professor of psychiatry in Quebec City, was impressed at the time by the anxiety and emotional disturbance of these patients (Villeneuve, personal communication). Certainly, no further reports suggesting the occurrence of a distinct disorder different from startle disease have appeared in the literature since, even though the interest in these phenomena has been increasing. Nonetheless, occasional reports still attempt to perpetuate an unfounded distinction between the genetic disorder (hyperekplexia, sic.) and the sporadic form (hyperekplexia).[12] Gastaut and Villeneuve[21] corrected the spelling and suggested that the term hyperekplexia be used. Authors aware of this distinction have generally accepted this spelling, though startle disease is still preferable for the sake of clarity. There consequently is no good evidence that the patients with sporadic startle disease differ from the familial cases described by Suhren et al.[8] Our own cases, whether familial or sporadic, appear to have the same syndrome. These two forms thus appear to represent a single genetically determined disorder.

Spontaneous clonus

Suhren et al[8] and Gastaut and Villeneuve[21] suggested that, since jerking of the legs occurred only at night, it presumably represented an exaggerated form of hypnagogic myoclonus. However, 2 of our patients did experience such attacks in the daytime as well; all limbs were involved, though the legs always more than the arms. When the attacks occurred at night, the patients woke with a feeling described as unsteadiness, which was similar to their diurnal state when unexpected stimuli would be particularly likely to provoke a fall; the jerking would begin later, lasting for several minutes. There were no electrographic features to suggest an epileptic etiology. Clinically, these attacks resemble spontaneous generalized clonus.

De Groen and Kamphuisen[22] studied the periodic nocturnal myoclonic jerks of one of Suhren and Bruyn's

patients. They concluded that these were due to spontaneous arousal reactions, caused mainly by an increase in excitability of motoneurons, by hyperexcitability of the brainstem arousal system, and by the markedly increased influence of respiratory variables on reticular hyperexcitability.

LABORATORY FINDINGS

EEG

The electroencephalographic (EEG) correlates of startle were similar in the patients reported by Gastaut and Villeneuve,[21] Suhren et al,[8] and Andermann et al.[16–18] The EEG response consisted of an initial spike recorded from the centroparietal vertex followed by a short-lasting train of slow waves, and then by desynchronization of background activity lasting 2 to 3 seconds. The response was abolished by intravenous diazepam. This complex discharge, the most consistent electrographic correlate of excessive startle, may represent an evoked response to various sensory stimuli.

EMG

The electromyographic (EMG) changes were initially described by Gastaut and Villeneuve[21] as follows: isolated or grouped volleys of 10 to 12 elements, with a latency of 10 to 40 milliseconds (starting from the frontal muscles and going to those of the leg). According to the number of motor units recruited, the amplitude varied from 1 to 10 millivolts while the duration ranged from 20 to 60 milliseconds. Activity of interferential type followed, sometimes after an interval of about 20 milliseconds, lasting from a fraction of a second to several seconds, thus lengthening the initial jerk. These muscle potentials were generalized to the agonist and antagonist muscles without reciprocal innervation. Their amplitude decreased from the head and neck to the trunk, from the root of the limbs to their extremities, and from the upper to the lower limbs.

Latency of auditory and limb responses and effect of clonazepam

The auditory startle response has been well studied in animals, especially in rats. In this species, brainstem circuitry has been well delineated. It probably involves five synaptic relays consisting of the auditory nerve, ventral cochlear nucleus, later lemniscus nuclei, pontine reticular formation nuclei, spinal interneurons, and lower motor neurons.[23] The average latency of the rat's startle response is about 8 milliseconds in the hind limbs. Other modality induced startle responses (ie, tactile and visual) have not been very well studied in animals or in man.

Normal startle responses in man have been studied for more than 50 years, initially by the use of mechanical recording devices and later using sequential photographs. With the development of more sophisticated neurophysiological equipment, it could be established that an acoustically induced startle response due to noncalibrated sound had a latency in the orbicularis oculi of about 40 milliseconds, in the arms of about 120 to 160 milliseconds, and in the legs of around 150 to 200 milliseconds. Using calibrated sound stimulation in the 90 to 114 decibel range, Rossignol[24] and Fox[25] found the latency in the orbicularis oculi response to be of the order of 40 milliseconds and in the distal leg muscles, 125 to 150 milliseconds.

Three patients with startle disease were studied in our laboratory. One was recorded while receiving and later while no longer taking clonazepam, and the other two were studied while taking regular doses (2 to 4 mg/day) of clonazepam. Conventional nerve conduction studies, including reflex amplitude wave ratio, were normal. Somatosensory evoked potentials, performed by stimulation of the median nerve at the wrist, were entirely normal—both in latency and in amplitude—contrary to a previous report (Rosenblatt and Majnemer, personal communication).

Startle responses were studied using noncalibrated metallic sound, obtained by percussion of a metallic drum with a sweep triggering hammer. Recordings were obtained using a 4-channel EMG machine (Disa 1500). Surface electrodes were fixed over the motor point of the right biceps, triceps, quadriceps, and tibialis anterior. Tactile stimulations were also performed by gentle percussion of the tip of the nose, the forehead, and the upper and lower midline abdomen. An example of the recording is seen in *Figure 1*, with the latency expressed in milliseconds. As can be seen from *Table 2*, average response latencies to auditory stimulation were similar in the 3 patients.

Auditory stimulation was the most potent startle stimulus in terms of capacity to induce a response. Nose tapping—the most effective tactile stimulus—although often giving less well-defined muscle responses, was invariably associated with shorter startle latencies compared to auditory stimulation (*Table 3*). Other sites of tactile stimulation gave much less reproducible results and were not used in the evaluation of this study.

Results in the patients studied when receiving and

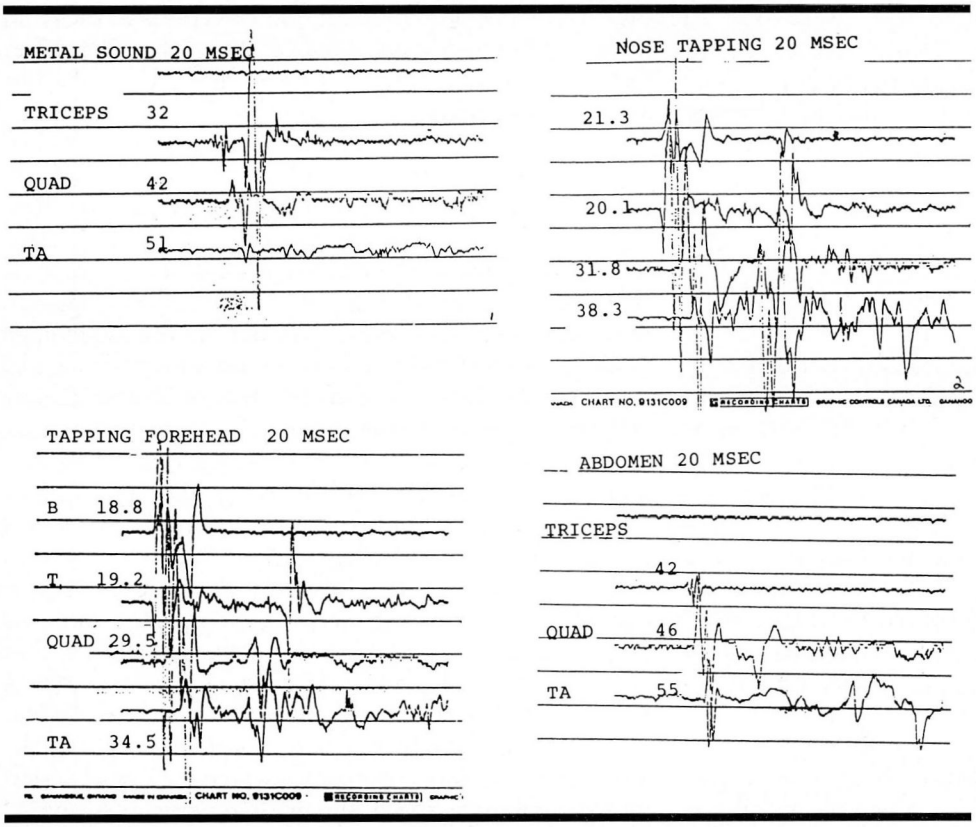

FIGURE 1. Patient 1 when not receiving clonazepam. Surface recordings. Sensitivity 200 uv/div; time in msec indicated at the onset of response; total sweeptime: 160 msec. (See text for details.)

TABLE 2
STARTLE DISEASE: AVERAGED LATENCIES (IN MSEC) TO AUDITORY STIMULUS (N=3)

Patient	Biceps	Triceps	Quadriceps	Tibialis anterior
I	—	32	42	51
II	27	30	36	39
III	36	47	46.5	43.5

when not receiving clonazepam are presented in *Table 4*, which lists the latencies according to the type of stimulation.

Amplitude and duration of the responses were also qualitatively analyzed and diminution of the response was found while the patient was receiving medication (*Figure 2*).

When the latencies found in these 3 patients were compared with historical normal values of latency to an uncalibrated auditory stimulus, the values of our patients were found to be roughly half those of the normals. This finding supports earlier observations made by Suhren et al[8] and by Gastaut and Villeneuve,[21] who reported markedly shortened latencies in patients with startle disease compared to normal individuals.

The latency to tactile facial stimulation, although less regularly associated with muscle responses, had an overall shorter latency compared to audiogenic stimulation. The clonazepam-induced modification of the clinical syndrome did not seem to modify the latency to stimulation but reduced both the amplitude and the duration of this response. Finally, no amplitude abnormality of the scalp-recorded somatosensory evoked potential was detected in our 3 patients; their average amplitude was 2.6 millivolts.

Other laboratory findings

Other polygraphic features described by Gastaut and Villeneuve[21] were sudden lowering of skin resistance, variable but often persistent tachycardia, rise of arterial blood pressure (mainly systolic), and a fall in systolic peripheral blood flow. Frequently, the most intense stimuli induced—after the early muscular potential—an interferential muscular activity sufficient to engender a tonic spasm lasting several seconds. The spasm was accompanied by a vegetative discharge bringing on apnea lasting several seconds and a heart rate accelerated by 100%.

In their recent review, Wilkins et al[5] suggested that hyperekplexia could represent the known combination of reticular reflex myoclonus and cortical reflex myoclonus, as described by Hallett et al.[26] They tentatively concluded that, for the present, hyperekplexia should be included as an independent phenomenon within the spectrum of stimulus-sensitive myoclonic disorders.

Suhren et al[8] considered the disorder to be nonepileptic. They believed that the abnormality in these

TABLE 3
STARTLE DISEASE: AVERAGED LATENCIES (IN MSEC) TO NOSE TAPPING (N=3)

Patient	Biceps	Triceps	Quadriceps	Tibialis anterior
I	21.3	20.1	32	39
II	23	22	34	39
III	0	0	0	0

patients probably resulted from retarded maturation of control of brain stem centers by higher inhibitory mechanisms, particularly by the rhombo-mesencephalic reticular formation. Epileptogenic EEG abnormalities were found in several of their patients who fell, and many had excessive slow activity which they attributed to the repeated head injuries.

Some patients, however, display evidence of more widespread cerebral dysfunction, not explainable by a maturational defect in a specific system alone, and unlikely to be due merely to the repeated falls. One of the 3 patients of Andermann et al mentioned earlier had an active generalized spike-wave discharge and another had a parietal sharp wave focus, though neither had epileptic seizures or episodes other than the specific clinical phenomena just described. Indeed, the spike-wave discharge was blocked by startle. Several of the patients reported by Gastaut and Villeneuve[21] had a low convulsive threshold, and one had seizures as well. Four of their patients had or were suspected to have mild mental retardation. Low average intelligence was also encountered in 2 of our own 3 patients with the major form of startle disease, suggesting diffuse cerebral dysfunction. Their hypertonicity and hyperreflexia implied an abnormality of the pyramidal system. No pathological studies of individuals with this condition are available.

DIFFERENTIAL DIAGNOSIS, COURSE, AND PROGNOSIS

The diagnosis of startle disease should not be difficult if one is aware of this syndrome. The condition is probably rare; one would suspect that it is commonly misdiagnosed as epilepsy, as it had been initially in most patients. Hypertonia in infancy is easily misinterpreted as spastic quadriplegia, as it was in the cases reported by Andermann et al, where its disappearance was quite baffling. The most puzzling symptom is the unsteady gait, which the physician may attribute to a cerebellar disorder rather than to the uncertainty and the fear of falling which actually cause it.

TABLE 4
PATIENT 1 WITH STARTLE DISEASE STUDIED WHILE RECEIVING (ON) AND AFTER CESSATION OF (OFF) CLONAZEPAM (LATENCIES IN MSEC)

	Biceps	Triceps	Quadriceps	Tibialis anterior
Sound				
On	0	32	42	51
Off	27	30	36	
Nose-tapping				
On	21.3	20.1	31.8	38.3
Off	22	23.2	33.2	39.8
Forehead-tapping				
On	20	—	31	38.3
Off	18	19.2	29.5	34.5
Lower abdomen-tapping				
On	30	—	43	53
Off	—	42	46	55

The course of startle disease is variable.[27] Some patients with early onset eventually improve; in others, symptoms only arise or increase later in life. There has been little change over the years in our own patients, although, on the whole, the manifestations were more severe in childhood, when the hypertonicity was striking and the falls very frequent. We have not been aware of changes in the severity of symptoms related to cold although this has been mentioned by Morley et al.[12]

Startle disease is not entirely benign considering the risk of sudden death in infancy attributable to spasm of respiratory muscles and the possible complications of hernias. Later in life, patients may suffer multiple fractures (including skull fractures) as well as repeated lacerations and cerebral concussions.

TREATMENT

At the present time, clonazepam—a benzodiazepine and potent serotonin agonist—and valproic acid appear to be the drugs of choice in the treatment of startle disease. In small doses (0.1 mg/kg), clonazepam abolishes the falling attacks and greatly reduces the episodic jerking. There is a remarkable disappearance of the gait uncertainty and patients walk more freely, no longer holding someone's hands or continuously touching the wall for support. Although clonazepam does not cause the startle response to return to normal, its effect is greater than that of diazepam and appears to be sustained. Excessive head retraction on forehead or nose tapping persists, however; it appears to represent residual reticular reflex myoclonus. Under conditions

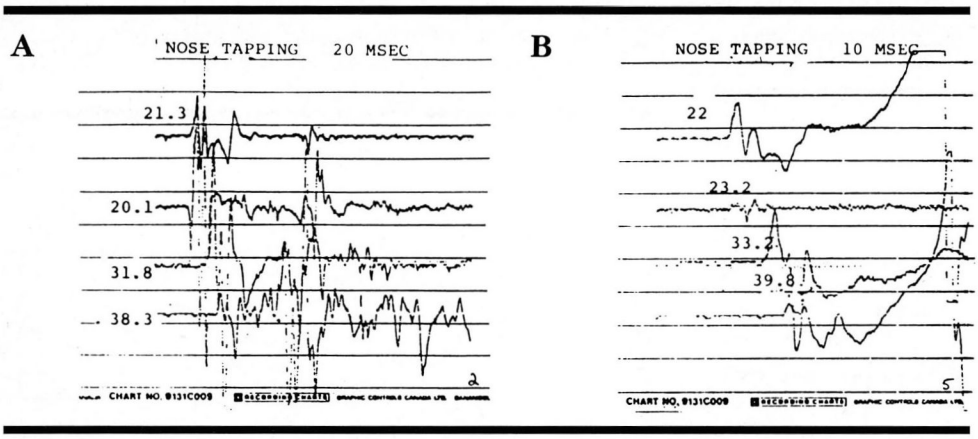

FIGURE 2. A. Patient 1, when not receiving clonazepam. Sensitivity 200 μv/div. Total sweeptime: 160 msec. B. Patient 1, when receiving clonazepam. Sensitivity 200 μv/div. Total sweeptime: 100 msec.

of exceptional emotional stress, falling or nocturnal leg jerking may occasionally recur in a treated patient. The beneficial effect of clonazepam suggests that a serotonergic mechanism may be involved. Valproic acid abolished the clinical manifestations of startle disease in a patient studied by Dooley and Andermann.[15] According to Saenz Lope et al,[28] 5-hydroxy tryptophan and piracetam may also be helpful. Alcohol, phenobarbital, phenytoin, primidone and chlordiazepoxide—even though they do have some effect on the falling attacks, excessive startle and repetitive jerks—are not the drugs of choice for the treatment of this disorder.

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