PANIC DISORDER AND ALCOHOLISM

TOSHIFUMI KISHIMOTO, YOSHINOBU NORIYAMA, JUNZO IIDA,
FUMIYO UEDA, KAZUYA MATSUMURA, HIROYUKI UEDA,
MASAKAZU MIYAKE, GENRO IKAWA, KIYOKO KINOSHITA*,
HIROAKI ORIBE** and NAOKI MINAMI***

Department of Psychiatry, Nara Medical University
**Psychiatric Service, Kokubu Hospital, Osaka*
***Nara Health Division, Kansai Branch, NTT Co. Ltd., Nara*
****Psychiatric Service, Soyokazeso, Shimoichi Hospital, Nara*

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Abstract: We report four patients used alcohol to self-medicate primary panic disorder and phobias, in whom prolonged alcohol intake and reported withdrawal episodes might have exacerbated and provoked panic attacks. Alcoholism and panic are probably mutually reinforcing, that is, panic may lead to drinking and also result from prolonged use or withdrawal of alcohol. We discuss the interaction of alcohol abuse/dependence with panic disorder, possible causal relationships, biologic relationships, and implications for therapeutic interventions. Possible biologic relationships involve the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex and central noradrenergic system. Cognitive-behavioral psychotherapy is effective as well as medication for treatment.

Index Terms

panic disorder, alcoholism, panic attack, alcohol withdrawal

Alcohol has long been used to relieve stress and anxiety. The calming effects of alcohol have been thought to reinforce further drinking[1]. The relationships between alcoholism and anxiety disorders has a long and complicated history. For example, Hippocrates noted that "wine drunk with an equal quantity of water puts away anxiety and terrors"[2], while Westphal[3] in 1871 noted that patients with agoraphobia consumed alcohol to cope with irrational fears. A number of studies have reported that subjects with anxiety disorders have a higher than expected prevalence of alcohol abuse and conversely, alcoholics have a higher than expected prevalence of anxiety disorders[4]. This link between anxiety states and alcoholism may have important implications for understanding the etiology of, and for rationally preventing and treating, both disorders.

There are very few reports about the relationships between neurosis and alcoholism in our country[5]. This is the first report about coincidence of alcoholism and panic disorder in Japan. We discuss how they may relate to each other and the implications for therapeutic interventions.

Address reprint requests to Toshifumi Kishimoto M. D., Ph. D., Department of Psychiatry, Nara Medical University, Shijocho, Kashihara, Nara 634, Japan

CASE REPORTS

Case 1

A 45-year-old man was discharged from Kokubu Hospital after his second admission for two months of treatment for alcoholism and panic disorder. He was the second of three children. After graduating from a junior high school, he worked for an electronics company for a year. Then he had been working with his father as a rice dealer. He was married at the age of 24 and fathered two children.

At the age of 15, he abruptly suffered from chest pain and feeling of choking and perceived palpitation and trembling while he was working in the field with his father. He consulted his doctor and was found to be organically sound. After that he was always suffering from the feeling of impending death. He took alcohol habitually in order to resolve his tension and anticipation.

At the age of 38, since panic attacks occurred repeatedly, he consulted the Psychiatric Service at Nara Medical University Hospital. He was ordered to keep abstinence and take medication; however, he did not take medicine regularly and took to drink to remove his anxiety. More frequently than before he experienced panic attacks, more excessive volume he came to drink. He caused troubles so many times while intoxicated that he was admitted for two months to Nara Medical University Hospital for his first time at the age of 41. He showed good response to psychopharmacotherapy during his admission. After discharge, his compliance was bad and he was in an alcohol dependent state again; also he was suffering from panic attacks. He actually needed his second admission, but his prognosis was supposed to be unfavorable.

Case 2

A 46-year-old man was treated for alcoholism at the outpatient clinic of Psychiatric Service of Nara Medical University Hospital. He was the second of four children. After graduating from a university, he ran a small company. He was married at the age of 23, fathered two children and divorced his wife at his age of 29. He remarried at the age of 36 and he fathered one child.

At the age of 39, he abruptly felt dizzy and faint and suffered from palpitation. He cosulted his doctor and diagnosed tentatively as of arrhythmia. Then he was referred to and admitted to a university hospital for investigation. In spite of the fact that no organic abnormality was found, he became very nervous that arrhythmia would occur to him again.

At the age of 45, he felt pounding heart and anticipatory anxiety of arrhythmia attack. Then he began to suffer from a phobic anxiety state, i. e. he became unable to drive a car alone or ride a train alone. He consulted our clinic and took anxiolytic drugs, however, he took to drink to relieve his stress and anxiety despite missing work as a result. Being admitted to our ward for three weeks, panic attacks and anticipation disappeared with treatment. He still needed his treatment of alcoholism.

Case 3

A 22-year-old man kept his treatment for supportive psychotherapy for his social adaptation

at the outpatient clinic of the Psychiatric Service of Nara Medical University Hospital. He was the second of three children. After graduating from a high school, he had been studying the art of music at a professional school.

At the age of 21, he felt abruptly palpitation, shortness of breath and tingling sensation on a train, then he got off the train and consulted a physician. One month later, he suffered from a similar panic attack and consulted our clinic. He was diagnosed as panic disorder, administered anxiolytic drugs and became asymptomatic. Soon getting a part time job, he began to suffer from persistent concern about having additional attacks and to drink away to remove his anticipatory anxiety. He showed automatism repeatedly in which he hurt himself unconsciously, like psychomotor seizures during alcohol withdrawal. He was admitted to our hospital for three months due to alcohol dependence. He maintained fairly good adaptation to his society in spite of showing agoraphobia and some avoidant behavior.

Case 4

A 57-year-old man was the first of four children. He had such an antisocial personality disorder that he disregarded and violated social norms. He began to drink in his junior high school age. He left a high school due to his injurious assault.

At the age of 33, he felt abruptly choking and chest pain and drank to remove his discomfort to find that alcohol was anxiolytic. Then he used alcohol every day to self-medicate preexisting anxiety. Prolonged abuse of alcohol made him suffer from hepatitis somatically and made him more anxious psychologically because acute or subacute withdrawal states actually increased anxiety levels. From the age of 41, he had been suffering from agoraphobia while he felt sensations of shortness of breath outside.

At the age of 43, he consulted the outpatient clinic of Psychiatric Service of Nara Medical University Hospital. He showed hypochondriac symptoms, i. e. chest pain, general fatigue and abdominal distress. He showed good response to medication; however, intermittently he showed an unstable phase in which he visited the emergency unit every night while drunk complaining of such hypochondrial pains. From the age of 48, he had been suffering from pentazocine abuse and repeatedly performed acts that were ground for arrest. He almost always stayed in either hospitals or jails. At the age of 57, he was killed in a traffic accident while drunk.

DISCUSSION

Cause and effect

Diagnostic criteria for panic disorder have changed considerably over the past 15 years. Panic disorder was only described as a separate entity in 1980, and before this was included, together with what we would now label generalized anxiety disorder, under "anxiety neurosis".

The essential feature of Panic Disorder is the presence of recurrent, unexpected panic attacks followed by at least 1 month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks, or significant behavioral change related to the attacks[6]. Individuals with panic disorder display characteristic concerns or attributions about the implications or consequences of the panic attacks. Some fear that the

attacks indicate the presence of undiagnosed, life-threatening illness (e. g., cardiac disease, seizure disorder). Despite repeated medical testing and reassurance, they may remain frightened and unconvinced that they do not have a life-threatening illness. Others fear that the panic attacks are an indication that they are "going crazy" or losing control or are emotionally weak. Some individuals with recurrent panic attacks significantly change their behavior (e. g., quit a job) in response to attacks, but they deny either fear of having another attack or concerns about the consequences of their panic attacks. Concerns about the next attack, or its implications, are often associated with development of avoidant behavior that meet criteria for agoraphobia on DSM-IV[6], in which case panic disorder with agoraphobia is diagnosed.

There was a clear relationships between anxiety and alcoholism in our cases. In cases 1 and 2, the patients sought a physical explanation and treatment for panic attacks and could not find a way to cope with the attacks to increase their anxieties. Then they found that alcohol was indeed effective as self-medication for panic and associated phobias, which was linked to psychological dependence on alcohol. In case 3, in spite of appropriate diagnosis and treatment, the patient showed alcohol dependence to remove his excessive anxiety. In case 4, alcohol abuse of this patient developed to alcohol dependence due to his panic attacks. Repeated self-administration resulted in tolerance, withdrawal, and compulsive drinking behavior. Prolonged alcohol intake has been associated with increases in dysphoria, anxiety, and phobias[7]. After an initial decrease in anxiety, subjects displayed increasing anxiety as they continued to drink and they expected to feel even worse if they stopped drinking.

Alcohol withdrawal is clearly associated with severe anxiety symptoms. George et al.[8] asked 11 alcoholics with panic attacks to rate symptoms of panic and alcohol withdrawal. Ratings of alcohol withdrawal symptoms were strikingly similar to reports of panic symptoms, differing significantly only in that tremulousness was more severe during withdrawal.

Roelofs et al[9]. have described a more prologed, subacute alcohol withdrawal characterized by craving for alcohol with anxiety and hyperventilation. The authors also suggested the possibility that hyperventilation during prolonged withdrawal may increase the likelihood of relapse, since ethanal corrects respiratory irregularities. Interestingly, chronic hyperventilation is often associated with panic disorder[10]. Although the mechanism reponsible for lactate-induced panic is unknown, the provocation of panic by intravenous infusion of sodium lactate[11] has been widely used to investigate panic disorder. Brain lactate increases during a lactate infusion in subjects with panic disorder were observed with proton magnetic resonance spectroscopy (MRS)[12]. Hyperventilation is the most predictive physiological characteristic in lactate-induced panic. It was also demonstrated with ^{1}H MRS that individuals with panic disorder showed greater increases in brain lactate in response to hyperventilation than healthy controls[13]. Both hyperventilation and panic may be precipitated or exacerbated by alcohol withdrawal and ameliorated, at least initially, by resumption of drinking, thus reinforcing continued alcohol problems[14].

George et al.[4] have suggested that repeated withdrawal episodes may trigger panic through a kinding process. "Kindling" refers to the use of repeated, intermittent, identical subconvulsive stimuli to evoke increasing amounts of electrical excitability, culminating in both provoked and eventually spontaneous seizures. Alcohol withdrawal, with its associated increased central nervous system excitability, may have a "kinding" effect in susceptible individuals,

sensitizing limbic areas, such as the hippocampus, which has been implicated in the pathophysiology of panic, and resulting in panic attacks at first during withdrawal but eventually also during periods of sobriety. It has also been suggested that alcohol use may increase anxiety as a result of the many, realistically stressful like problems that result from substance use disorders[15], or from the process of conditioned tolerance, in which a state of hyperarousal occurs in situations associated with use of alcohol[4]. This is the body's attempt to offset the sedating effects of alcohol but could lead to increased anxiety if no alcohol is actually consumed.

In summary, it appears that alcohol is at least initially anxiolytic and may be used to self-medicate preexing anxiety. However, prolonged intake and especially acute or subacute withdrawal states actually increase anxiety levels. That is, panic and phobias lead to drinking as a way to reduce anxiety symptoms, but continued drinking and subsequent withdrawal exacerbate panic and phobias, reinforcing further drinking (Fig. 1).

Biology

The two neurotransmitter systems providing the strongest theoretical links between alcoholism and panic disorder are the γ-aminobutyric acid (GABA)-benzodiazepine receptor system and central noradrenergic pathways. Benzodiazepines, which have been effective in the treatment of panic disorder and generalized anxiety disorder, act by binding to specific, high affinity receptor sites and enhancing the effects of GABA, the major inhibitory neurotransmitter in the mammalian CNS[4]. Cross-tolerance between benzodiazepine and ethanol suggests that repeated episodes of withdrawal may cause changes in GABA-benzodiazepine receptor function, increasing vulnerability to panic attacks[14].

Many symptoms of panic attacks, such as palpitation, sweating, and tremulousness, suggest increased sympathetic nervous system activity. Challenge tests with clonidine, an α_2-agonist, and yohimbine, an α_2-antagonist, which decrease and increase locus ceruleus activity, respectively, showed exaggerated responses in patients with panic disorder, suggesting a hyperactive noradrenergic system in these patients[16]. Ethanol also inhibits the excitation of locus ceruleus noradrenergic neurons by glutamate and NMDA initially. Over time, NMDA desensitizes

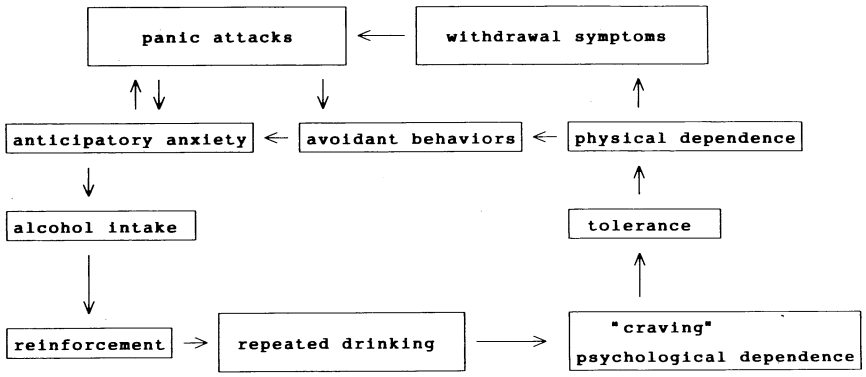

Fig. 1. Schematic representation showing possible mutual interactions between panic disorder and alcoholism.

NMDA-evoked norepinephrine release, but this desensitization process can be prevented by acute administration of ethanol, as well as by the competitive NMDA antagonist AP-5[17]. After acute withdrawal from chronic ethanol administration, however, the locus ceruleus is more sensitive to NMDA and quisqualate and displays hyperactivity. It is the up-regulation of glutamate receptor in the locus ceruleus that accounts for these changes with ethnol withdrawal[18]. The indirect effect of this catecholaminergic system through the NMDA receptor may account for the autonomic instability and behavioral agitation observed in alcohol withdrawal and delirium tremens[19]. To the extent that increased noradrenergic activity is involved in panic, alcohol use, and particularly withdrawal states, would be expected to provoke or exacerbate panic in vulnerable individuals[14].

Although other biologic systems are perhaps involved, we still have a rather primitive understanding of synaptic neurochemical mechanisms responsible for the diverse clinical manifestations of human alcoholism and panic disorder. To date, our preliminary data regarding the biology of panic and of alcohol intoxication and withdrawal suggest common pathophysiologic mechanisms that may increase the likelihood of an individual with either disorder developing the other, given an underlying vulnerability.

Clinical recognition and treatment

Panic disorder is often is difficult to be diaganosed in primary-care settings, since these patients frequently present complaining of somatic symptoms. In addition, many of us are ill-equipped to identify or manage patients with alcohol dependence.

The first step in recognizing dually disordered patients is to know the diagnostic criteria for these disorders[6] and be willing to question patients specifically about alcohol use. Once panic disorder, or indeed any anxiety disorders identified, the clinician should be careful to look for other disorders and for associated problems, such as major depression, suicidal ideation, and phobias. Alcohol or substance use or withdrawal are probably the most significant medical differential diagnoses for panic disorder.

Medication treatment of panic involves primarily the use of antidepressants or benzodiazepines. With cognitive-behavioral psychotherapy, patients can be advised to avoid caffeine and educated about panic attacks and their possible interaction with alcohol use[14], especially about alcohol dependence. Alcohol potentiates the CNS depressant effects of all of antidepressants and benzodiazepines. In addition, tricyclic antidepressants lower the seizure threshold and increase the risk of withdrawal seizures. Alcohol decreases the therapeutic efficacy of MAOI antidepressants and may cause hypo-or hypertension in combination with these medications. And also, regular visits and careful record amounts and dates of prescriptions will help to monitor for excessive benzodiazepine use. The rationale and goals of the treatment should be discussed in detail between patient and doctor.

CONCLUSION

While some patients use alcohol to self-medicate primary panic disorder and phobias, prolonged alcohol intake and repeated withdrawal episodes may exacerbate or provoke panic in susceptible individuals. Once present, alcoholism and panic are probably mutually reinforcing. On a receptor level, panic and alcoholism may interact via noradrenergic or GABAergic

mechanisms.

Recognition of patients with both alcohol dependence and panic requires a high index of suspicion. Patients with either condition should be questioned closely about symptoms of the other. Cognitive-behavioral approach is effective as well as medication for treatment.

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