Identifying Pseudobulbar Affect in Alzheimer's Disease and Dementia

David W Crumpacker, MD[1] and William A Engelman, MD[2]

1. Psychiatrist and Neurologist, Private Practice, Plano, Texas, US; 2. Clinical Scientist and Senior Research Associate, Evidera, Lexington, Massachusetts, US

Abstract

Pseudobulbar affect (PBA) can be challenging to differentiate from the symptoms of various neurological diseases with which it is associated. In patients with Alzheimer's disease (AD) and dementia such a diagnosis can be particularly difficult as illustrated by a case of an elderly male with sudden tearful outbursts, which is reported and discussed here. PBA attacks are often incorrectly attributed to emotion or distress in response to memory loss or a result of depression or dementia. PBA is common, affecting between 10–40 % of people with AD but is frequently not detected or is misdiagnosed. Multiple authors have published clinical criteria for identifying PBA; in sum, it is described as a condition affecting the brain with episodes of laughing or crying that are sudden and unpredictable, occur without warning and are excessive, exaggerated, or not appropriate to the stimuli and are involuntary and difficult to control. Differentiating PBA from depression and other behavioral disturbances in AD and dementia is helpful to patients by identifying a specific cause of their symptoms and enabling appropriate management. Various different approaches have been taken in the treatment of PBA. A combination of dextromethorphan and quinidine has been shown in well-controlled trials and in clinical use to control the symptoms of PBA associated with several neurological diseases including AD and to reduce the burden on patients and their caregivers.

Keywords

Pseudobulbar affect, Alzheimer's disease, dementia, case report, differential diagnosis, epidemiology, diagnostic criteria, management

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Correspondence: William A Engelman, MD, 430 Bedford St, Ste 300, Lexington, MA 02420, US. E: william.engelman@evidera.com

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An estimated 5.3 million people in the US have Alzheimer's disease (AD),[1,2] the incidence of which increases with age.[3] Defined as a 'progressive mental deterioration manifested by loss of memory, ability to calculate, and visual-spatial orientation, confusion and disorientation;'[4] the symptoms, clinical presentation, and prognosis of AD are well known among clinicians. It is also widely appreciated that AD may be associated with any of several neuropsychiatric symptoms including depression, agitation, anxiety, insomnia, and paranoia.

Given this potentially complex clinical background, onset of frequent crying episodes may seem neither unusual nor worthy of further exploration. However, this apparently sensible and pragmatic thinking is flawed, since it risks overlooking a major cause of such symptoms —pseudobulbar affect (PBA). Affecting as many as two in five people with AD[5,6]—but widely under-recognized by clinicians—this important condition must be considered when assessing patients like PJ (see *Box 1*).

The Differential Diagnosis

The psychiatrist treating PJ assumed that he had depression associated with AD. However, the clinical symptoms described and the lack of therapeutic response raise the possibility of treatment-resistant depression or that depression is not the problem. A list of differential diagnoses would therefore include the following:

Depression

PJ's crying episodes make it hard to ignore the possibility that he is depressed. However, it is important to note that frequent crying spells do not automatically indicate depression and that tearfulness is not a necessary or sufficient criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) for diagnosing major depressive disorder (MDD).[7] Also, while many health care providers make the seemingly reasonable assumption that increased crying is a symptom of depression, there are limited data to support the idea that depressed patients have an increase in crying episodes.[8–11] Evidence against the assumption includes

the work of Rottenberg and colleagues,[9] who compared crying episodes in patients with MDD to those in a control group of non-depressed participants, by using a cry-evoking stimulus (a sad movie). They found that crying was no more likely in the depressed than in the control group, who, surprisingly, showed greater crying-related emotional activity than the MDD group. Also, using patient self-reported episodes of crying to compare depressed versus non-depressed elderly individuals, Hastrup and colleagues[11] found only a weak link in increased frequencies of crying episodes among elderly adults with depression, and concluded that crying could not be interpreted as a symptom or sign of depression.

Establishing if a patient with AD also has depression is further complicated by the overlapping features of the two conditions. For example, apathy and poor concentration are common symptoms found in dementia; anhedonia and nihilism also commonly occur in depression.[7,12] Neurovegetative symptoms are common in both conditions and include disturbances in sleep and appetite, changes in weight , decreased sexual desire, decreased energy, psychomotor retardation or agitation, and poor concentration.[13,14] Interestingly, depressed patients with apathy or neurovegetative symptoms may have fewer episodes of crying compared with someone without depression. When crying is caused by underlying depressive illness, it is associated with the patient's reports of pervasive low mood.

Behavioral Disturbances

Behavioral disturbances are common in people with AD and other forms of dementia. For example, Lyketsos and colleagues studied patients with dementia using a screening questionnaire followed by a clinical assessment and found that 61 % exhibited one or more mental or behavioral disturbances within the past month, with apathy, depression, and agitation/aggression being the most common forms.[15] Given their nature and high prevalence, behavioral disturbances could account for crying in patients with dementia.

Essential Crying

Essential crying is an uncommon disorder and is included for completeness.[15] Those with essential crying have a lower threshold for weeping when compared with the normal population.[14] This may be a variant of the emotional domain of temperament. Patients with the condition do not necessarily have an underlying neurological disorder.[16,17] Crying would not be a new finding, but rather characteristic of the individual.

Pseudobulbar Affect

PBA is a disorder of regulation of emotional expression, caused by neurological disease or injury affecting the brain. PBA is characterized by sudden, uncontrollable episodes of crying, laughing, or both. These episodes are excessive, inconsistent with or disproportionate to circumstances or the patient's underlying mood at the time.[18]

PJ's symptoms are most likely to reflect either behavioral disturbances of dementia or PBA. The former will be familiar with clinicians who have experience caring for people with dementia, but what exactly is PBA and how can it be identified and managed?

Pseudobulbar Affect Definition

PBA is defined as an affective disinhibition syndrome associated with various neuropathologies and characterized by involuntary and uncontrollable outbursts of crying and/or laughter.[19,20] Occasionally, other ancillary symptoms are described, such as anger, frustration, or depression, but these are not considered as part of the diagnostic classic construct of PBA.[21–23]

While PBA is well characterized as a distinct clinical entity resulting from neurological disease or injury, the widespread use of the term 'PBA' is a relatively recent development. In particular, inappropriate crying and laughing have been variably described and not uniformly classified, leading to inconsistency in terminology and descriptions in the literature. This lack of standardization may be a result of the same disorder occurring in multiple neurological conditions, but being called different things by different specialties. Examples of terms that may have been used to label cases of PBA include 'pathological laughing and crying' (PLC), 'affective lability' (AL), and 'emotional incontinence.' However, things are changing in this regard, with, for instance, PBA emerging as a preferred term for this disorder of emotional expression when it follows neurological injury.[16]

Despite being described in several neurological conditions, PBA is thought to have common manifestations and neuropathophysiology in these settings. Initially it was described as a disinhibition syndrome. A more recent theory proposes that PBA is related to dysfunction in circuits that involve the cerebellum,[24] while others suggest it is caused by lesions in the descending motor pathways of the cerebral cortex, basal ganglia, or brainstem.[25] Parvizi has extensively evaluated PBA pathophysiology, and describes it as a dysregulation or lack of coordination of emotion response due to lesions along the pathways connecting the cortex, brain stem, and cerebellum.[26,27] Evidence to date indicates that the location of brain lesions or injury, rather than their etiology, dictates PBA symptoms. This could explain why such features can result from a diverse range of neurological conditions including not only AD and dementia, but also

Box 1: Composite Case Report

PJ is a 67-year-old married, white male with a history of hypertension. Following onset of progressive memory problems, he was initially seen by his primary care doctor and subsequently by a geriatric psychiatrist, whose assessment eventually led to a diagnosis of dementia of probable Alzheimer's type. PJ was then started on an acetylcholinesterase inhibitor (AChEI). At follow-up several months later, his family reported frequent, tearful outbursts that they assumed represented PJ's understandable sadness about his failing memory. However, the psychiatrist thought it was more likely to be clinical depression linked to the dementia. The patient denied feeling sad or depressed, even when he was visibly crying; however, because of his cognitive difficulties his statements were considered to be unreliable. As the symptoms were persistent, PJ was started on an antidepressant, to which the psychiatrist later augmented with an anticonvulsant. Despite these medications, the frequent crying episodes continued, with the family finding them increasingly embarrassing and describing them as 'attacks' that came on suddenly for little or for no apparent reason and stopped within a minute or two.

multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (and other movement disorders), stroke, traumatic brain injury (TBI), supranuclear palsy, multiple system atrophy (cerebellar type), mass lesions, and other diseases that damage the central nervous system (CNS).[28–30]

Epidemiology of Pseudobulbar Affect in Alzheimer's Disease

The prevalence of PBA in AD is estimated to be between 10 % and 40 %.[5,6] This wide range is likely due to differences in methods of ascertaining PBA as well as the difficulty in distinguishing PBA from depression or typical behavioral symptoms of AD. The PBA Registry Series (PRISM) was specifically conducted in order to estimate the prevalence and clinical symptoms of PBA in various neurological conditions. This study reported a prevalence for PBA symptoms among AD patients to be 29.3 %.[31]

Pseudobulbar Affect Diagnostic Criteria

Diagnosing PBA in AD may be more challenging than diagnosing PBA in patients with other conditions. Due to their cognitive and memory deficits, patients with AD may be unable to accurately recall or report their symptoms, or may use crying to communicate physical symptoms, such as pain. Additionally, other neuropsychiatric disturbances may be present that could also be associated with crying.[32] Consequently, PBA symptoms may be mischaracterized as 'agitation' or 'behavioral disturbances of dementia' and are often mistaken for depression.[25] Matters are further complicated by the fact that depression can co-exist with PBA. In such circumstances, the health care provider might end up dismissing all symptoms of crying as being 'just the depression.' Therefore, the PBA may easily go unrecognized or untreated. To avoid such outcomes, understanding the clinical presentation and distinguishing features of PBA is essential. The most widely cited diagnostic descriptions or clinical criteria are summarized here:

Criteria of Poeck

In 1969, Poeck published criteria on PBA that included the presence of a 'cerebral disease of the most diverse etiology and location'[33] and the following four criteria:

1. The episodes are inappropriate to the situation and can be precipitated by non-specific stimuli, such as contraction of facial muscles, removal of bedcovers, or the approach of someone toward the patient.
2. There is no close relation between the emotional expression and the patient's mood at the time of the episode.
3. The episodes are relatively stereotyped, paroxysmal, and ritualistic; and it is difficult for the patient to control the extent and duration of the episodes.
4. There are no episodic mood changes that appropriately correspond to the episodes, which may be either consistent or inconsistent with mood. There is no sense of relief as the emotions are expressed, and an absence of corresponding mood beyond the length of an episode.[33]

Criteria of House and Colleagues

House and colleagues used the term emotionalism to describe symptoms of inappropriate crying and laughing in stroke patients and included the following three sets of questions into a standardized psychiatric assessment for patients suspected of having the condition:

1. Have you been more tearful since the stroke than you were beforehand? Have you actually cried more in the past month (not just felt like it)?
2. Does the weepiness come on suddenly, at times when you aren't expecting it? (Suddenly means without warning or within only a few moments, and not after several minutes of trying to control yourself.)
3. If you feel the tears coming on, or if they have started, can you control yourself enough to stop them? Have you been unable to stop yourself crying in front of other people? Is that a new experience for you?[34]

Criteria of Kim and Colleagues

Kim and colleagues conducted a study on diagnosing inappropriate and excessive laughing and crying following stroke in which they included relatives in the patient interview and subsequently developed diagnostic criteria that incorporated responses from relatives. These criteria stated that 'emotional incontinence' could be diagnosed when both the patient and relatives agreed that inappropriate or excessive crying and/or laughing in excess of premorbid state occurred more than twice. In this context, 'inappropriate' refers to crying and/or laughing while talking, listening, meeting people, or watching television that is not particularly amusing or sad to 'ordinary people.'[35]

Diagnostic Criteria of Cummings and Colleagues

Cummings and colleagues (2006) published the following diagnostic criteria for what they termed involuntary emotional expression disorder (IEED):[36]

1. Episodes of involuntary or exaggerated emotional expression that result from a brain disorder, including episodes of laughing, crying, or related emotional displays.
   a. Episodes represent a change from the person's usual emotional reactivity.
   b. Episodes may be incongruent with the person's mood or in excess of the corresponding mood state.
   c. Episodes are independent or in excess of any provoking stimulus.
2. The disturbance causes clinically significant distress or impairment in social or occupational functioning.
3. The symptoms are not better accounted for by another neurological or psychiatric disorder (e.g., gelastic or dacrystic epilepsy, facial dystonia, facial or vocal tics, facial dyskinesias, mania, depression, panic disorder, psychosis).
4. The symptoms are not the direct physiological effect of an administered substance (e.g., drug abuse or medication).

These authors described supportive observations and descriptive characteristics.[36] They also acknowledged the confusion in the literature nomenclature for this syndrome, and recommended calling it IEED because this term, '…assists in recognition, diagnosis, and management; is not pejorative to patients (such as 'emotional incontinence'); and is medically accurate and phenomenologically descriptive.' More recently, however, Rosen and Cummings referred to the condition as PBA, a term that is increasingly adopted by experts, and published criteria that stress three major points for its diagnosis in persons with neurological conditions or brain injury:

1. Episodes that are incongruent with or are greatly exaggerated compared with what the patient is feeling.
2. Episodes with a paroxysmal quality at onset and that often occur in an inappropriate context.

3. A 'wait-out' period that must occur before the patient can return to his or her pre-episode activities (typically a few seconds or minutes).[18]

Summary of Diagnostic Features

While these diagnostic recommendations differ somewhat in language and detail, they emphasize four common attributes:

- The condition occurs in patients with neurological conditions affecting the brain.
- The episodes are sudden and unpredictable, and can occur without warning signs.
- The episodes are excessive, exaggerated, or not appropriate to the stimuli.
- The episodes are involuntary and difficult to control.

How to Differentiate Pseudobulbar Affect

It is important to try to establish the pervasive mood of the patient with frequent crying episodes, particularly to assess the likelihood, or confirm the presence, of depression. As in other aspects of AD, concerns about patients' recall mean it is common to rely on family members and/or caregivers for recent relevant clinical history; but from this, it may be very difficult (or even impossible) to elicit the mood of the patient during particular episodes. Getting a complete history may be difficult if depression in a patient with AD is itself producing symptoms of dementia,[37] creating problems in eliciting the mood of the patient during the crying episode. It is also possible that PBA episodes may be mischaracterized as 'psychomotor agitation' and 'aggression' associated with AD.[37] Assessment may be particularly complicated where patients with AD-related PBA have symptoms of excessive laughing (in addition to or instead of crying episodes); caregivers or clinicians could wrongly presume such features indicate that the patient is very content or are a manifestation of the underlying disease.

Differentiating Pseudobulbar Affect from Depression

Crying due to PBA may be commonly mistaken as a symptom of depression. However, in almost all instances, the affect (crying) in a patient with depression is congruent with the individual's mood. Specifically, the patient will have pervasive feelings of sadness, 'the blues,' or depressed mood associated with the crying.[16] In many cases, apathy, anhedonia, sleep impairment, and social withdrawal are the presenting symptoms for depression in AD or dementia, and these can provide further pointers to a depression diagnosis.[37] Patients with depression may also have a feeling of frustration and could express this with an outward affect of anger.[32]

The diagnosis of depression is clearly challenging in AD given that affected individuals may have little or no capacity to comment on their own mood.[37] However, the major difference to bear in mind is that PBA is a disorder of affect, while depression is a disorder of mood. Also, in order to distinguish PBA, it is essential to remember that the affectual episodes are incongruent with or are greatly exaggerated compared with the patient's mood. This may have a particular bearing where a patient is able to describe that episodes of crying do not reflect their mood[18,33] —as did PJ. In some cases, the crying is triggered by a physical event (e.g., chewing) rather than the patient's mood.[33] Another diagnostic clue is that the crying event may be described as something that the patient or caregiver has to 'wait out.'[18] Also, episodes are paroxysmal, but are distinct from seizure disorder, there is no postictal (or 'wind-down') period and patients can resume normal activity immediately afterwards.

Differentiating Pseudobulbar Affect from Other Behavioral Disturbances in Alzheimer's Disease and Dementia

PBA episodes may be confounded by behavioral disturbances of AD and dementia that represent a constellation of symptoms of varying etiologies. Given their etiology, nature, and high prevalence, these behavioral disturbances could account for frequent episodic crying in patients with dementia. Such disturbances have various possible causes including: i) confusion-related cognitive, language, or memory impairment; ii) frightening, paranoid delusions, or misinterpretation of events; iii) pain or discomfort; iv) depression in a patient too impaired to verbally communicate depressive symptoms; v) sleep disorders; and/or vi) fear or anxiety.[37] The occurrence of one or more of these causes in the context of behavioral disturbances could help in distinguishing symptoms of the underlying AD/dementia from those of PBA. It is frequently helpful to note the absence of labored breathing, negative vocalization, groaning, tense body language, and other items from the Pain Assessment in Advanced Dementia (PAINAD) scale[38] in order to help distinguish PBA from pain. Furthermore, a score of 0 on the Wong-Baker FACES pain rating scale helps solidify the diagnosis. Also, outbursts of laughter may be a prominent sign that PBA is the underlying neurological condition or, possibly, that the patient has witzelsucht (a rare condition in which the affected individual inappropriately finds situations funny that others do not). Of note, the symptoms and signs described above that potentially differentiate PBA from behavioral disturbances in AD/dementia may be more relevant in the moderate stages of AD/dementia. As the dementia progresses, behavioral disturbances may become less prominent, in contrast to features of PBA, which may remain unchanged or become more marked.

Management

After diagnosing PBA in the patient, explaining the condition to the patients and their caregivers is an important next step. Armed with such knowledge, these individuals might feel reassured that there is a specific cause for the affective episodes and so be better placed to cope with them as a result, without further specific management. In other cases, the effects of the outbursts on, for example, well-being and social functioning may mean that more active treatment is wanted. Several controlled and open-label trials have evaluated various drug therapies (mostly antidepressants) for treatment of PBA; however to date, only the combination of dextromethorphan and quinidine (DMQ) (Nuedexta®) has received approval for this indication from a regulatory body (both the US Food and Drug Administration and the European Medicines Agency).

Evidence of the efficacy and safety of DMQ was demonstrated in a pivotal 12-week, double-blind, randomized, controlled trial, in which patients received either placebo or DMQ at a dose of dextromethorphan HBr 30 mg and quinidine SO_4 10 mg (DMQ-30), or dextromethorphan HBr 20 mg and quinidine SO_4 10 mg (DMQ-20). The study reported an incremental reduction in the PBA episode rate of 46.9 % ($p<0.0001$) for DMQ-30 and 49.0 % ($p<0.0001$) for DMQ-20, each over the reduction seen with placebo. In addition, approximately half (47–51 %) of the participants were shown to be in remission during the final 14 days of treatment (regardless of DMQ dose) compared with approximately 30 % of those on placebo. Clinical trial

evidence also indicated that compared with placebo, the most common adverse events were diarrhea, dizziness, cough, vomiting, asthenia, and peripheral edema.[39]

Because dextromethorphan bioavailability is extremely dependent upon first-pass effect in the liver, DMQ incorporates a very low dose of quinidine (a potent inhibitor of CYP 2D6) in order to decrease dextromethorphan metabolism and thereby increase its plasma concentration thus increasing potential CNS availability. Potential drug–drug interactions need to be kept in mind when using DMQ in patients with dementia who may be taking other medications metabolized by the CYP 2D6 enzyme, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, beta-blockers, and some antipsychotics. Dosing of these medications may need to be adjusted when adding DMQ. Although dextromethorphan has pharmacological activity as a weak, uncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, a drug–drug interaction study with the uncompetitive NMDA receptor antagonist memantine (Namenda®) did not find evidence of meaningful pharmacokinetic or pharmacodynamic interaction. Finally, although the dose of quinidine is small and unlikely to produce significant QTc prolongation, DMQ should still not be used in patients with significant risk for QTc prolongation or dysrhythmia (see Nuedexta prescribing information[40] for full warnings and precautions).

Conclusion

AD exacts a heavy burden on patients and their caregivers particularly as a result of common symptoms such as depression and neurobehavioral symptoms. Therefore, there is an automatic tendency to view a patient who presents with frequent excessive crying episodes, through the prism of these two common psychiatric features of dementia. While understandable, such an approach risks overlooking or misdiagnosing a substantial number of patients in whom these symptoms will be the result of PBA. Recognizing such patients can present a considerable diagnostic challenge. However, the key here is establishing whether or not the affective episodes are consistent with or in proportion to the mood, which is not the case in PBA; and even in the absence of a clear history from the patient or caregiver, there may be other clues that help in ruling this condition in or out. The time and effort required in deciding whether PBA is present can make a major difference in management, not only through providing patients and carers with a specific explanation for distressing symptoms, but also in opening up the possibility of potentially effective treatment for those in need of it. ■

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