Palliative Care Rounds

Pseudobulbar Affect or Depression in Dementia?

Young D. Chang, MD, Mellar P. Davis, MD, Joshua Smith, MD, and Terrence Gutgsell, MD
Department of Supportive Care (Y.D.C., J.S.), Moffitt Cancer Center, Tampa, Florida; and Harry R. Horvitz Center for Palliative Medicine (M.P.D, T.G.), Cleveland Clinic Foundation, Cleveland, Ohio, USA

Introduction

As palliative or hospice health care providers, we often witness crying or laughing episodes in patients with advanced stage neurologic disease. What if the caregiver felt that this patient's emotional expression was incongruous with the current situation or condition? This could lead to significant emotional and physical burden to caregivers and patients. The negative impact on a patient's quality of life and dignity with embarrassing emotional expression would be substantial.[1] From a health care provider perspective, it is challenging to make a diagnosis and treatment plan with lack of education about pseudobulbar affect (PBA). It is often underrecognized, leading to ineffective treatment because of a wrong clinical impression such as pain, anxiety, depression, and so forth, as was true for our patient.[2] Therefore, we share our case so that we may decrease time to diagnosis and treatment as well as save health care resources with a straightforward assessment and plan.

Case Description

A 92-year-old Caucasian woman was referred for evaluation of episodic crying throughout day. She was a retired high school teacher with a medical history of well-controlled hypertension. She maintained good health until she became forgetful and had decreased cognition and was diagnosed with Alzheimer dementia at 87 years old. She progressively declined in functional status thereafter and was hospitalized with severe sepsis because of a urinary tract infection. After this hospitalization, she was enrolled in home hospice for advanced stage of Alzheimer dementia.

Crying episodes started three months ago. Episodes occurred a few times a day without provocation and lasted about 10–20 minutes. The woman would utter "help me," and she would stop crying abruptly without any intervention. On questioning by the family, the patient was unable to communicate the reason for her outbursts. There was no discernible clinical change, environmental concern, or reason to cry socially. In between episodes, the family noted that the patient showed no signs of distress, appearing comfortable. They did not feel that the patient had auditory or visual hallucinations during episodes. It was causing significant distress to the family as they were worried about her quality of life. Her episodes were not improved with lorazepam or opioid analgesia. In fact, her symptoms worsened with these medications. Haloperidol sedated her during the day time, and the episodes did not diminish.

The patient had urinary and bowel incontinence, no meaningful communication skills, was able to sit with assistance, but was bedridden most of the time. Her body mass index was 16.3. She was able to drink water without signs of aspiration. She had poor appetite with more than 10% weight loss within three months. She was afebrile; other vital signs were unremarkable, and she had good oral hygiene. The patient had a nontender Stage II pressure ulcer in the left hip and buttock area. Although she had urinary incontinence and used adult diapers, family noticed no change of urinary habit. She had regular bowel movements. She had shallow breathing, but no wheezing or crackles. The abdomen was soft, nontender, no organomegaly, but hypoactive bowel sounds. She had weak peripheral pulses on her bilateral dorsalis pedis, and no peripheral edema. The patient was alert, blinking both eyes occasionally. Pupils were equally round, 3 mm, reactive to light reflex appropriately. She had a symmetrical face and moved all four extremities without difficulty. Further neurologic examination including psychiatric evaluation was not available because of her poor cooperation.

Address correspondence to: Mellar P. Davis, MD, Cleveland Clinic Main Campus R35, 9500 Euclid Avenue, Cleveland, OH 44195, USA. E-mail: davism6@ccf.org

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Given her advanced stage of Alzheimer dementia, PBA was suspected. Dextromethorphan/quinidine is the only Food and Drug Administration–approved treatment for PBA.[3] The selective serotonin reuptake inhibitor (SSRI) sertraline was part of the hospice formulary, and given published cases suggesting that SSRIs can be useful in the treatment of PBA,[4] a trial was initiated with 25 mg at bedtime. Her symptoms resolved within five days with no relapse crying episodes.

Comment

Charles Darwin described a syndrome of involuntary laughing and crying in 1872.[5] PBA was commonly found in pseudobulbar palsy patients in the past. Oppenheim first used the term "pseudobulbar affect" in 1911.[6] In 1924, Wilson clearly described PBA, defining it as a stereotype emotional display with characteristically uncontrollable, involuntary outbursts of laughing or crying, which is a type of pathologic behavior that mimics an emotional expression, but not reflecting on actual appropriate mood status.[7] There are many other terms, but PBA or pathologic laughing/crying are most commonly used to describe this syndrome. It is distinguishable from mood disorders in which emotional expressions are associated with actual mood or feelings; PBA is a disorder of emotional expression rather than a primary disturbance of feeling.[8]

Recognition of PBA is challenging for many reasons. Physicians may be unaware of the criteria for diagnosing PBA, the patient's emotional response is noted as disproportionate and, therefore, overlooked as poor coping or depression, or changes are attributed to the patient's baseline neurocognitive disease and left unaddressed. Often, patients are misdiagnosed as having depressed mood. This is not surprising as 30%–35% of patients with PBA are depressed. Duration and type of symptoms can help delineate depression from PBA. Depression tends to have a longer clinical course, whereas PBA is often of a brief nature with episodic occurrences. The exaggerated response of patients with PBA, as well as the discordant response, is also exclusive to PBA. Neurovegetative symptoms such as sleep and appetite disturbances are relegated to depression and are not associated with PBA.[9–18]

Poeck defined four criteria for PBA in 1969[16] (Table 1), which were modified by Cummings in 2006 and are the current diagnostic criteria for PBA.[17] Two tools are commonly used for screening for PBA: the Center for Neurologic Study-Lability Scale (CNS-LS; Table 2) and the Pathologic Laughter and Crying Scale. The CNS-LS is a valid objective screening tool for PBA in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) patients.[19] It is a seven-item questionnaire where each question has a range of scores from one to five, with a maximum total score of 35. A cutoff score of 13 accurately predicted a neurologist clinical diagnosis of PBA in 82% and 78%, respectively, in ALS and MS patients. A cutoff of 17 for the patients with MS revealed improvement of specificity without meaningfully affecting the sensitivity. In addition, the CNS-LS with a cutoff value of 13 was used during the PBA Registry Series (PRISM) study, which was large cohort study for the prevalence of PBA with other common neurologic conditions including Alzheimer dementia, ALS, MS, Parkinson disease, stroke, or traumatic brain injury. The Pathologic Laughter and Crying Scale is an interviewer-administered instrument comprising 18 questions with score ranges between 0 and 3 for each question. A cutoff score of 13 yielded satisfactory outcomes with high sensitivity and specificity of 0.96 in both, and a positive predictive value of 0.83.[19] (Table 3).

Table 1
Diagnostic Criteria of PBA

Poeck (1969)	Cummings (2006)
I. The emotional response is situationally inappropriate	I. A change from previous emotional responses
II. The patient's feelings and the affective response are not closely related	II. Inconsistent with or disproportionate to mood
III. The duration and severity of the episodes cannot be controlled by the patient	III. Not dependent on a stimulus, or are excessive relative to that stimulus
IV. Expression of the emotion does not lead to a feeling of relief	IV. Cause significant distress or social/occupational impairment
	V. Not accounted for by another psychiatric or neurologic disorder
	VI. Not due to a drug

PBA = pseudobulbar affect.

The pathophysiology of PBA is not fully understood. Although clinical symptoms of PBA often mimic those of mood disorders, the pathophysiology of PBA appears to be at least partly distinct from that of mood disorders. In 1924, Wilson hypothesized that lesions to the motor cortex resulted in a loss of voluntary inhibition of brainstem nuclei that control emotional expression. In this way, involuntary laughing and crying were believed to be disinhibited.[7] This theory has undergone multiple expansions leading to the concept of dysfunction of the corticopontine-cerebellar circuit in PBA.[8] This circuit includes motor, limbic, and association cortices with descending pathways to the brainstem, basis pontis, and cerebellum. The neurologic functional role of the cerebellum has been expanded as a great modulator in neurologic function, not only motor but also sensory, such as learning conditioned response, regulation of linguistic cognition, and affective functions especially emotional expression in PBA.[19]

Table 2
CNS-LS Questionnaire for Pseudobulbar Affect

Applies Never	Applies Rarely	Applies Occasionally	Applies Frequently	Applies Most of the Time
1	2	3	4	5

Assessment Questions	Answer
1. There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all.	
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny.	
3. I find myself crying very easily.	
4. I find that even when I try to control my laughter, I am often unable to do so.	
5. There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.	
6. I find that even when I try to control my crying, I am often unable to do so.	
7. I find that I am easily overcome by laughter.	

CNS-LS = Center for Neurologic Study-Lability Scale.

The particular role of the cerebellum in PBA acts as a key modulation rather than generation in emotional responses so as to keep them appropriate to the social situation and to the patient's mood based on input from the cerebral cortex. Disruption of corticopontine-cerebellar circuits results in impairment of this cerebellar modulation, causing PBA. The motor input is, in turn, modulated by inhibitory input from the somatosensory cortex leading to reduction of the inhibitory input resulting in disinhibition of the cerebellum. In PBA, disruption of the corticopontine-cerebellar connection would produce a lowered threshold for emotional response or a response incongruent to the patient's circumstances.[19–21]

Neuroanatomical analysis would be helpful to understand the linkage between specific brain regional functions in terms of emotional expression. In their retrospective review of cases with autopsy in 33 patients with PBA,[22] Davison and Kelman concluded that PBA may occur with multiple brain region abnormalities rather than one single abnormality. In 2008, Ghaffar et al. provided their meaningful findings, a case-control study using-detailed MRI-based quantification of brain pathology with ($n = 14$) or without ($n = 14$) PBA symptoms in MS patients. They reported that there are some patterns of brain lesions with PBA on MRI. Wide dispersed neural networks including brainstem hypointense lesions, bilateral inferior parietal and medial inferior frontal hyperintense lesions, and right medial superior frontal hyperintense lesions were linked with the disorder, and there was no association with global atrophy. However, it did not reveal any significant differences in the cerebellum in this study although it was strongly considered that cerebellar pathologic change might be linked with PBA symptoms in several previous case reports along with MRI findings. The authors discussed that it was probably more a reflection of Type II error than a rebuttal of the region's functional importance.[23]

Table 3
Prevalence of PBA in Different Neurological Diseases

Traumatic brain injury	11%
Cerebrovascular disease	11%
Alzheimer dementia	18%
Multiple sclerosis	10%
Amyotrophic lateral sclerosis	49%

PBA = pseudobulbar affect.
Prevalence varies depending on study.

In 2008, Haiman et al. reported a controlled cross-sectional electrophysiological study of event-related potentials with 11 MS patients with PBA symptoms and 11 healthy controls supporting the concepts of corticopontine-cerebellar circuit dysfunction. In this study, event-related potential current densities were significantly greater with PBA than the no PBA symptoms group. It also appeared that there were differences at early (in sensory area) and later processing stages (premotor or supplementary cortical area) between the two groups, suggesting the sensory processing differences between the groups preceded the motor processing differences.[24] Subsequently, Haiman et al. reported in 2009 that this change of current density in PBA was significantly normalized with dextromethorphan/quinidine treatment. These data reasonably support the concepts of corticopontine-cerebellar circuit and a "gate-control" mechanism controlling emotional expression within this theory.[25,26]

Serotonin and glutamate appear to be particularly relevant in pathophysiology and, therefore, treatment of PBA. Serotonergic projections and serotonin receptors are widespread in the central nervous system, predominantly in the brainstem and corticolimbic area, which are involved in memory, learning, sleep, sex, and appetite. However, its density is relatively low in the cerebellum. The disturbance of these serotonergic functions is characteristic of mood and anxiety disorders. Serotonin may be involved in the pathophysiology of PBA through the diffuse corticolimbic networks involved in emotion or via serotonergic

neurotransmission in the cerebellum. Glutamate is an excitatory neurotransmitter in the central nervous system, and glutamate cell bodies are disseminated throughout the brain, particularly in the cortex, thalamus, hippocampus, and cerebellum.

Because of the lack of a clear neurophysiologic explanation, treatment for PBA has been challenging, with different case reports or small sample uncontrolled studies. Numerous reports existed, and given the implications of glutamine and serotonin as the major players in the disease process, medications targeting these transmitters were evaluated.

Memantine, which blocks glutaminergic neurotransmission, has been studied in the treatment of PBA in patients with severe Alzheimer disease. Although memantine was effective, aggressive behavior and/or agitation were 3.5 times higher than with placebo, and the study was prematurely stopped for safety reasons.[27,28]

SSRIs including sertraline have been reported to improve the pathological crying and laughter following a stroke (subarachnoid hemorrhage). Responses have occurred within a week of instituting sertraline. The appeal of the continuing role for antidepressants, particularly SSRIs, is based on numerous positive reports and trials, the potential unique benefit of treating PBA and concomitant depression without using multiple drugs, and the need to tailor treatment to the individual patient. In addition, a recent study found platelet serotonin concentrations were significantly lower in patients with Alzheimer disease and coexisting PBA compared to Alzheimer disease patients with aggressive behavior or control patients. This could potentially be a marker of PBA in Alzheimer disease and by speculation (although there is currently no clinical evidence) predict response to SSRIs.[29–34,35]

Dextromethorphan, an uncompetitive *N*-methyl-D-aspartate receptor antagonist as well as a sigma-1 agonist, affects both glutamate and serotonin in the brain. In 2001, Brooks et al. conducted a randomized, double-blind, controlled study for PBA in patients with ALS comparing dextromethorphan 30 mg plus quinidine 30 mg to dextromethorphan 30 mg and quinidine 30 mg, the latter two as single agents, with all arms receiving twice daily dosing. After four weeks of treatment, patients treated with dextromethorphan plus quinidine had a significant reduction in their CNS-LS scores as well as significant improvement in their quality of life and relationships scores.[36] In 2006, Panitch et al.[37] published the first double-blinded, randomized, placebo-controlled study evaluating the efficacy of dextromethorphan-quinidine. One hundred fifty patients with MS and PBA were evaluated over 85 days, receiving dextromethorphan 30 mg/quinidine 30 mg or placebo twice daily. Again, significant reductions in CNS-LS scores occurred with reductions in the number of inappropriate episodes of laughing or crying, higher rates of complete remission, improved quality of life and relationships, and decreased pain scores for the treatment group.[37] Finally, a 12-week, randomized, double-blind, placebo-controlled study was conducted by Pioro et al., assessing the efficacy of dextromethorphan/quinidine in 326 ALS and MS patients with PBA. Comparing dextromethorphan 30 mg/quinidine 10 mg, dextromethorphan 20 mg/quinidine 10 mg, and placebo, frequency of PBA events, CNS-LS scores, and rates of remission were all significantly higher with both treatment groups than placebo.[38] These studies led to the approval by the FDA in October 2010 of dextromethorphan 20 mg/quinidine 10 mg for the treatment of PBA, given as a daily dose for one week and then twice daily dosing thereafter.[39]

Conclusion

PBA is often present in common chronic neurologic disease. There are highly efficient, simple screening and diagnostic tools; however, PBA is still underdiagnosed by health care providers. Nonetheless, PBA can be managed quickly with pharmacologic intervention. Dextromethorphan/quinidine is the first-line drug of choice for PBA treatment, as all other options including SSRIs have only anecdotal evidence or require further randomized control study. But, in our case, we used an SSRI because of cost-effectiveness under hospice financial constraints.

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