Agrypnia Excitata: Current Concepts and Future Prospects in Management

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Agrypnia excitata is an extremely rare, life-threatening syndrome characterized by autonomic activation, persistent insomnia, and generalized overactivity. Agrypnia excitata describes a triad of three separate conditions: delirium tremens, Morvan's chorea, and familial fatal insomnia (FFI). Each of the aforementioned three conditions have sleep disturbances as a unifying theme and results in distinct neurophysiological findings. The following is an overview of agrypnia excitata with a particular emphasis placed upon each of the three individual conditions that constitute the syndrome with recommendations on appropriate management.

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"Agrypnia excitita as described constitutes a triad of three separate conditions, delirium tremens, Morvan's chorea, and familial fatal insomnia (FFI). This triad of conditions has sleep disturbances as a unifying theme."[1] When considered individually, each of the aforementioned three conditions results in distinct neurophysiological findings including deterioration of the thalamolimbic system.[1,2] All three conditions lead to generalized autonomic sympathetic activation associated with a stuporous state and marked motor and autonomic sympathetic activation.[1,2] In addition to persistent agrypnia, the three conditions all characteristically exhibit complete loss of slow-wave sleep on polysomnogram evaluation. The elevated autonomic state that typifies agrypnia excitata often manifests in the form of diffuse sweating, tachypnea, hypertension, elevated plasma cortisol, and catecholamine levels. Agrypnia excitata evolves rapidly and runs a uniformly fatal course with most patients dying within months of symptom onset. The following is an overview of agrypnia excitata with a particular emphasis on each of

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the three individual conditions that constitute the syndrome.

Fatal Familial Insomnia

Fatal familial insomnia (FFI) is an extremely rare neurodegenerative prion disease.[3] It is transmitted in an autosomal dominant pattern and is characterized by behavioral problems, autonomic instability, hallucinations, and ultimately death.[3] The disease arises from a mutation in the gene responsible for the expression of a protein resulting in the generation of insoluble proteins called prion proteins that contribute to the deterioration of vital neurological structures within the CNS.[2] Over time these insoluble proteins congregate to form amyloid plaques throughout the CNS, particularly in the areas within or near the hypothalamus, leading to the characteristic deficits in hypothalamic function in individuals afflicted with FFI. Fatal familial insomnia is characterized by a devastating clinical course that includes recurrent sleep disorders, neurological dysfunction, and eventual death. Because of the extreme rarity of FFI, a paucity of reliable data exists on approaches and maximal treatment strategies for this disorder. The following is a thorough examination of FFI with a particular focus placed on current concepts in diagnosis and management as well as future prospects for the condition.

Clinical Manifestations Fatal familial insomnia is characterized by behavioral disturbances, ataxia, pyramidal signs, autonomic problems, and widespread neurological compromise.[3] After the initial onset of symptoms, FFI evolves rapidly, and death occurs months after the first symptom sets in.[3,4] The symptoms of FFI are directly related to the area of neurological involvement in the disorder. Since the thalamus and associated thalamic structures are the most affected in FFI, it stands to reason that bodily functions controlled by the thalamus are commensurately affected in patients with FFI. The thalamus is a prominent mass of gray matter located above the brainstem that controls bodily functions including motor control and somatosensory and visual sensory signals. It also relays sensory signals to and from the cerebral cortex and vital anatomical structures throughout the body. Typically, patients complain of persistent insomnia, frequent nocturnal awakenings, and persistent daytime fatigue.[1,5,6] Autonomic activation in the form of excessive salivation and perspiration along with elevated blood pressure, tachycardia, pyrexia, and appetite disturbances are also common.[1,6,7] Bizarre dreams often occur and tend to be superseded by a stupor-like state that eventually leads to coma and death.[1]

During sleep, the ability of the thalamus to effectively relay such signals becomes compromised, allowing the body to succumb to the sleep state. Therefore, the thalamic dysfunction that ensues in FFI yields a myriad of problems associated with the aforementioned thalamic functions, namely those related to or affected by sleep. The disease runs a uniformly fatal course that manifests in four stages (Table 1). Ultimately, patients expire 18 months after the onset of symptoms.[2] Common clinical features of FFI include hallucinations, phobias, dementia, decreased reflexes, and an inability to lacrimate or appreciate pain.[1,2] Later stages of the disease lead to autonomic dysfunction, which manifests as dementia, coma, and loss of sphincter control.[1] The wide array of symptoms in FFI has led experts to classify it as a pleiotropic disease, or a disease with one mutant gene that yields one mutant protein but results in many pheno-

TABLE 1. The Four Stages of Fatal Familial Insomnia[1,2]

Stage	Duration	Symptoms
Stage I	8-12 weeks following onset	The patient experiences progressive difficulty napping during the day and persistent insomnia at night followed by panic attacks and bizarre phobias.
Stage II	14-20 weeks	The patient is overcome by hallucinatory behavior and may lose contact with his/her surroundings. Panic attacks, persistent agitation, and uncontrollable sweating are also hallmarks of this stage.
Stage III	8-12 months	The patient is completely incapable of sleeping during this stage leading to exacerbation of aforementioned symptoms. The patient may also manifest complex and well-organized motor gestures and rapid weight loss during this stage.
Stage IV	14-24 weeks	The patient's condition deteriorates with vital neurological functions lost. Patients in Stage IV often become unresponsive to stimuli, suffer significant dementia, lose sphincter control and other neurological functions, followed ultimately by death.

typic abnormalities. The pleiotropic basis of the disorder may account for the significant variation in disease presentation from individual to individual, even in patients from the same family.

Epidemiology Fatal familial insomnia is transmitted via autosomal dominant inheritance, meaning it affects both genders with equal frequency.[8,9] On average, individuals with the mutant gene most often develop symptoms between the ages of 40 to 60 years, with an average of onset at 51 years old.[10] Death ensues by 32–72 weeks after first onset of symptoms.[5–7,10]

Pathophysiology Fatal familial insomnia results from a genetic mutation in the prion protein gene, or *PRNP* gene, that results in the replacement of asparagine with aspartic acid at codon 178, along with substitution of asparagine for methionine at codon 129.[1,3,11] Although the exact function of the *PRNP* gene remains uncertain, it is likely involved in the cell signaling in the CNS. The inborn genetic error in FFI results in a dramatic accumulation of protease resistant prion protein, which is responsible for the cognitive dysfunction that characterizes the disorder.[1] The mutation yields significant thalamolimbic impairment, which is believed to cause the striking phenotypic and clinical features of FFI.[1,3] Pathology and imaging studies corroborate this finding by demonstrating widespread hypometabolism throughout the thalami of patients with FFI.[3] Furthermore, the presence of atrophy, gliosis, and neuronal loss in the thalami along with spongiosis in the cerebellum is a common finding in patients with FFI.[1,3,9] The atrophic changes within the thalamus that characterize FFI are believed to underlie the sleep, autonomic, and circadian disturbances that appear in FFI.[1,4]

Diagnosis A number of tests are used to diagnosis FFI. Since FFI is familial in origin, a thorough family history may help in arriving at an accurate diagnosis. A thorough physical examination and detailed history are recommended to rule out systemic or exogenous conditions as a cause of clinical presentation. The physical exam of FFI patients often demonstrates bilateral hyperreflexia and reflex myoclonia.[3] Laryngeal examination may also demonstrate paralysis of the laryngeal cords.[3] Although exact cause of death in FFI remains unclear, experts have pointed to the paralysis of laryngeal cords in FFI as a possible cause of laryngospasm-induced death in such patients.[3,4] Given the many neuropsychological sequelae of FFI, comprehensive neuropsychological testing is warranted. Depending on the stage of disease development, the patient may demonstrate any of a wide array of symptoms from hallucinations, behavioral disturbances, autonomic disturbances, alteration in attention and immediate memory, or a propensity to confabulate.[3] The patient's history will reveal significant sleep disturbances in the form of insomnia and repeated nocturnal awakenings. As with other patients with deterioration of sleep function, a polysomnogram is considered necessary for the diagnosis of FFI and typically reveals the complete absence of spindles and slow-wave sleep along with extended REM periods without muscle atonia.[1,3,4,12] Stridor, nocturnal groaning, loud snoring, and persistent talking and moving may also be present during polysomnogram testing in FFI patients.[3] Finally, given the genetic nature of the disease, genetic testing for mutations in the *D178N* gene in codon 129 can help confirm the diagnosis.[3,8,11]

Treatment Although FFI runs a fatal course, recent data suggest that the use of vitamins, sedative-hypnotics (e.g., ethchlorvynol, zolpidem, or diazepam), stimulants, sensory deprivation, exercise, light entrainment, and growth hormone may offer promising methods of managing FFI patients.[13–17] Electroconvulsive therapy may improve symptoms in such patients through forced sleep and the use of vitamins, sedative-hypnotics, and stimulants may yield improved quality of life by minimizing stupor-like states that often accompany periods of prolonged sleeplessness.[13,14,17] Despite improving a patient's ability to sleep, ECT should be used with caution due to the myriad of side effects such therapy courts, including memory loss and cognitive damage.[13,18,19] Despite advances in therapeutic strategies and the resultant improvement in symptoms of FFI, a cure for FFI continues to elude clinicians. The need for broader research on the topic is warranted considering the fact that all patients expire within 32–72 weeks after first onset of symptoms.[5,7]

Morvan's Chorea

Morvan's chorea, or "fibrillary chorea," describes the rare condition in which neuromyotonia (involuntary contraction of muscles at rest) occurs in the setting of peripheral nervous system hyperexcitibility.[1,3,20] The typical movements in Morvan's chorea most commonly

affect bilateral calves and the posterior part of the thigh. The peripheral nerve hyperexcitibility that dominates in Morvan's chorea typically results in neuromyotonia as well as hyperhydrosis, paresthesias, dysautonomia, myalgias, incontinence, palpitations, and sleep dysfunction.[3,20,21] Similar to the other two components of agrypnia excitata, Morvan's chorea also shares the same clinical features as both FFI and delirium tremens: agrypnia, mental confusion, and a significant reduction of slow wave sleep (Table 2).[1–3,18] Unlike the other components of agrypnia excitata, however, Morvan's chorea can arise at any age and may occur with painful cramps.[1,21] Like patients with FFI, Morvan's chorea also may manifest with hallucinatory behavior, a stuporous confused state, and peculiar motor disturbances, but these features are very rare in Morvan's chorea.[1,22] Like the other subtypes of agrypnia excitata, polysomnograms in patients with Morvan's chorea reveal the persistent absence of sleep rhythms for up to 4 months with the typical loss of slow-wave sleep.[1,21] Patients with Morvan's chorea will exhibit REM without atonia and will also demonstrate hypercortisolemia and hypercatecholemia in the plasma.[2,21]

The exact pathophysiology of Morvan's chorea remains uncertain. However, it is believed that the condition arises via autoimmune mechanisms.[21] The presence of voltage-gated potassium channel antibodies is also commonly found in the serum of patients with Morvan's chorea.[20,21,23] The effect of these antibodies is believed to cause neuronal hyperexcitability by disrupting the ability of voltage gated potassium channel antibody to repolarize motor nerves effectively.[21,24]

Unlike FFI, which runs a uniformly fatal course, Morvan's chorea may resolve overtime but can, in some cases, result in death.[1,2] In severe cases encephalopathy, dementia, or reduplicative paramnesia may ensue.[2,20,23] Notwithstanding, given the potentially fatal course of other diseases that mimic Morvan's chorea, consideration of a thorough differential diagnosis is critical to help minimize misdiagnosis.[25] Accurately recognizing Morvan's chorea may help prevent misdiagnosis in the setting of clinically similar diseases such as in patients suffering from acquired forms of peripheral nerve hyperexcitability. Acquired peripheral nerve hyperexcitability can occur following timber rattlesnake envenomation or Guillain-Barre' syndrome, two conditions that can lead to devastating sequelae.[22,25] Fortunately, Morvan's chorea is, for the most part a treatable condition.[1,2,3] Unlike the other two components of agrypnia excitata, appropriate therapeutic approaches can reverse the course of Morvan's chorea.[26] Plasmapheresis, thymectomy, and long-term immunosuppressive therapy can yield complete resolution of symptoms in patients with Morvan's chorea.[20,26]

Delirium Tremens

Delirium tremens describes the third and final element of agrypnia excitata. Delirium tremens often arises in

TABLE 2. Clinical, Neurophysiological, and Pathological Comparison of Delirium Tremens, Morvan's Chorea, and Fatal Familial Insomnia*

Behavior	Delirium Tremens	Morvan's Chorea	Fatal Familial Insomnia
Insomnia	Present	Persistent for months	Present early (subwakefulness)
Hallucinations/onericism	Severe	Present	Present in fully developed disease, with enacted dreams
Motor hyperactivity	Present	Neuromyotonia	Persistent through the 24th
Autonomic hyperactivity	Severe	Present	Present early
Cortisolemia	Increased	Increased	Increased
Plasma catecholamines	Increased	Increased	Increased
Spindles/ K complexes	Reduced/absent	Reduced/absent	Reduced/absent
Slow wave sleep	Severely reduced/absent	Absent	Reduced/absent
REM sleep	Increased, abnormal without atonia	Without atonia	Without atonia
PET/ Pathology	Atrophy of thalamus, mammillary bodies, temporal and orbitomesial cortex	Antibodies in thalamus and striatum	Atrophy of anterior and dorsomedian thalamus and cingular cortex

*Table adapted from Montagna et al.[1] and reprinted with permission of authors.

the setting of sudden withdrawal in chronic alcoholics or individuals on barbiturates or benzodiazepines for extended periods.[19,27] Delirium tremens is a potentially fatal and debilitating disorder whose clinical features include delirium, visual and tactile hallucinations, formication, severe anxiety, and severe, involuntary tremors of the extremities. When occurring in the setting of agrypnia excitata, delirium tremens arises with an acute confused state associated with bizarre hallucinatory behavior, agrypnia, and motor and autonomic agitation.[1,27] The autonomic activation in agrypnia excitata-type delirium tremens may be so severe that it results in the death of the patient.[1] Polysomnogram evaluation of patients in delirium tremens reveals findings similar to those found in the other two components of agrypnia excitata. Polysomnogram recordings of delirium tremens patients demonstrate significantly reduced or completely absent slow-wave sleep in conjunction with sleep fragmentation and persistent nocturnal awakenings.[2,28,29] Furthermore, REM sleep without muscular atonia is also found in delirium tremens.[2,30]

The degree of slow-wave sleep loss in all three forms of agrypnia excitata corresponds to the amount of atrophic change that occurs in the brain at the time of testing.[31,32] Similar to the other two components of agrypnia excitata, delirium tremens also demonstrates increased cortisol and catecholamines as well as tachypnea, irregular breathing, pyrexia, and hypertension throughout the day.[1,33–35] Although pathophysiologic mechanisms underlying delirium tremens remain unclear, deterioration of the thalamus and its related structures has been established as a primary factor in the development of the disorder.[1,36–38] Incidentally, imaging studies reveal significantly reduced activity in the thalamus of patients with delirium tremens.[39] The management of delirium tremens centers on supportive therapy in conjunction with pharmacologic management. The current mainstay of treatment includes benzodiazepines and mood-stabilizers until symptoms subside.[19,39]

CONCLUSION

Agrypnia excitata represents a triad of three conditions that are characterized by insomnia, secondary drowsiness, and a stuporous mental state. The inability to sleep exacerbates the symptoms in such patients, leading to extreme exhaustion, coma, and ultimately death. Thalamic deterioration has been linked to the onset and course of agrypnia excitata and accounts for the typical clinical features of the disorder. The inability to generate sleep in such patients remains a primary challenge facing clinicians. Finally, a need exists for increased funding for controlled studies in order to offer improved insight into this devastating disease. In addition, these studies can improve current therapeutic approaches to agrypnia excitata and bring those individuals affected by the disease one step closer to living normal lives.

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