National
Multiple Sclerosis
Society
733 Third Avenue
New York, NY 10017-3288

Clinical Bulletin
Information for Health Professionals

Pseudobulbar Affect (Uncontrollable Laughing and/or Crying)

Sarah Minden, MD

Individuals with multiple sclerosis (MS) can experience episodes of uncontrollable laughing and/or crying similar to people with other diseases that affect the central nervous system (for example, Alzheimer's disease [AD], stroke, traumatic brain injury [TBI], amyotrophic lateral sclerosis [ALS], Parkinson's disease [PD], and other causes of brain injury). This phenomenon is variously referred to as pseudobulbar affect (PBA), pathological laughing and crying (or weeping), emotional lability, emotional incontinence, emotionalism, and involuntary crying.

PBA is characterized by involuntary displays of crying and/or laughing, typically without inner feelings of sadness, depression, happiness, or joy. While such feelings may sometimes be present, the crying and or/laughing are not clearly related to the underlying mood. Although they may start as a response to a situation—perhaps a sad or funny movie—the feelings are more intense and last longer than would be expected. The crying and/or laughing are difficult or impossible to stop. In short, the crying and laughing of PBA are not within voluntary control and are essentially disconnected from external circumstances and internal mood states. Episodes of anger and frustration may also occur. The emotional toll of such symptoms, both on people with MS and on their family members, friends, and colleagues, tends to be quite high. Patients and families are often worried and embarrassed by this behavior, and apprehensive about it happening again. When severe, PBA may interfere with daily functioning and relationships (Work et al., 2011; Moore et al., 1997; Wortzel et al., 2008; Schiffer & Pope, 2005; Parvizi et al., 2009; Duda, 2007).

ETIOLOGY

Wortzel and colleagues (2008) write: "The generation and regulation of emotion is predicated on the structural and functional integrity of several large-scale, distributed neural networks." These networks include the limbic system and paralimbic networks that are modulated by the cerebellum (Parvizi et

al., 2001). Disease of or injury to these networks can result in "a loss of voluntary control over the generation, intensity, and contextual appropriateness of affect", i.e., of emotional expression. The neurotransmitters associated with depression and mania—serotonin, dopamine, norephinephine, and glutamate—are also involved in PBA. Although medications used to treat depression are also effective for PBA, they work far more quickly for PBA, underscoring the fundamental difference between these disorders. (See also Davison & Kelman, 1939; Langworthy & Hesser, 1940; Ironside, 1956; Parvizi et al., 2009.) Psychometric testing of individuals with confirmed PBA has suggested that the syndrome may be mediated, at least in part, by damage to the prefrontal cortex (Feinstein, 1999).

PREVALENCE

Prevalence estimates of PBA in MS have ranged from 7% to 95%, depending on terminology, diagnostic criteria, and populations being studied (Feinstein, 1997). Using criteria established by Poeck (1969)—sudden loss of emotional control (crying or laughing or both) on multiple occasions over one month, which occurs in response to nonspecific stimuli and lacks an associative, matching mood state—Feinstein and his colleagues obtained a point-in-time prevalence of 10% in a clinic sample that was representative of a large, community-based sample of MS patients. This 10% prevalence rate is similar to that proposed in two earlier studies (Langworthy et al., 1941; Surridge, 1969), but significantly lower than that previously suggested by others (Cottrell & Wilson, 1926; Pratt, 1961; Sugar & Nadell, 1943), presumably because the strict diagnostic criteria used in the study helped to differentiate those with PBA from the larger number of patients exhibiting non-specific emotional lability. Using the two validated screening instruments described below, Work and colleagues (2011) also found a 10% prevalence among people with MS.

RELATIONSHIP TO OTHER MS DISEASE FACTORS

In their case-controlled study matching MS patients with confirmed PBA with MS patients without PBA on age, gender, level of physical disability, duration of MS, and premorbid IQ, Feinstein and his colleagues (1997) found that PBA occurred equally among men and women and tended to be associated with more progressive disability and greater intellectual impairment. Patients with PBA had greater brain lesion volume than similarly disabled patients without PBA, but those with PBA were no more depressed than those without.

DIAGNOSIS

PBA is often unrecognized, undiagnosed, and untreated. Work et al. (2011) found that among 937 people with a variety of neurological conditions who had positive screenings for PBA, only three-quarters had discussed their symptoms with their physician. Of these, none had received a diagnosis of PBA. About half the patients received treatment with a medication, usually an antidepressant.

Prompt and accurate diagnosis is important in order to provide the appropriate medical treatment for the person with MS as well as education and support for the patient and family. A comprehensive clinical assessment consists of a thorough history, detailed characterization of the episodes of crying

and/or laughing, and complete medical, neurologic, and mental status examinations (Arciniegas et al., 2005). This approach will distinguish PBA from depression, but an electroencephalogram may be needed to rule out partial complex epilepsy that very rarely produces episodic laughing and/or crying (Wortzel et al., 2008).

Two instruments designed to facilitate the diagnosis of PBA have been validated in populations other than MS. The Pathological Laughing and Crying Scale (PLACS), a clinician-administered interview, quantifies several aspects of laughing and crying episodes, including their duration, relationship to external events, degree of voluntary control, inappropriateness in relation to concurrent emotions, and extent of distress following the episode (Robinson et al., 1993). The PLACS has since been used in studies of MS patients (Feinstein et al., 1997; Work et al., 2011).

The Center for Neurologic Study–Lability Scale (CNS–LS) is a self-report measure of affective lability developed by Moore and colleagues (1997). The scale reliably quantifies patients' perceptions of several aspects of PBA episodes, including frequency, intensity, lability, degree of voluntary control, and inappropriateness to context. The CNS–LS, which was initially developed for use in patients with ALS, has since been used to study patients with MS (Smith et al., 2004; Brooks et al., 2004; Work et al., 2011).

TREATMENT INTERVENTIONS

Until recently, the management of PBA relied primarily on antidepressant medications in both the tricyclic (e.g., amitryptiline, imipramine, desipramine, nortriptyline), and selective-serotonin reuptake inhibitor classes (fluoxetine, fluvoxamine, citalopram,paroxetine, sertraline). No single agent appears to be more effective than others. Confirming the disassociation between PBA and depression, improvement occurs at doses generally lower than those used to treat depression and much more quickly, often in less than one week (Wortzel et al., 2008; Arciniegas et al., 2005). Success has been reported with other agents, but with the limited research evidence, they should be reserved for people who cannot take or do not respond to first-line treatments. The include levodopa, reboxetine, venlafaxine, mirtazapine, lamotrigine, methylphenidate, dexamfetamine, and amantadine (Wortzel et al., 2008).

Trials sponsored by Avanir Pharmaceuticals with patients with MS and ALS led to FDA approval in 2010 of Nuedexta, an orally-administered combination of dextromethorphan and quinidine (Brooks et al., 2004; Panitch et al., 2006; Smith et al., 2006; Miller, 2006; Pioro et al., 2010; Garnock-Jones, 2011). It may take longer to notice an effect (Wortzel et al., 2008) up to 4–5 weeks of treatment—compared to antidepressants (Panitch et al., 2006; Wortzel et al., 2008). All medications have side effects, many interact with other drugs being taken, and some are contraindicated for certain individuals. It is important to discuss these issues thoroughly with a physician and periodically reassess the need for medication because some patients improve spontaneously. Good communication and a solid patient–doctor relationship are essential components of effective treatment.

REFERENCES

Arciniegas DB, Lauterbach EC, Anderson KE, et al. The differential diagnosis of pseudobulbar affect (PBA): Distinguishing PBA among disorders of mood and affect. Proceedings of a roundtable meeting. *CNS Spectrums* 2005; 10: 1–14.

Arciniegas DB, Topkoff J. The neuropsychiatry of pathologic affect: An approach to evaluation and treatment. *Seminars in Clinical Neuropsychiatry* 2000; 5: 290–306.

Brooks BR, Thistead RA, Appel SH, et al., for the AVP-923 ALS Study Group. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: A randomized trial. *Neurology* 2004; 63: 1364–1370.

Duda, JE. History and prevalence of involuntary emotional expression disorder. *CNS Spectrums* 2007; 12(Suppl 5): 6–10.

Feinstein A, Feinstein K, Gray T, O'Connor P. Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. *Archives of Neurology* 1997; 54: 1116–1121.

Feinstein A, O'Connor P, Gray T, Feinstein K. Pathological laughing and crying in multiple sclerosis: A preliminary report suggesting a role for the prefrontal cortex. *Multiple Sclerosis* 1999; 5: 69–73.

Garnock-Jones KP. Dextromethorphan/quinidine: In pseudobulbar affect. *CNS Drugs* 2011; 25: 435–445.

Miller, A. Pseudobulbar affect in multiple sclerosis: Toward the development of innovative therapeautic strategies. *Journal of the Neurological Sciences* 2006; 245: 153–159.

Moore SR, Gresham LS, Bromberg MB, et al. A self report measure of affective lability. *Journal of Neurology, Neurosurgery, and Psychiatry* 1997; 63: 89–93.

Panitch H, Thisted R, Smith R, Wynn D, Wymer J, Achiron A, Vollmer T, et al. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Annals of Neurology* 2006; 59: 780–787.

Parvizi J, Anderson SW, Martin C, et al. Pathological laughter and crying: A link to the cerebellum. *Brain* 2001; 124: 1708–1719.

Parvizi J, Coburn KL, Shillcutt SD, et al. Neuroanatomy of pathological laughing and crying: A report on the American Neuropsychiatric Association Committee on Research. *Journal of Neuropsychiatry and Clinical Neuroscience* 2009; 21: 75–87.

Poeck K. Pathophysiology of emotional disorders associated with brain damage. In Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology.* Amsterdam: North Holland Publishing, 1969: 343–367.

Robinson RG, Parikh RM, Lipsey JR, et al. Pathological laughing and crying following stroke: Validation of a measurement scale and double-blind treatment study. *American Journal of Psychiatry* 1993; 150: 286–293.

Schiffer R, Pope LE. Review of pseudobulbar affect including a novel and potential therapy. *Journal of Neuropsychiatry and Clinical Neuroscience* 2005; 17: 447–454.

Smith R, Berg J, Pope L, et al. Validation of the CNS emotional lability scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients. *Multiple Sclerosis* 2004; 10: 679–685.

Smith RA, Licht JM, Pope LE, et al. Combination dextromethorphan and quinidine in the treatment of frustration and anger in patients with involuntary emotional expression disorder (IEED). *Annals of Neurology* 2006; 60(Suppl 3): S50.

Work SS, Colamonico JA, Bradley WG, Kaye RE. Pseudobulbar affect: an under-treated neurological disorder. *Adv Ther* 2011; 28(7): 586–601.

Wortzel HS, Oster TJ, Anderson CA, Arciniegas DB. Pathological laughing and crying: Epidemiology, pathophysiology and treatment. *CNS Drugs* 2008; 22: 531–545.

ARTICLES OF HISTORICAL INTEREST

Cottrell SS, Wilson SAK. The affective symptomatology of disseminated sclerosis. *Journal of Neurology and Psychopathology* 1926; 7: 1–30.

Davison C, Kelman H. Pathologic laughing and crying. *Archives of Neurology and Psychiatry* 1939; 42: 595–643.

Ironside R. Disorders of laughter due to brain lesions. *Brain* 1939; 79: 589–609.

Langworthy OR, Hesser FH. Syndrome of pseudobulbar palsy: An anatomic and physiologic analysis. *Archives of Internal Medicine* 1940; 65: 106–121.

Langworthy OR, Kolb LC, Androp S. Disturbances of behavior in patients with disseminated sclerosis. *American Journal of Psychiatry* 1941; 98: 243–249.

Pratt RTC. An investigation of the psychiatric aspects of disseminated sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 1961; 14: 326–335.

Sugar C, Nadell R. Mental symptoms in multiple sclerosis. *Journal of Nervous and Mental Disorders* 1943; 98: 267–280.

Surridge D. An investigation into some psychiatric aspects of multiple sclerosis. *British Journal of Psychiatry* 1969; 115: 749–764.

The National Multiple Sclerosis Society acknowledges Teva Neuroscience and Novartis for their educational grant support of this bulletin.