

A Flood of Emotions

Treating the uncontrollable crying and laughing of pseudobulbar affect.

BY DEBRA GORDON, M.S.

They come into the neurology office of Mustafa Saad Siddiqui, M.D., convinced they are depressed. And they have reason to be depressed: Most have Parkinson's disease or another movement disorder. Besides, what else could explain the sudden, uncontrolled crying that seems to come out of nowhere?

Yet quite often, Dr. Siddiqui—an assistant professor of neurology and neurosurgery and director of the Parkinson's and Movement Disorders program at Wake Forest Baptist Medical Center in Winston-Salem, NC, and a member of the American Academy of Neurology (AAN)—finds none of the other classic signs of depression. These include changes in sleep and appetite or loss of interest in usual activities. “You're not depressed,” he tells many of these patients. “You have pseudobulbar affect.”

References to pseudobulbar affect (PBA) date back more than a century. Naturalist Charles Darwin noted in 1872 that “certain brain diseases, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping.”

PBA is not a disease in and of itself but the result of brain changes from other neurologic diseases, such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), multiple sclerosis (MS), Alzheimer's disease, stroke, traumatic brain injury, and Parkinson's disease. Symptoms include inappropriate, uncontrollable crying and, less often, laughing. People with PBA may also express inappropriate anger and frustration.

Researchers don't know exactly what causes PBA, but they suspect it's related to some disconnect between the brain stem—the oldest part of the brain, where our emotions originate—and the frontotemporal lobes, the part of the brain that determines how we express those emotions. Current theories also link the condition to abnormalities related to the neurotransmitter glutamate, which plays a role in how brain cells communicate, says



FOR FEAR OF CRYING
For Richard Anderson, who has PBA, the extreme episodes of crying have mellowed with treatment.

neurologist Robert Miller, M.D., of California Pacific Medical Center in Sacramento, CA, and an AAN Fellow.

DEPRESSION OR PBA?

Pseudobulbar affect is often misdiagnosed as depression. However, there are significant differences between the two. The major one is that the crying of PBA, which is what typically leads to a diagnosis of depression, occurs unexpectedly and is often unrelated to any specific cause. These episodes are also unpredictable and short lived, while crying with depression is more likely to be related to a specific thought or feeling—and to be far less intense.

In addition, while people with depression tend to lose interest in activities they used to enjoy, people with PBA tend to avoid activities they enjoy out of embarrassment or shame, not a loss of interest.

“There's a lot we don't understand about how the brain mediates emotion and how we control our emotions,” says Howard Rosen, M.D., an associate professor of neurology at the University of California in San Francisco and an AAN member, who conducts research into PBA and emotions. [Disclosure: Dr. Rosen has received consulting fees from Avanir Pharmaceuticals, which manufactures the only drug approved by the U.S. Food & Drug Administration (FDA) for the treatment of PBA (brand name Nuedexta).]

According to recent research, the condition affects between



1.8 and 7.9 million people in the United States (depending on which screening assessment is used), most with one or more underlying neurologic conditions. According to one study published in 2011, between 28 and 50 percent of people with ALS will develop PBA; the study also found that between 9 and 39 percent of those with Alzheimer's disease and between 4 and 28 percent of those with stroke will develop the condition.

THE EMOTIONAL TOLL

PBA “takes an emotional toll on the patient as well as the family,” Dr. Siddiqui says. Patients are often embarrassed because they can't control their emotions, so they stop venturing out and shut themselves off from activities they once enjoyed. Dr. Siddiqui and his team have conducted several studies showing the condition has a significant impact on the quality of life of people with movement disorders beyond the effect of the movement disorder itself.

Dr. Rosen recalls one patient with PBA who refused to attend a close friend's funeral because he was afraid he'd laugh. “They fear they're going to lose control and have an outburst, and they can't explain that they have a disease,” Dr. Rosen says. “People look at you funny.”

PBA is “socially isolating and embarrassing in a major way,”

says Dr. Miller. “It has a major negative impact on the quality of life.”

For Richard Anderson, 54, who sustained a traumatic brain injury (TBI) eight years ago when he was hit by a car, PBA has meant shame and isolation. “You call yourself a loser,” explains Anderson, who held a high-level job in New York City government before his accident. “People say, ‘Look at the big strong guy crying like that,’ and you beat yourself up.”

His crying began soon after he came home from the rehabilitation hospital, says his wife, Rose Anderson. “He had many crying episodes. I thought it was part of the healing process of his injury and him just feeling overwhelmed by things.” The crying continued, however, isolating Anderson more than the TBI ever had. Eventually, he told his doctor and received a diagnosis of PBA.

Other people are not so lucky. A recently published Harris survey of 2,300 people with neurologic conditions found that of the 937 people who screened positive for PBA, 73 percent had told their doctor about their symptoms but only 43 percent received any diagnosis. Patients were typically diagnosed with depression or told their symptoms were due only to their underlying neurologic condition. None were diagnosed with PBA.

Other studies find that patients are often misdiagnosed with

Dr. Rosen recalls one patient with PBA who refused to attend a close friend's funeral because he was afraid he'd laugh.

Pseudobulbar affect is often misdiagnosed as **depression**.

bipolar disorder, schizophrenia, generalized anxiety disorder, personality disorder, or epilepsy. The Harris survey, funded by Avanir Pharmaceuticals, also found that only about half of those with the condition were prescribed medication, primarily antidepressants or antipsychotics.

Dr. Miller stresses the importance of recognizing that PBA is the result of an underlying neurologic condition, not a separate disease or something the patient can deliberately control. It is also critical to get the right diagnosis, he says, because treatment for PBA may differ from that of depression.

TREATING PSEUDOBULBAR AFFECT

Until recently, antidepressants were the primary treatment option for PBA. Although none are approved for this use, doctors often prescribe them “off label.” Richard Anderson, for example, was prescribed an antidepressant, which helped improve his PBA symptoms.

Six published studies comparing the antidepressants fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), nortriptyline (Aventyl, Pamelor), or amitriptyline (Elavil) against placebo—five in stroke patients, one in 12 MS patients—found the medication reduced the number of laughing and weeping episodes more than placebo. Antidepressants also improved patient scores on screening tests used to assess emotions. Side effects varied depending on the medication used but were relatively mild.

The first FDA-approved treatment for PBA was discovered by accident. Researchers were testing a combination of dextromethorphan (DM), a common ingredient in cough syrup, and quinidine, an older medication used for heart rhythm abnormalities. They happened upon the combination because, among its various effects, DM protects cells against glutamate, a neurotransmitter involved in memory and learning. Either too much or too little glutamate can damage brain cells, and glutamate toxicity is believed to be involved in several neurologic diseases, including ALS. Researchers added the quinidine to maintain higher blood levels of DM.

Although the combination had no effect on the progression of ALS, patients told researchers it stopped their emotional outbursts. That the combination went on to be developed for PBA “was purely luck and good observation on the part of the neurologist,” says Dr. Rosen.

The first two studies of the combination were conducted in 125 people with ALS and 150 with MS. Researchers used a dosage of 30 mg DM and 30 mg quinidine and compared it to placebo, DM alone, or quinidine alone. While those taking the combination medication had significantly fewer episodes of



laughing and crying, about a fourth of those with ALS and 15 percent of those with MS stopped taking the drug because of side effects including nausea, dizziness, and drowsiness. Some patients also experienced heart rhythm abnormalities.

A third study, this one in 326 patients with ALS or MS, used a lower dose of quinidine (10 mg) with either 20 mg or 30 mg of DM. After 12 weeks, participants receiving either dose of DM/quinidine had about half as many emotional episodes as before they started the medication, with fewer side effects, while those receiving a placebo saw little change.

In October 2010, the FDA approved the lower dose of the drug for PBA. It is taken once a day for seven days followed by the maintenance dose of every 12 hours. Patients are warned against using it if they are taking serotonin-acting antidepressants or have any risk of a heart rhythm problem.

Experts aren't sure just how DM/quinidine works in the brain to control emotional outbursts. However, they suspect its benefits may be related to its effects on proteins called sigma-1 receptors, which may play a role in emotions.

Today, Dr. Miller says he treats PBA almost exclusively with the drug. “I used antidepressants in the past with mixed results,” he says. “Nuedexta is effective in 90 percent of patients.”



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— RICHARD ANDERSON

Work is underway to quantify the emotional outbursts of people with PBA, according to Dr. Miller. This will help researchers better evaluate the potential benefits of other treatments in clinical trials, he explains. One clinical trial is slated to begin this year to evaluate any potential benefit of DM/quinidine on speech or swallowing difficulties that tend to occur in people with PBA.

SUCCESS—FOR SOME

Daniel Kantor, M.D., AAN member, president of the Florida Society of Neurology, and medical director of Neurologique (an organization dedicated to patient care, research and education) has used the drug with his patients. [Disclosure: Dr. Kantor has received honoraria for speaking/consulting to Avanir Pharmaceuticals and is an investigator in Avanir-sponsored clinical trials.]

He says it is more effective than an antidepressant, with few, if any, side effects. It costs more than most antidepressants, however: about \$489 a month, according to a company spokesperson, although the manufacturer offers a copayment assistance program.

Dr. Siddiqui would love to try the drug in his movement

disorder patients with PBA but hesitates because it has not been tested in patients with those conditions.

“Parkinson’s disease is a different disease, and we use a different set of medications,” he says. In particular, he worries that the DM/quinidine could interact with the commonly used Parkinson’s disease medication, selegiline. Until he sees evidence of its safety in people with Parkinson’s disease, he says he will continue counseling his patients about the condition and, when needed, at least try antidepressants. He also reminds his patients and their families that when it comes to emotions, PBA is like the weather—intense but short-lived—whereas depression is like climate—always around.

Richard Anderson started on the drug in the spring of 2011. “It has made a major difference,” he says. Although he is still prone to crying, he says, “The intensity is not close to how I used to cry before the medicine.” In addition, he was able to stop taking the two antidepressants he’d been using for seven years.

To his wife, the best part is regaining control. “He’s lost so much [since his accident],” Rose says. “He no longer has his sense of taste or smell, and he started to experience pituitary problems and attention deficit disorder. So to be able to say that he can control his emotional outbursts is huge.” NN