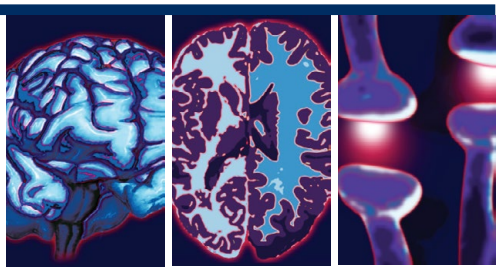
Review



Pathological Laughing and Crying Post-stroke: Liaison Psychiatrist Beware

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Abstract

Pathological laughing and crying (PLC) has been known by a number of different names, but the most widely used terms are "pseudobulbar affect," "emotional lability," "emotional incontinence," and "pathological laughing and crying." The cardinal feature of PLC is a pathologically lowered threshold for the exhibition of behavioral responses that include laughter, crying, or both. An affected individual exhibits episodes of laughter and / or crying without an apparent motivating stimulus or in response to stimuli that would not have elicited such an emotional response before the onset of their underlying neurologic disorder. Symptoms of PLC can be severe, and episodes can be persistent and unremitting.

PLC is a clinical condition that occurs in patients with various neurological disorders. The majority of evidence relates to stroke patients. The review summarizes the available data about pharmacological and behavioral treatment efficiency for this condition. Furthermore the management of these patients adds a rich avenue to the future understanding of emotional behavior.

Clinical Case

Mrs. E., an 88-year-old female, was referred to our clinic for possible apathy and / or depression. She had been admitted to the hospital for stroke rehabilitation following a right brain stem infarct with subsequent left arm weakness, left gaze and speech difficulties. She was observed by the stroke team to refuse group activities and to be tearful at times. Upon admission, Mrs. E. expressed frustration with her inability to walk without assistance.

When assessed, she denied feeling depressed. There was no evidence of neurovegetative symptoms of depression and she remained hopeful. When asked about tearfulness, she admitted to occasional bursts of "giggling" at certain times and bursts of "crying" at others. These bursts came "out of nowhere" and were uncontrollable. She reported that the episodes were embarrassing when they occurred in front of members of the care team or co-patients in the group, which caused her to avoid group activities. She reported that her subjective experience did not reflect the external manifestation of her tears. She was not confused and was not experiencing hallucinations or delusions.

Based on her symptoms and history, Mrs. E. was diagnosed with a condition called pathological laughing and crying (PLC). She was started on citalopram 10 mg, and her tearfulness and giggling subsided completely within 36 hours. Her engagement with her overall treatment plan improved as a result, and her rehabilitation was able to proceed uninhibited.

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Mrs. E.'s case demonstrates the critical importance of understanding the features of PLC and distinguishing its symptoms from those of other psychiatric conditions in order to appropriately treat this debilitating condition.

Definition of Pathological Laughing and Crying (PLC) and Clinical Presentation

Pathological laughing and crying has been known by a number of different names, but the most widely used terms are "pseudobulbar affect," "emotional lability," "emotional incontinence," and "pathological laughing and crying." First episodes of involuntary laughter and / or crying in patients with neurological conditions appeared in the literature in 1872. Charles Darwin described it as "Certain brain diseases, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping" [1]. Recently, a group proposed the term "involuntary emotional expression disorder" or IEED as more phenomenologically descriptive and less pejorative to patients [2].

The cardinal feature of PLC is a pathologically lowered threshold for the exhibition of behavioral responses that include laughter, crying, or both. An affected individual exhibits episodes of laughter and / or crying without an apparent motivating stimulus or in response to stimuli that would not have elicited such an emotional response before the onset of their underlying neurologic disorder. Symptoms of PLC can be severe, and episodes can be persistent and unremitting. The onset can be sudden and unpredictable, and has been described by some patients as similar to the onset of a seizure. Outbursts associated with PLC have a typical duration of a few seconds to several minutes and may occur several times a day [3].

In some patients, the emotional response is exaggerated in intensity but may still be provoked by a stimulus with an emotional valence congruent with the character of the emotional display. For example, a sad stimulus may provoke a pathologically exaggerated weeping response instead of a sigh, which the patient would otherwise have exhibited in that situation. In other instances, the stimulus may have an emotional valence contrary to the expression. For example, patients can laugh in response to sad news or cry in response to a moving hand in the visual field, and the expression of laughter can abruptly change to crying. Once provoked, an individual may alternate between laughing and crying without provocation [4]. In many patients, pathological behaviors are often indistinguishable from normal acts of laughter and crying. Because outbursts may occur at socially inappropriate times, this can lead to significant social stigmatization and suffering.

Causes and Prevalence of PLC

In the case of PLC, laughter and crying—emotional responses that would typically be considered healthy biological phenomena—are exhibited in inappropriate circumstances and are beyond an individual's control, suggesting a biomedical pathology. Indeed, PLC is a clinical condition that occurs in patients with various neurological disorders [2]. Estimated rates vary from 40% among patients with Alzheimer's disease (AD) [5], 7% to 10% among patients with multiple sclerosis [6], and 19% to 49% among patients with amyotrophic lateral sclerosis (ALS) [7, 8]. The incidence and prevalence of PLC among persons with traumatic brain injury (TBI) are not well established. The reported frequency of PLC during the first year after injury is 5% to 11% [9].

Among neurophysiological causes of PLC, the majority of evidence relates to stroke patients. The prevalence of PLC has been reported to be approximately 10% to 20% among patients who have experienced stroke [10], though other estimates vary widely from 7% to 48.5% of stroke survivors. The prevalence found in inpatient populations and in those assessed during the acute post-stroke period appear to be greater [11], with emotionalism affecting about 20% to 25% of survivors in the first six months after stroke and declining in frequency and severity over the first year to a rate of 10% to 15% of survivors with persistent and severe problems [12].

Neurophysiology of Post-stroke PLC

Humor is a complex phenomenon with a range of components: the perception of an unexpected incongruence (occipitotemporal area, prefrontal cortex), emotional responses (reward circuit), and volitional responses (temporal and frontal cortex). Located at the mesencephalic-pontine junction is a central coordinator of the nuclei that innervates the muscles involved in laughter (facial expression, respiratory, and phonatory). This centre receives connections from three systems: inhibitory (pre-motor and motor cortex), excitatory (temporal cortex, amygdala, and hypothalamus), and modulator (cerebellum).

Functional magnetic resonance imaging studies do not suggest a prominent role of the right frontal lobe in processing humor, as has been postulated previously [13].

In contrast, sadness is associated with feelings of being disadvantaged, loss, despair, helplessness and sorrow. It may also be called psychological pain, mental pain, emotional pain, psychic pain, spiritual or soul pain, or suffering. Research suggests that physical pain and psychological pain are of the same origin [14]. Brain regions that were consistently found to be implicated in both types of pain are the anterior cingulated cortex and the prefrontal cortex, and this may extend to other regions as well [15]. The insular cortex, posterior cingulated cortex, thalamus, parahippocampal gyrus, basal ganglia and cerebellum have also been found to be involved in the pathophysiology of sadness [16]. Crying is often an indication of sadness.

The causes of pathological laughing and crying syndrome can be classified in two ways: altered behavior associated with unmotivated happiness (Angelman syndrome, schizophrenia, mania, dementia) and interference with inhibitory/excitatory mechanisms (gelastic epilepsy, fou rire prodromique in strokes, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease and Parkinson-plus, traumatic injuries, tumors). Fou rire prodomique, or prodrome of crazy laughter, is a rare form of pathological laughter of unknown pathophysiology as the first manifestation of the stroke in the pons region [17].

According to an article published by Giacobbe and Flint [11], PLC is one of the most common post-stroke affective disorders. While the etiology of PLC in stroke patients is unknown, several physiological causes have been suggested, including lesion and imbalance in serotonergic neurotransmission. It should be noted that, in the absence of a unified definition and standardized method for diagnosing PLC used in studies cited below, conclusions must be drawn cautiously.

■ Lesion

As observed by Parvizi and colleagues in a review of the literature on the neuroanatomy of PLC, many conditions resulting in a clinical phenotype of PLC result in widespread damage to the brain, making it difficult to pinpoint regions implicated [18]. Imaging studies conducted in post-stroke patients do provide some evidence for areas that may by particularly implicated. In assessing the location of lesions in 148 post-stroke patients using MRI or CT, Kim and colleagues found that those individuals who experienced stroke in the lenticulocapsular region, basis pontis, medulla oblongata or the cerebellum were more likely to display emotional incontinence, including excessive or inappropriate laughter [19]. In a study of patients acute paramedian pontine infarcts, only those with paramedian basilar infarct were found to display pseudobulbar affect with pathological laughing [20]. Indeed, several studies provide evidence suggesting that damage to the base of the pons may be related—in particular, to the paramedian basis pontis region [3, 21-23], where it has been suggested that damage may result in the disruption of descending pathways from the brain to the cerebellum and basis pontis [18].

The study about PLC and CBT was done by Kasprisin [24]. The study group suggested an expanded neuroanatomic model was suggested emphasizing the prefrontal cortex as the center integrating information from a complex emotion and sensory loop with motor information destined for the faciorespiratory nuclei in the brainstem. Disturbance at any level in the loop was proposed to produce EI by degrading information to or from the prefrontal cortex, disrupting its inhibitory control of the nuclei.

■ Serotonergic neurotransmission

Given the significant body of evidence suggesting that PLC responds well to treatment with selective serotonin reuptake inhibitors, dysfunction of serotonergic neurotransmission has been investigated as a potential cause. However, findings have been mixed. One study using positron emission tomography in post-stroke patients identified reduced baseline serotonergic binding potentials in patients with post-stroke depression and pathological crying, with the highest binding potentials observed in limbic areas and the raphe nuclei and negligible potentials in basal ganglia and cerebellum [25]. Similarly, another study of patients with post-stroke pathological crying applied single-photon emission computerized tomography and found that serotonin transporter protein density in the midbrain and pons was lower than in controls, though this effect disappeared once a significant outlier in the patient group was removed [26].

Psychiatric Differential and Comorbidity

PLC is a disorder of emotional expression rather than a primary disturbance of feelings. Therefore, it is distinguishable from regular laughter or

crying where emotional expression is consonant with triggering stimuli and from mood disorders where a similar consonance between expression and feeling is observed. For example, laughter may be associated with feelings of happiness as in cases of excessive and pervasive elation associated with mania, and crying may accompany sadness associated with cases of excessive and pervasive depression. However, the actual laughter or crying behaviors (e.g. facial expressions, tears, etc.) are identical in PLC, mood disorders, and normal emotional expression [3]. For this reason, a diagnosis of PLC may not be immediately clear and other psychiatric differential diagnoses must be considered.

■ Mood disorders

Mania can be differentiated from PLC by the presence of irritability, grandiosity, racing thoughts, risk-taking, and hyperactivity. Evidence suggestive of social withdrawal, anticipatory anxiety or phobia related to impending episodes of laughing or crying may also be an important indicator of PLC rather than mania. Similarly, differentiating PLC and depression involves careful questioning of the patient to reveal the context of the episodes and the subjective feelings of the individual. The presence of mood, affective, cognitive and neurovegetative features of depression can facilitate the diagnosis.

However, PLC and mood disorders may also co-exist, and the possibility of this is similarly important to evaluate through careful assessment. Depression and adjustment disorder with depressive features are common in hospitalized patients who have pathological crying and have been referred to a C/L service. Of 46 hospitalized medical and surgical patients described in one study, 63% had an exclusive or co-morbid psychiatric diagnosis, with major depression being the prominent psychiatric disorder (25% of the referred patients) [27].

Reports on the relationship between depression and PLC in post-stroke patients are conflicting. In a study by House et al. [28], post-stroke patients with emotionalism scored significantly higher on measures of mood disorder (Beck Inventory mean score 7.2 vs. 5.1, $p = 0.02$, and Present State Examination mean score 10.5 vs. 6.4, $p = 0.003$). Similarly, patients with Alzheimer's disease who exhibit pathological crying have a higher frequency of depression and dysthymia than those with no PLC or with mixed PLC [29].

It should not be difficult to differentiate PLC from schizophrenia's inappropriate affect. A careful review of history, premorbid functioning, and presence of psychosis and thought form abnormalities help make the diagnosis.

Assessment Tools

Recognition is crucial for the treatment of PLC. There are several scales that have been developed to facilitate documentation of PLC and to aid in its diagnosis and assessment. One such tool available to clinicians for use with post-stroke patients is the Pathological Laughter and Crying Scale (PLCS). In 1992, Robinson and colleagues evaluated the reliability and validity of this measure among patients who had experienced stroke [30]. They enrolled 82 patients with ischemic brain injury—54 of whom had been hospitalized with acute stroke and 28 others who had requested treatment for pathological laughing and crying. Participants received standardized psychiatric and neurological assessments and completed the PLCS. The responses of the 54 acute stroke patients on the PLCS were used to evaluate the measure's psychometric properties.

In terms of screening for PLC in general, Lawson and Mcleod [31] have used the observer rating scale to grade crying or laughing and facial distress when provoked by increasingly emotion-laden stimuli. This scale has not been validated. The Centre for Neurologic Study Lability Scale (CNS-LS) is a 7-item self-administered scale that measures pseudobulbar affect, which has been validated in a large population of ALS patients [32]. Among patients with more severe cognitive and/or self-awareness deficits, structured interview of a knowledgeable informant using the Neuropsychiatric Inventory (NPI) is a useful method of screening for symptoms of PLC [9].

However, none of these scales have been rigorously validated using traditional methods. Lacking a precise clinical tool, diagnosis should involve both assessment with available scales as well as careful evaluation of the frequency of episodes and the nature of stimuli that precipitate them [12].

Treatment Evidence: Pharmacological

A patient's competence to make decisions regarding treatment and family concerns regarding the relative's disability are essential issues in management. Clinicians need to balance dealing with issues of mood and adapting to illness with

efforts to minimize provocation of pathological affect **(Table 1)**.

There is a paucity of double-blind placebo controlled studies that address the issue of treatment for PLC in patients post-stroke. The few published reports suffer from methodological problems, low numbers of treated patients, short follow-up duration, and failure to document complete neurological/cognitive/psychiatric findings, psychosocial/cultural contribution and the patients' premorbid personalities. Favorable results were reported in five double-blind placebo controlled trials involving the use of three tricyclic antidepressants and two selective serotonin reuptake inhibitors **(Table 2)** [30, 31, 33-35].

Traditionally, selective serotonin reuptake inhibitors (SSRIs) (Sertraline 12.5-200 mg daily, Escitalopram 5-20 mg daily, Citalopram 5-40 mg daily) are efficacious, safe, and well-tolerated treatments for PLC and are recommended as first-line treatments for this condition. Levodopa, Lamotrigine and the association of Dextromethorphan 30 mg / Quinidine 30 mg can be effective in managing certain cases of pathological laughing and crying [36]. Tricyclic antidepressants (Nortriptyline, Amitriptyline 15-75 mg daily), or dopaminergic agents may also be useful alternative treatments in patients in whom SSRIs are ineffective or poorly tolerated [37].

There is also some published evidence associated with treatment of PLC secondary to other conditions, such as multiple sclerosis [35] and amyotrophic lateral sclerosis (ALS) [38]

Other psychopharmacological treatments evaluated for pathological states of laughing and crying include amitriptyline [39], fluoxetine [40, 41], sertraline [42], fluvoxamine [43], L-dopa [44], lamotrigine [45], quetiapine [46] and mirtazapine [47].

Treatment Evidence: Psychosocial

Cognitive behavioral therapy has been reported as effective in case of PLC in 2004 by Kasprisin [24]. The author analyzed the occurrence, impact, diagnosis, and neuroanatomic substrates underlying proposed mechanisms producing PLC were outlined and related to traditional drug treatment. An alternative cognitive therapy for PLC was developed to compensate for deficits resulting from structural lesions by strengthening undamaged pathways, which is achieved by superimposing volitional movement on muscles affected during an EI episode. Treatment of 17 patients showed significant reductions in PLC severity and occurrence in two to eight treatment sessions over one to three weeks, and in contrast to drug treatments, the effect was sustained at 3- to 6-month follow-up.

Finally, education of patients, families, and caregivers is an important component of the appropriate treatment of PLC. Crying associated with PLC may be incorrectly interpreted as depression; laughter may be embarrassing. It is therefore critical for families and caregivers to recognize the pathological nature of PLC. Above all, individuals affected should be reassured that PLC is an involuntary syndrome that can be managed.

Long-Term Prognosis

PLC has significant effects on quality of life. One U.S. survey of 399 patients with pseudobulbar affect and 653 control patients found significantly worse scores on measures of health status, quality of life and social and occupational functioning within the PBA group (REF1). For 24% of those

Table 1: Terms employed and features implied in describing pathological affective states.

Term	Subjective emotion	Objective emotion	Defining feature
Emotional lability			Subjective and objective emotions are proportionate
Emotional incontinence			Subjective and objective emotions are out of proportion
Pseudobulbar affect	-		Presence of bulbar signs
Emotionalism			Subjective and objective emotions are appropriate
PLC	-		Objective emotion is inappropriate

Table 2: Placebo-controlled trials for PLC treatment.

Drug	Condition	PC/PL/PLC	Responders	Dose (mg)	Days to respond
Imipramine (31)	stroke	5/2/0	5/7	30-60	7
Nortriptyline (30)	stroke	13/1/0	14/14	20-100	14-42*
Citalopram (34)	stroke	12/0/3	13/15**	10-20	1-21***
Amitriptyline (33)	MS	8/2/2	8/12	25-75	2
Sertraline (40)	stroke	14/0/0	12/14	50	14
DM, Q, AVP-923 (36)	ALS	0/0/140	129/140	30/30/30+30	15

PC: Pathological Crying; PL: Pathological Laughing; PLC: Pathological Laughing and Crying; DM: Dextromethorphan Hydrobromide; Q: Quinidine Sulfate; AVP-923: A combination of DM and Q; MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis

*Majority of the patients responded in 14 days

**Patients also demonstrated the significant improvement in regards to depressed mood

***¾ of the patients responded in 3 days

surveyed, PBA was found to be a significant factor leading them to become housebound; for 9%, it was associated with being moved to supervise care.

Evidence suggests that pharmacological treatment with antidepressants may reduce frequency of laughing and crying episodes, diminish episodes of tearfulness, reduce emotional lability and improve scores on the PLCS [REF4]. This effect does not appear to be specific to particular drugs or classes of drugs or to be dependent on differences between groups. However, evidence for treatment effects is mixed and little information relating to long-term prognosis is available.

Conclusion

Inappropriate emotional expression in the form of pathological laughing and crying manifest to a varying degree in a very wide range of neurological disorders. Psychiatrists, Neurologists, and all clinicians who come in contact with these patients population need to be aware of the organic basis of this behavior. One should not presume that this is a manifestation of psychiatric illness per sé, notwithstanding the observation that clinical psychiatric treatments (pharmacological and behavioral) may be effective in this condition. Furthermore the management of these patients adds a rich avenue to the future understanding of emotional behavior.

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