Panic Attacks in an Individual With Bilateral Selective Lesions of the Amygdala

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**Objective:** To describe the unique case of a patient with panic attacks and bilateral selective amygdala lesions due to Urbach-Wiethe disease.

**Design:** Case report.

**Setting:** Epilepsy Monitoring Unit, Medical University of Vienna.

**Patient:** A 38-year-old man with Urbach-Wiethe disease developed spontaneous panic attacks and depressive mood, which ceased after antidepressive treatment.

**Interventions:** Video electroencephalography monitoring, magnetic resonance imaging, and neuropsychological testing.

**Results:** Extended video electroencephalography monitoring excluded an epileptic etiology of the panic attacks. Results of cranial magnetic resonance imaging showed bilateral selective calcifications of the whole amygdaloïd complex. Neuropsychological testing revealed selective memory impairment of autobiographic episodes with preserved memory for autobiographic facts.

**Conclusions:** Our findings indicate that the occurrence of panic attacks does not critically depend on the integrity of the amygdala. Furthermore, the neuropsychological findings in our patient suggest that the amygdala represents an essential neural substrate for the processing of episodic autobiographic memories.

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PANIC ATTACKS IN HUMANS ARE characterized by discrete periods of intense anxiety accompanied by physical symptoms such as hyperventilation, palpitations, and the feeling that something catastrophic is about to happen. Anxiety and fear are closely related, as both are reactions to harmful or potentially harmful situations. Anxiety in panic attacks is usually distinguished from fear by the lack of an external stimulus that elicits the reaction. The neuroanatomical basis for fear has been well characterized in preclinical models. The structures that function in combination with the amygdala during fear learning include mesiotemporal cortical structures, the sensory cortices and thalamus, the orbital and medial prefrontal cortex, the anterior insula, the hypothalamus, and multiple brainstem nuclei. A specific “panic network,” however, has not yet been delineated. Despite the similarities between the physiological and behavioral responses to a conditioned fear stimulus and a panic attack, animal models of fear, which are all based on the conditioned-fear paradigm, may not truly reflect the analog of human panic disorders. Neuroimaging studies in humans have confirmed the activation of the amygdala during conditioned fear acquisition and extinction, but both methodological and technical limitations of positron emission tomography and functional magnetic resonance imaging studies have so far hampered the identification of key structures implicated in the generation of spontaneous panic attacks. In the present study, we describe the unique case of a patient with bilateral lesions in the amygdala due to Urbach-Wiethe disease (UWD) who also experienced panic attacks.

REPORT OF A CASE

Urbach-Wiethe disease is an extremely rare autosomal recessive entity characterized by the deposition of hyaline material in the skin and other tissues of the body. Bilateral selective calcifications of the amygdala are present in 50% of patients. The fact that the amygdala plays a critical role in the recognition of fear in facial expressions has already been shown by Adolphs et al in a patient with bilateral amygdala damage. Herein, we present a patient with bilateral selective lesions of the amygdala.
due to UWD who developed panic attacks in the course of his disease. At the age of 4 years, the patient was diagnosed as having UWD because of the pathognomonic skin manifestations. Up to the age of 38 years, there were no additional manifestations of the patient’s UWD. In particular, the patient had a normal emotional development and exhibited a normal range of mood and affect, without abnormalities in his experience of fear or panic. At the age of 38 years, he developed spontaneous panic attacks, which were characterized by the acute onset of unprovoked and intense anxiety accompanied by rapid breathing, palpitations, and the feeling of imminent death. The attacks occurred in intervals of several days at different times of the day and without any external trigger. In particular, there was no evidence that hyperventilation or increased carbon dioxide or lactate levels triggered panic episodes. The diagnosis of panic attacks was confirmed by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. None of the attacks, which lasted from 5 to 20 minutes, was accompanied by loss of consciousness, motor phenomena, amnesia, or any other epileptic symptoms. There was no history of any psychiatric disease or epilepsy, but at the time of the panic attacks the patient developed depressive mood with lack of interest, apathy, sleep disturbances, and social withdrawal. Magnetic resonance imaging revealed bilateral selective calcifications of the amygdala (Figure) without any additional abnormalities in the brain. As the patient did not have any neurological symptoms prior to the onset of his panic attacks, no previous neuroimaging studies were available for a statement as to when the lesions occurred. The patient underwent extended video electroencephalography monitoring over a period of 5 days, including bilateral sphenoidal electrode recordings, which excluded an epileptic etiology of the symptoms. The patient’s neuropsychological profile was found to be within the normal range for cognitive parameters, including IQ, memory, attention, and executive functions (Table). In a detailed interview, however, the patient reported that he had noticed a significant decline in his ability to recollect autobiographical episodes over the last years. For example, several weeks after his vacations, the patient was able to recall all cities he visited during his travels but could not remember specific episodes he experienced there. These specific memory deficits were also confirmed in a standardized autobiographic memory interview (Table). After antidepressive treatment with venlafaxine hydrochloride (75 mg/d), both the panic attacks and the depressive symptoms gradually ceased. The memory impairment, however, persisted.

The neural pathways involved in generating panic attacks in humans are still poorly understood. In contrast to fear, which can be objectively measured in the laboratory with classical conditioning methods by pairing a neutral stimulus with an aversive stimulus, anxiety as seen in panic attacks is usually not clearly associated with a single eliciting stimulus and it may last longer than fear once activated, making any experimental manipulation difficult. As a consequence, there exists a large body of evidence indicating that the amygdala plays a critical role in conditioned fear, while the function of the amygdala in anxiety disorders or panic attacks is much less clear. Within the amygdala, the basolateral and central nuclei appear to have the necessary neuroanatomical connections and neurotransmitter systems to regulate learned fear responses and panic attacks, respectively. Disruptions of the normal regulatory balances in this region trigger panic-like responses and initiate anticipatory anxiety in rats. Based on these preclinical data, recent pathophysiological concepts of panic responses in humans suggest that either dysfunction of cortical inhibition or excessive cortical activation of caudal limbic structures may finally lead to activation of phylogenetically conserved amygdalofugal pathways.

The findings in our patient with bilateral lesions of the amygdala, however, contradict previous assumptions that the amygdala represents the final and most essential “bottleneck structure” for the generation of panic responses. The fact that many other central nervous system sites, including the prefrontal cortex, insula, thalamus, and septohippocampal system as well as the locus coeruleus and raphe nuclei, have been implicated in the regulation of panic responses suggests that a regulatory dysfunction at any key site in this network could lead to the development of panic symptoms. Furthermore, some of the aforementioned brain areas are closely connected with the organism’s internal milieu via the circumventricular organs, which lack a blood-brain barrier; as a consequence, the internal physiological changes could be de-
ected at these sites and activate the panic system. This would also explain why panic attacks can be easily trig-
gered in patients with panic disorders by means of lac-
tate infusions, hyperventilation, or carbon dioxide inha-
lation. In this regard, Shekhar and Keim7 have found that
direct injection of lactate into the organum vasculosum
lamina terminalis in rats elicits robust anxietylike re-
sponses, suggesting that this may be the neuroanatomi-
cal basis for lactate response in panic disorder. In the case
of our patient, it would be conceivable that the absence
of the amygdala and its reciprocal connections could have
made the patient susceptible to panic reactions. Our find-
ings also correlate with studies in rats, where benzodi-
azepines have consistently been shown to have anxioly-
etic effects in certain tests, yet lesions of the amygdala
failed to have the same effects.24

Several studies on patients with UWD have con-
An abbreviation for cerebral lesions, revised version
Abbreviations: ISA, Intelligenzstrukturanalyse; LVT, Linienverfolgungstest; NA, not applicable; WST, Wortschatztest
*Poor performance in recalling autobiographic episodes.
†High scoring in depressive mood and religiosity (spirituality).
‡Raw score not applicable.
tion of emotional autobiographical memories.\textsuperscript{27,28} The fact that memories related to autobiographical episodes are often imbued with emotional salience would in this regard explain our patient’s selective deficit for the recollection of autobiographical episodes.

With regard to the occurrence of panic attacks in our patient, a recent volumetric magnetic resonance imaging study demonstrated selective amygdalar atrophy in patients with panic disorder, although it was not possible to establish a causal relationship between the amygdalar atrophy and panic disorder.\textsuperscript{29} Our finding, however, implies that panic responses are possible in the absence of the amygdala, an intriguing finding that, to our knowledge, has not yet been demonstrated in humans.

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REFERENCES


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