Mesiotemporal Disconnection and Hypoactivity in Klüver-Bucy Syndrome:

Case Series and Literature Review

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ABSTRACT

Objective: Klüver-Bucy syndrome (KBS) is often perceived as rare and limited to cases with bilateral amygdala destruction. In fact, various alternate mechanisms may be involved, warranting exploration of the syndrome's presentation, pathophysiology, prognosis, and management.

Data Sources: Clinical management and the electronic medical records were examined for 2 patients diagnosed with partial KBS (*ICD-10* F07.0) after experiencing ≥ 3 of the following: placidity, indiscriminate dietary behavior, hyperorality, hypersexuality, visual agnosia, and hypermetamorphosis. A literature search was performed in April 2015 by using the keyword *Kluver-Bucy* in PubMed and Ovid databases for English language publications since inception. Additionally, the authors reviewed the reference list of these publications in order to identify additional reports.

Study Selection: Studies were included if they had information about presentation, pathophysiology, syndrome treatment or management, and course of KBS.

Data Extraction: Information about our KBS cases was obtained by reviewing electronic medical records and by direct observation of the patients. A total of 186 (PubMed) and 137 (Ovid) publications were identified in each database. We ultimately reviewed 109 articles containing information about KBS, finding 51 publications addressing relevant aspects of this syndrome.

Results: The first case demonstrates KBS secondary to mesiotemporal structural atrophy, and the second illustrates transient KBS due to functional, postictal, hypoactivity within such structures. Literature review and discussion regarding both prognosis and treatment of KBS follows.

Conclusions: Klüver-Bucy syndrome may be underreported due to a limited understanding of the syndrome as one necessitating bilateral amygdaloid destruction. The syndrome can be seen with damage/hypofunction of the hippocampal-amygdaloid complex and its projections. The prognosis of KBS is variable, and its treatment is based on a combination of environmental and pharmacologic measures.

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Klüver-Bucy syndrome (KBS) was first reported in 1939 upon identification of a unique pattern of behavioral changes in rhesus monkeys following bilateral temporal lobe resections.[1,2] Characteristic features include placidity, indiscriminate dietary behavior, hyperorality (tendency to explore objects with the mouth), hypersexuality, visual agnosia, and hypermetamorphosis (tendency to attend to and manipulate objects within the visual field).[2–6] Klüver-Bucy syndrome rarely occurs in its complete form in humans, whereas partial KBS is diagnosed based on the presence of 3 or more of the aforementioned symptoms.[5,6] The *International Classification of Diseases, Ninth Revision* (*ICD-9*), includes a diagnostic code for KBS (310.0), which was changed to "organic personality disorder" in the *ICD-10*.[7] The first case[8] of partial KBS in humans was reported in 1955 in a patient who underwent bilateral temporal lobe resection. This patient experienced all KBS features with the exception of hyperorality. The first case[9] of complete human KBS was published in 1975 in a patient with possible limbic encephalitis. Multiple authors have reported KBS in patients with a wide variety of pathologies, such as herpes encephalitis, trauma, seizures, neoplastic processes, hypoxia, Alzheimer's disease, frontotemporal dementia, multiple sclerosis (MS), systemic lupus erythematosus, and adrenoleukodystrophy.[10–20]

Klüver-Bucy syndrome is rather uncommon, with fewer than 200 academic publications devoted to the condition in PubMed. It was initially believed that KBS was caused by bilateral damage to the anterior temporal lobes, specifically amygdalae, but this syndrome has also been observed in patients with smaller bilateral lesions affecting only the hippocampi,[3] neuronal connections from the amygdala,[21] unilateral lesions,[22,23] or no lesions at all,[12,24] suggesting the syndrome may occur as a consequence of hypofunction within mesiotemporal structures regardless of etiology. We offer 2 clinical examples of this broadened model of KBS, the first suggesting structural connectivity loss within mesiotemporal structures and the second illustrating transient symptoms due to functional hypoactivity between such structures. We then discuss the prognosis and treatment of this condition based on prior academic publications on this subject.

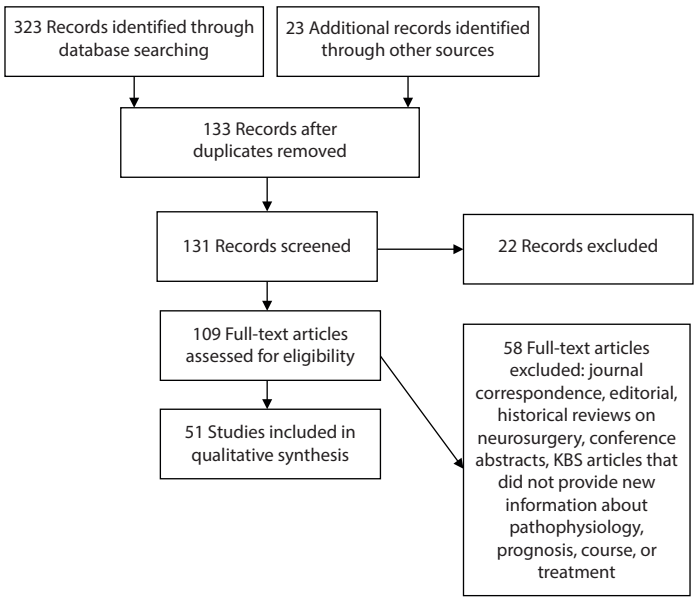
METHODS

Two cases of KBS, including clinical presentation, etiology, treatment, and disease course, are presented. Data were obtained from direct clinical observation and electronic medical record review. Institutional review board approval was obtained to utilize data collected during routine clinical practice. Additionally, we conducted PubMed and Ovid (Ovid, Ovid MEDLINE,

Clinical Points

- Klüver-Bucy syndrome (KBS) is a rare neurobehavioral syndrome consisting of placidity, indiscriminate dietary behavior, hyperorality (tendency to explore objects with the mouth), hypersexuality, visual agnosia, and hypermetamorphosis (tendency to attend to and manipulate objects within the visual field). The diagnosis of the complete form of the syndrome is based on the occurrence of all aforementioned symptoms, whereas the more common partial version of KBS is based on the presence of 3 or more symptoms.
- Klüver-Bucy syndrome may be underrecognized due to limited understanding of the syndrome as one necessitating bilateral amygdaloid destruction. The syndrome offers important lessons in the neural connectivity and functional neurophysiology of mesiotemporal structures, particularly the hippocampal-amygdaloid complex and its projections to the orbitofrontal cortex. Functional or anatomic impairment in these connections may account for many instances of undiagnosed KBS.
- Klüver-Bucy syndrome has been reported in a wide range of conditions. Therefore, its prognosis and course depends on the reversibility of the underlying condition. Management of behavioral disturbances in this syndrome consists of environmental treatments and a combination of multiple pharmacologic treatments.

Figure 1. PRISMA Flowchart of Search Strategy



Abbreviation: KBS = Klüver-Bucy syndrome.

PsycINFO, and Embase) database searches in April 2015 using the keyword *Kluver-Bucy* for English language publications in this field since inception. Furthermore, we reviewed the reference list of these publications in order to identify additional reports.

RESULTS

A total of 186 PubMed and 137 Ovid publications were initially identified. Twenty-three publications were obtained from other sources (review of references). Zotero (George Mason University, Fairfax, Virginia) reference management software was used to organize, retrieve, and identify duplicate publications. Publications not addressing KBS, duplicate publications, articles without an abstract, non-English publications that were erroneously filtered as English, retracted articles, errata, and cat studies were excluded, leaving 131 unique publications assessed for eligibility. Of these, 19 were excluded due to lack of access to the full text of the article, and 3 were excluded due to non-English language of the article. We ultimately reviewed 109 publications and screened them for clinically relevant information about KBS presentation, pathophysiology, prognosis, or treatment, obtaining a total of 51 articles (Figure 1 depicts PRISMA flowchart[25]).

Case 1: Klüver-Bucy Syndrome as Structural Connectivity Syndrome

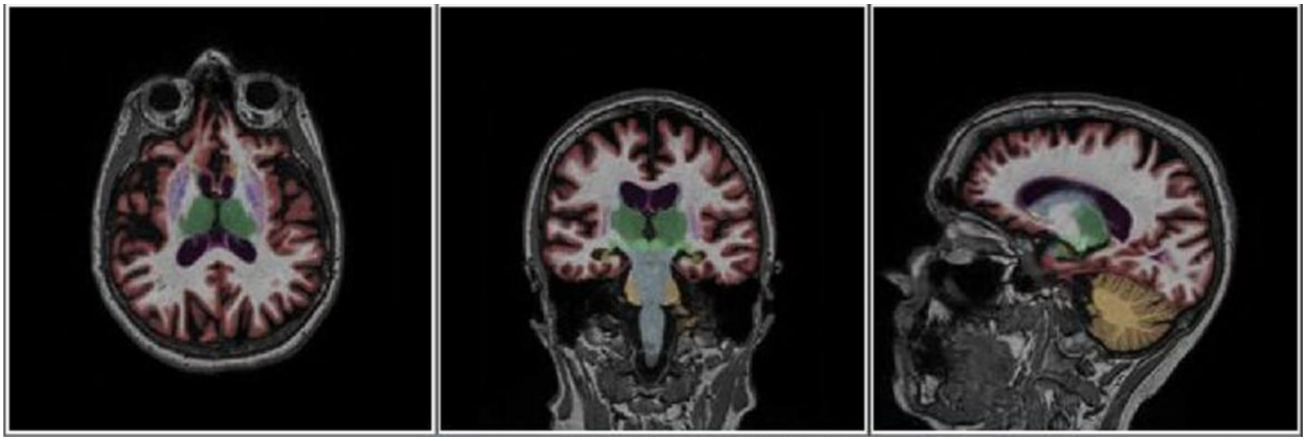
Ms A was a woman in her fifties, who progressively developed memory, attention, and social deficits over a 15-month period. Her past medical and psychiatric history included narcolepsy diagnosed 15 years prior to hospitalization, which was successfully treated with amphetamine–dextromethamphetamine salts combination for several years. She stopped taking this medication 14 months prior to hospitalization, as she experienced insomnia, which she attributed to the medication side effect. She also had chronic depression, which had been previously treated with venlafaxine and bupropion several years prior to admission. No such medications were prescribed prior to the onset of her presenting symptoms. Family history was lacking of any neurodegenerative, psychiatric, or genetic abnormalities.

Ms A's symptoms were initially observed by relatives noticing a marked change in personality consisting of inappropriate laughter and uncharacteristic insomnia. She gradually developed impulsive behavior and poor judgment, resulting in traffic violations and legal charges. She progressed to making socially inappropriate sexual comments in various settings. This decline led to Ms A's move into her parents' home, as they were concerned about her ability to function without supervision. Ms A developed a voracious appetite, consuming several packs of gum serially and eating meals 2 to 3 times larger than her usual portions (she in fact required restraint from the refrigerator in order to keep her from consuming everything inside). Ms A gradually developed prominent memory and hygiene problems, wearing the same clothes for a span of 3 months.

Six weeks prior to admission, Ms A developed mood symptoms, reporting depressed mood and suicidal ideation with a plan to jump in front of traffic. She was admitted to the dementia unit of an academic medical center where she underwent neurologic assessment, was diagnosed with

Figure 2. Results of Volumetric Measurement of Brain Structures on Magnetic Resonance Imaging[a]

Morphometry Results



Brain Structure	Volume (cm2)	% of ICV (5%–95% normative percentile*)	Normative Percentile[b]
Hippocampi	4.47	0.31 (0.44–0.58)	< 5[a]
Lateral ventricles	42.77	2.97 (0.81–3.16)	91
Inferior lateral ventricles	6.19	0.43 (0.10–0.26)	> 95[a]

Brain Structure	LH Volume (cm^2)	LH Volume (% of ICV)	RH Volume (cm^2)	RH Volume (% of ICV)	Asymmetry Index (%)
Hippocampus	2.40	0.17	2.07	0.14	15.08
Amygdala	1.05	0.07	0.85	0.06	21.02

[a]Volumetric analysis of Ms A's mesiotemporal structures revealed dramatically reduced hippocampal volume bilaterally (less than 5th percentile) as well as unilateral (right) amygdaloid atrophy.
[b]Normative values provided for reference purposes only.
Abbreviations: ICV = intracranial volume, LH = left hemisphere, RH = right hemisphere.

recurrent major depression, and was prescribed mirtazapine. Although results from brain computed tomography were normal, a noncontrast brain magnetic resonance imaging (MRI) revealed bilateral ventricular temporal horn prominence with moderate to severe loss of hippocampal volume. Upon discharge from the dementia unit, Ms A was referred to a specialized neurodegenerative clinic and an elective admission was arranged to rule out causes of rapidly progressing decline including viral, limbic/paraneoplastic, or spongiform encephalitides.

Consultation psychiatry was requested to evaluate unusual behavior and "agitation," as Ms A was getting out of bed several times per minute without any particular goal. Upon psychiatric evaluation, Ms A was alert, oriented to self and situation (but not time or place), and disheveled; she was easily redirectable with verbal interventions despite repeated, purposeless attempts to leave her bed. She also engaged in tactile exploration of multiple objects within her visual field without any overt goals. Her mood was "depressed and hungry"; her affect appeared incongruent and odd, with intermittent bouts of inappropriate laughter and complaints of intense hunger. Her thought process was concrete, and no delusions were noted. Ms A reported passive thoughts of death, but no suicidal ideation, homicidal ideation, or hallucinations. Her comprehension was below average, and her usual baseline and both insight and judgment were severely impaired. Her Montreal Cognitive Assessment (http://www.mocatest.org/) score was 23/30, with significant deficits in delayed recall and minor deficits in language and attention. Subsequent psychiatric examinations throughout the 8-day hospital admission evidenced frequent hypermetamorphosis, hyperphagia (eg, she attempted to eat food from the trash, chased other patients' food carts), easily redirectable and placid affect, hypersexuality (eg, attempted to grab the genitals of both male and female hospital staff), and hyperorality, meeting *ICD-10* criteria for partial KBS. She did not exhibit visual agnosia, although previously performed neuropsychological testing reports, despite limitations due to poor patient participation, did show impairment of visual reasoning. Results of laboratory analyses for human immunodeficiency virus, Lyme disease, anti–*N*-methyl-D-aspartate receptor antibodies, glutamic acid decarboxylase antibodies, other paraneoplastic encephalitides, syphilis, methylmalonic acid and homocysteine abnormalities, thyroid pathology, central nervous system infections (bacterial, viral, fungal, and prion), seizure disorders, and demyelinating disorders were all negative. Repeated brain MRI with volumetric data measurement (Figure 2) revealed diffuse parenchymal volume loss, bilateral hippocampal atrophy (below the 5th percentile), and right-sided amygdala atrophy. A brain positron emission tomography (PET) found diffuse cortical hypometabolism, more pronounced in bilateral caudate nuclei and bilateral anterior frontal and temporal lobes. The patient was diagnosed with frontotemporal dementia with partial KBS.

A consultation psychiatrist initiated oral olanzapine (5 mg at bedtime as needed) targeting insomnia and

impulsivity, but Ms A received only 1 dose throughout her admission. Simple and effective verbal redirection by hospital staff precluded the initiation of additional pharmacotherapies. Mirtazapine was discontinued, because it can lead to increased appetite and weight gain. Due to the neurodegenerative etiology of her symptoms and her family's inability to care for her, Ms A was subsequently discharged to a locked dementia unit. In this case, our patient developed KBS in the setting of extensive neurodegeneration involving both hippocampi, right amygdala, and bilateral frontal and temporal cortices.

Klüver-Bucy syndrome has traditionally been described in cases of bilateral amygdalae damage; however, our patient had no identifiable damage to the left amygdala and there was no electroencephalographic data suggesting peri-ictal hypofunctioning of temporal lobe structures, thus raising the hypothesis that KBS occurred due to damage to the projections of the left amygdala in addition to structural damage to the right amygdala proper.

Case 2: Klüver-Bucy Syndrome as Functional Hypoactivity Syndrome

Mr B was a man in his late twenties with a past medical history of traumatic brain injury (secondary to repeated football concussions), generalized tonic-clonic seizures for 5 years, and recently diagnosed bipolar disorder. One year prior to admission, Mr B was evaluated for his seizure disorder, and brain MRI revealed mildly enlarged ventricles as well as FLAIR signaling in parasagittal midfrontal deep white matter, left anterior superior subinsular matter, and the right occipital lobe. These lesions were described as nonspecific white matter lesions of unknown significance.

Several months prior to admission, Mr B became grossly disorganized and intermittently agitated, prompting inpatient psychiatric evaluation involving stabilization with oral haloperidol. His outpatient psychiatrist quickly changed haloperidol to quetiapine, and, suspecting underlying neurologic issues, ordered a second brain MRI, which revealed an interval increase in size of supratentorial (left frontal, right frontal, and right parietal) white matter lesions and development of new infratentorial lesions in the cerebellar hemispheres. Although the possibility of MS or some other demyelinating process was raised, no treatment was sought at that time.

Mr B experienced breakthrough seizures at various points during this time, and serial electroencephalograms demonstrated focal epileptogenic activity in each temporal region with global generalization. His complex epileptic findings prompted formal evaluation on an epilepsy monitoring unit at a large academic medical center. Very shortly after admission, Mr B exhibited behavioral symptoms consisting of extreme agitation alternating with placidity, hypersexuality (eg, attempts to grab genitalia of hospital staff as well as his own genitalia, licking his lips while yelling at others to get closer to him), and hyperorality/hyperphagia (eg, lip smacking, overeating, attempts to eat inedible objects such as electrodes and plastic wrappers). Psychiatric consultation was obtained for these symptoms as well as postural tremors, thought to be secondary to valproic acid. Mr B required constant observation, 4-point restraints, and intramuscular administrations of haloperidol for behavioral control. Interestingly, previous publications[6,23,26,27] have reported alternating periods of agitation in this version of KBS, despite having placidity as 1 of the diagnostic criteria. He was observed to intermittently present as quite docile and placid, responding particularly well to presence of relatives. He simultaneously exhibited placidity, hypersexuality, hyperorality, and hyperphagia, thus meeting *ICD-10* diagnostic criteria for partial KBS.[5,6] Video electroencephalographic monitoring revealed numerous instances of postictal temporal activity correlating with KBS symptoms, suggesting that our patient developed KBS in the setting of postictal hypofunction of temporal lobe structures. A repeated brain MRI could not be performed due to Mr B's agitation. He responded to changes in his antiepileptic agents (from valproate to topiramate) and a regimen of quetiapine, propranolol, benztropine, and haloperidol.

Mr B was diagnosed with MS during this hospitalization, presenting with transient, postictal KBS. He was discharged with ambulatory neurologic and psychiatric follow-up but was unfortunately readmitted 25 days later due to severe social withdrawal, minimal verbal output, staring episodes, and urinary incontinence. Electroencephalographic monitoring revealed diffuse encephalopathy and nonconvulsive status epilepticus. A repeated MRI showed 11 enhancing lesions and an increase in MS burden. Psychotropics were held, and he received aggressive antiepileptic, steroid (methylprednisolone), and plasma exchange treatments. Mr B's affect, behavior, and cognition gradually improved during his 30-day readmission, without return of KBS symptomatology.

DISCUSSION

Klüver-Bucy Syndrome as a Mesiotemporal Disconnection and Hypoactivity Syndrome

Our first patient experienced most KBS features, with the exception of visual agnosia. Evidence suggests higher behavioral symptomatology burden and lower visual agnosia/prosopagnosia in human KBS as compared to primate KBS.[6] Given her frontotemporal neurodegeneration, Ms A faced irreversible changes and symptoms.

Our second patient initially experienced various KBS symptoms in the setting of advancing white matter lesions later identified as an aggressive form of MS. Mr B's bilateral frontotemporal epileptic output was followed by KBS symptoms, particularly when postictal. These symptoms of KBS improved once seizures were adequately controlled. As such, previous case reports describe patients manifesting KBS following status epilepticus[12,24,28] as well as MS.[13]

Neuroanatomically, the basolateral amygdala projects directly to the orbitofrontal cortex, hippocampus, striatum, and the central nucleus of the amygdala. These

structures are involved in behavioral control, emotionality, memory consolidation, spatial learning, approach and avoidance behaviors, and activation of the autonomic nervous system.[29–31] Therefore, bilateral damage or altered functioning in the amygdala, its neuronal projections, or the areas reached by these projections could theoretically cause KBS symptoms. Klüver-Bucy syndrome was initially hypothesized to emerge as a result of overt structural damage to such neuroanatomy, particularly bilateral amygdaloid destruction, although more recent publications[3,26,32] have reported KBS without bilateral amygdala damage. Norman Geschwind[33] was the first to propose that KBS occurs as a disconnection syndrome caused by interruption of the visual input to the limbic system. Over time, KBS has been described in cases with amygdaloid sparing, such as in isolated bilateral hippocampal atrophy,[3] ischemic infarcts involving the anterior and posterior circulation without damage of temporal lobe structures,[26] after isolated bilateral thalamic strokes involving the mediodorsal nucleus,[32] and after unilateral temporal lobe resections in the absence of seizures.[23] Such cases suggest that KBS can occur secondary to damage of neuronal pathways connecting different temporal lobe structures with the orbitofrontal cortex. In other instances, KBS emerges in the ictal or postictal phase in patients that have intact mesiotemporal neuroanatomy or unilateral temporal lobe lesions.[12,27,28] Impaired peri-ictal functioning in contralateral[27,28] (in case of unilateral structural damage) or bilateral[12] (in cases of no structural abnormalities) temporal lobe structures has been reported as a cause of KBS in the absence of bilateral mesiotemporal structural damage, supporting the hypothesis that KBS can also occur as a consequence of abnormal functioning in the amygdalae and its connections. Interestingly, 1 study[24] of 269 subjects with temporal or frontal lobe epilepsy found that up to 3% developed peri-ictal hyperorality, one of the principal features of KBS.

Structural (case 1) and functional (case 2) etiologies of mesiotemporal hypoactivity leading to KBS suggest a seemingly direct relationship with symptoms. Despite the prominence of various disconnection syndromes as conceptual models in behavioral neurology,[33,34] it is unclear whether the degree of neural connectivity or functioning in the mesiotemporal regions can be expected to be directly proportional with KBS severity. Supporting the notion that KBS, regardless of etiology, is a syndrome of mesiotemporal hypofunction is Gastaut's observation of the reverse: in temporal lobe epilepsy, itself thought to be secondary to mesiotemporal structural hyperconnectivity and/or functional hyperactivity, patients often manifest symptoms opposite to KBS, such as increased emotionality, heightened attention to detail, and hyposexuality.[35]

Therefore, mesiotemporal lesions or other functional changes resulting in hypofunctioning in the amygdalae or its projections may lead to sustained or transient KBS, respectively. Our study is limited by a small patient sample due to the rarity of this syndrome, and by the exclusion of non-English language articles from our database search.

Management and Treatment Considerations

As mentioned, KBS is an uncommonly reported syndrome that has been observed in patients with a wide variety of neurologic illnesses resulting in bilateral damage or hypofunction of the amygdala or its neuronal connections. There is no specific treatment for KBS, as its course depends on the reversibility of the condition that is causing it. Some authors have reported the development of transient KBS in patients with seizures or in the postictal period, with disappearance of KBS features once seizures were adequately controlled with antiepileptic medications or upon resolution of the postictal period.[12,28] Reversible KBS has also been reported in patients recovering from transtentorial herniation,[36] gunshot wound to the head,[37] cerebral hypoxia,[38] head trauma,[39,40] cerebral edema,[41] and herpetic encephalitis.[42] These cases of reversible KBS were probably caused by a transient alteration in the function of the amygdala or its connections, with disappearance of KBS features once the local neuronal dysfunction improved.

Unfortunately, other cases of KBS, such as those occurring in the setting of neurodegenerative processes, anoxia, stroke, postradiation changes, systemic lupus erythematosus, and postencephalitic syndromes, can be irreversible.[6,19,43–46] Additionally, some features of KBS can be seen in other neurodegenerative process, such as frontotemporal dementia, where 20% of patients experience hyperorality and hypermetamorphosis.[47] There are no available treatments to target the underlying neuronal destruction in these cases. Therefore, the management should be tailored toward control of behavioral symptoms resulting in severe social impairment including risk of harm to self and others. Ideally, the treatment of agitation or impulsivity in KBS should begin with a safety assessment determining any level of threat to self or others. Management involves the least restrictive treatment options first. Behavioral interventions such as the use of a structured environment, close observation of the patient, and frequent redirection for undesired behaviors are often effective given the characteristically placid nature of people with KBS. Due to the underrecognition of KBS, there are no current treatment guidelines; challenges in the management of KBS are similar to those encountered in patients with advanced dementia, as both populations experience problems with memory, attention, concentration, agitation, impulsivity, and hypersexuality.

Pharmacologic options are limited; however, several reports offer anecdotal evidence of successful management of KBS with medications such as anticonvulsants,[15,48,49] antipsychotics,[46,50] and selective serotonin reuptake inhibitors.[51,52] Carbamazepine, an antiepileptic with known mood stabilization properties, has been successfully used in the treatment of behavioral symptoms in patients with KBS since the early 1970s and 1980s.[15,26,44,48,53] One patient developed peri-ictal KBS, with resolution of his symptoms when seizure control was achieved with a combination of carbamazepine and lamotrigine[12]; however, a separate group reported treatment failure in a patient with KBS with use of high-dose chlorpromazine, trifluoperazine, and

thiothixene.[4] Recent reports[12,21,27,46,54,55] indicate successful use of antipsychotics such as haloperidol, risperidone, and quetiapine in the treatment of KBS agitation. Selective serotonin reuptake inhibitors have also been added to other psychotropics; in 1 case series,[51] fluoxetine was added effectively to a regimen of trazodone and carbamazepine, while valproic acid, thiothixene, and olanzapine have been augmented by addition of sertraline. Interestingly, leuprolide, a gonadotropin-releasing hormone agonist producing a net decrease in testosterone levels via down-regulation of gonadotropin-releasing hormone receptors, has been used in the treatment of hypersexuality in a patient with KBS and dementia.[43] Methylphenidate has seen limited use in the treatment of KBS, with mixed results when added to other medications such as carbamazepine and antipsychotics.[46,56,57] Finally, the α_2 agonist clonidine has been helpful in decreasing the impulsivity and disinhibition when added to carbamazepine.[56,57] Ultimately, it appears a combination of multiple agents is needed in the management of behavioral disturbances in KBS.

CONCLUSION

Klüver-Bucy syndrome may be underrecognized due to limited understanding of the syndrome as one necessitating bilateral amygdaloid destruction. The syndrome offers important lessons in the neural connectivity and functional neurophysiology of mesiotemporal structures, particularly the hippocampal-amygdaloid complex and its projections to the orbitofrontal cortex. Functional impairment in these connections may account for many instances of undiagnosed KBS. Consultation psychiatrists and neurologists should be aware of this syndrome as one of mesiotemporal hypoactivity secondary to various structural or functional etiologies. They should also be aware that the prognosis and course of this syndrome depends on the reversibility of its underlying etiology and that treatment should be based on a combination of environmental and pharmacologic treatments. Future directions include broader conceptualization of the syndrome for clinical, research, and academic purposes.

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Drug names: amphetamine-dextromethamphetamine salts (Adderall and others), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Tegretol, Epitol, and others), clonidine (Catapres and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), leuprolide (Lupron Depot, Eligard, and others), methylphenidate (Ritalin and others), methylprednisolone (Medrol and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), propranolol (Inderal and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), thiothixene (Navane and others), topiramate (Topamax and others), valproic acid (Depakene and others), venlafaxine (Effexor and others).

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