Pathological Crying and Laughing in Motor Neuron Disease: Pathobiology, Screening, Intervention

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Pathological crying and laughing (PCL) has significant quality-of-life implications in amyotrophic lateral sclerosis (ALS); it can provoke restrictive life-style modifications and lead to social isolation. Despite its high prevalence and quality of life implications, it remains surprisingly understudied. Divergent pathophysiological models have been proposed, centered on corticobulbar tract degeneration, prefrontal cortex pathology, sensory deafferentation, and impaired cerebellar gate-control mechanisms. Quantitative MRI techniques and symptom-specific clinical instruments offer unprecedented opportunities to elucidate the anatomical underpinnings of PCL pathogenesis. Emerging neuroimaging studies of ALS support the role of cortico–pontine–cerebellar network dysfunction in context-inappropriate emotional responses. The characterization of PCL-associated pathophysiological processes is indispensable for the development of effective pharmacological therapies.

Keywords: pathological crying and laughing, pseudobulbar affect, emotional lability, involuntary emotional expression disorder, motor neuron disease, amyotrophic lateral sclerosis, biomarkers, magnetic resonance imaging

INTRODUCTION

The terms "pathological crying and laughing," "pseudobulbar affect," "emotional lability," and "involuntary emotional expression disorder" are often used interchangeably depending on geographical location and year of publication. Despite the differences in terminology, recurrent episodes of involuntary or exaggerated emotional expression, particularly in the form of crying and laughing, are common in several neurological conditions including, in order of prevalence: motor neuron disease (MND), traumatic brain injury (TBI), multiple sclerosis (MS), stroke, multiple system atrophy-cerebellar type (MSA-C), Alzheimer's disease (AD), and Parkinson's disease (PD) (1–6).

The disorder is particularly common in motor neuron diseases (MND): amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). Prevalence estimates vary, but between one quarter and one half of MND patients are thought to be affected (5, 7–11). While there is a paucity of studies comparing PCL prevalence across the spectrum of MND phenotypes, a recent study confirmed the relationship between clinical upper motor neuron dysfunction and PCL prevalence; PCL was most commonly identified in PLS and UMN-predominant patients (39%), followed by typical ALS (29%) and lower motor neuron (LMN) predominant groups (10%). Consistent with this pattern, there was a single case of PCL in a group of 12 patients with progressive

muscular atrophy (PMA) (12). While the manifestations of the episodes may be congruent with the person's contemporary emotional state (10, 13, 14), the magnitude of emotional responses is disproportionate to the emotive stimulus and the social context. Such episodes may cause significant distress, embarrassment, and ultimately may lead to social withdrawal (15).

The primary objective of this review is to systematically appraise PCL-related studies in MND from a dual academic and clinical perspective. We outline established and emerging disease-models based on neuroimaging, neurosurgical and neurophysiological studies. The spectrum of clinical presentations, diagnostic challenges, functional impact, and treatment options are also discussed. We preferentially use the term "pathological crying and laughing" (PCL) in this review, in its broadest sense: encompassing the entire spectrum of presentations. Furthermore, while PCL in ALS is the primary focus of this review, we draw further information from PCL studies in other neurological conditions to discuss unifying, symptom-specific, pathophysiological concepts.

METHODS

A formal literature search was conducted using PubMed/Medline and Embase using the terms "pathological crying and laughing," "pseudobulbar affect," "emotional lability," involuntary emotional expression disorder" separately, and in combination with terms "amyotrophic lateral sclerosis," "motor neuron disease," "pseudobulbar palsy," "clinical trials," "treatment," and "pathology." Only articles in English, published between 1988 and October 2018 were included. A total of 220 articles met these criteria; these were systematically reviewed for information relating to diagnosis, disease-mechanisms, anatomical localization, and treatment options.

Historical Context and Terminology

The abundance of terms used to describe this syndrome epitomizes the tireless efforts to characterize the underpinnings of both physiological and pathological emotional expression. Charles Darwin observed in 1872 that "certain brain-diseases, as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping" (16). Oppenheim (17) used the term "pseudobulbar affect" (PBA), based on the important observation that the disorder commonly occurs in association with motor features of pseudobulbar palsy, a condition resulting from

bilateral corticobulbar tract pathology. Although this association is still well-recognized (13, 18), the term PBA may be misleading; new evidence suggests that corticobulbar tract dysfunction alone is neither necessary, nor sufficient to cause PCL (19–23). "Emotional Lability" (EL) was described by Pierre-Marie as early as 1892, a term still commonly used in the literature (24). The term pathological crying and laughing (PCL) was used by Wilson in his influential essay of 1924, in which he introduced his unifying theory of the disorder (25). More recently, the term "involuntary emotional expression disorder" (IEED) has been proposed to encompass the wider range of emotional symptoms which may accompany the disorder (26).

Clinical Presentations, Diagnosis and Monitoring

A useful conceptualization of PCL is that symptoms may lie on a spectrum, (27) with infrequent, mood congruent but disproportionate episodes at one end, and frequent, mood incongruent episodes at the other. While there is considerable variability in episode type and character across patients, within individuals episodes tend to be consistent over time in terms of symptom type (i.e., uncontrolled laughing or crying), the context in which the episodes recur, the severity, duration, and the degree of voluntary control that the individual retains over the episodes (26, 28). The wide range of presentations coupled with the lack of unifying terminology, has hampered efforts to establish widely adopted diagnostic criteria. Several criteria have been proposed and later revised, reflecting evolving concepts of the PCL (29). *Poeck's* 1969 criteria (30), focus on episodes that are entirely situation inappropriate or unrelated to the patient's internal emotional state. Recent criteria are less restrictive, encompassing presentations across the entire spectrum (26, 27). Revised criteria proposed by Cummings et al. for "involuntary emotional expression disorder" (IEED) (26) are inclusive of episodes that are either disproportionate to the emotive stimulus or to the individual's internal emotional state. The episodes must represent a distinct change from the patient's emotional reactivity prior to the onset of a neurological disease. These criteria specifically require the exclusion of alternative causes for the symptoms; mood, facial tics, dystonia, or substance effects. More recently, Miller et al. proposed to include supportive features such as the presence of pseudobulbar signs and a proneness to anger (27). The latter reflects accruing observations from several studies (14, 23, 27, 31).

PCL needs to be carefully distinguished from mood disorders through careful clinical evaluation (1, 9, 32). A key difference is that crying in depression or excessive laughter in mania occur in the context of pervasive low or elevated mood, respectively (33). In the case of clinical depression, associated symptoms can also be identified such as anhedonia and insomnia (27, 34). Although some studies report an association between depression and PCL (12), more commonly, no significant association is found (8, 13, 35). The clinical distinction may be particularly challenging in cases where pathological crying co-exists with depressive symptoms (2, 36). Emerging evidence suggests that PCL may respond to selective serotonin reuptake

inhibitors (SSRIs) within days, whereas depression typically only responds to pharmacological intervention after several weeks (37).

Similarly to the multitude of diagnostic criteria proposed for PCL, several screening and symptom severity scoring instruments have been developed. While not all of these have been extensively validated, these tools have been used in both academic research and clinical trials. The pathological laughing and crying scale (PLACS) was validated for use in stroke patients with "PBA" in 1993. The authors used it as an efficacy measure in a small placebo-controlled trial of nortriptyline; treatment was associated with symptom reduction (38). The Center for Neurologic Study-Lability Scale (CNS-LS) was introduced as a self-reported measure of "affective lability" in ALS (39). This short, self-administered questionnaire consists of 7 items; 4 relating to labile laughing and 3 relating to crying. The scale evaluates subjective burden of symptoms over the preceding week, in terms of episode burden and severity. While this scale relies on retrospective patient account, it has been shown to be an accurate indicator of episode frequency (40). The CNS-LS has been adopted as an efficacy measure in several recent clinical trials (41–44). Another assessment tool, the "emotional lability questionnaire" (ELQ) has also been validated in ALS. It extends the period over which symptoms are assessed from one up to four weeks prior to screening, which helps to capture patients who experience less frequent episodes (45, 46). In addition to PCL, it also includes a specific section on abnormal smiling. One of the strengths of the ELQ is that it includes the caregiver's perspective, which helps to identify lack of insight if significantly discordant scores are given by the patient and the carer. Interestingly, in ALS, there is significant agreement between patient and caregiver scores, indicating that patients are keenly aware of PCL symptoms (45). This concordance contrasts with behavioral deficits in ALS-FTD, where patient reports may differ substantially from caregivers reports (47).

Although screening instruments are valuable tools for identifying and monitoring PCL, they don't evaluate the impact of PCL on individual patients. There is evidence, that PCL impacts on the quality-of-life and social functioning of affected individuals (48) and may contribute to carer distress (49). There is a growing effort to understand the individualized experiences of patients with PCL (14, 35, 50, 51).

DISEASE MODELS

Traditional and Revised Hypotheses

The traditional PCL model, proposed by Wilson in 1924 has, until recently been the most widely accepted one (25). Under physiological circumstances, it contends, emotional expression is influenced by both voluntary motor and involuntary emotional centers. These pathways descend onto the medullary "facio-respiratory" centers, which mediate the facial movements and breathing patterns necessary to convey emotion. This model predicts that disruption of the descending voluntary inputs to the brainstem, such as may occur in pseudobulbar palsy, results in disinhibition of involuntary emotional influence on expression. In support of this model, Wilson cited cases of dissociated emotional and voluntary facial expression, such as the observation that some patients with pseudobulbar palsy are unable to make voluntary facial movements but can be observed to smile, laugh or cry in response to emotional stimuli. This phenomenon is usually termed "voluntary facial palsy" (52). The contrary, "mimic palsy" or "emotional facial palsy" is sometimes observed, in which a patient with entirely normal voluntary facial movements, exhibits a complete lack of movement on one side of the face when reacting to emotional stimuli (53).

Parvizi et al. highlighted several limitations of the traditional model (54). Patients with bilateral voluntary facial paralysis, as in Wilson's example do not seem to be excessively prone to PBA, as would be predicted by the "disinhibition" model. Furthermore, patients with severe PBA symptoms are usually able to voluntarily mimic laughing or crying, indicating that involuntary expression can occur alongside intact voluntary control.

The revised model of PCL draws on the increasing appreciation of the role of the cerebellum in cognitive processes (55, 56). This model suggests that the cerebellum plays a key role in gating and modulating emotional output in response to contextual cues from cortical and limbic areas (54). Modulation is believed to be mediated through cortico-ponto-cerebellar pathways. In normal motor control, the cerebellum is known to modulate motor output in response to multiple sensory inputs; disruption of these inputs produces motor modulation deficits, including dysmetria. The involuntary emotional expression resulting from disruption of cortico-ponto-cerebellar emotional circuits has, analogously been termed "affective dysmetria" (57).

Insights From Imaging and Neurophysiological Studies Across Neurological Diseases

Research over the past 30 years has led to a revision of the traditional model of PCL; studies have provided strong evidence to refute a simple causal relationship between PCL and corticobulbar tract dysfunction (58). Instead, a disruption within a widely dispersed network of emotional control appears to underlie the disorder. **Tables 1**, **2** provide an overview of studies highlighting key anatomical regions implicated in the pathogenesis of PCL. An MRI-based lesion study in post-stroke pathological crying classified patients based on symptom severity (70). It found a positive pathoanatomical correlation between lesion size and location and pathological crying severity. Bilateral pontine infarcts were associated with greatest severity, while bilateral anterior hemispheric infarcts were associated with moderate PCL severity.

Among the likely neurotransmitters involved in the physiological expression of emotion, serotonin and glutamate have received particular attention (27, 71, 74). Evidence for dysfunction within these neurotransmitter pathways in PCL comes from the success of serotonergic (31, 38, 75), and anti-glutamatergic drugs (42) in PCL treatment. The selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are thought to work by increasing

TABLE 1 | Neuroanatomical regions implicated in PCL circuitry based on clinical observations.

References	Neurological condition	Terminology	n	Main study findings	Anatomical localization
CLINICAL CASES					
Parvizi et al. (3)	Cerebellar cyst	PC	1 PC+	Midline cerebellar cyst	Cerebellum (vermis)
Parvizi et al. (59)	MSA-C	PCL	PCL+: 1 PM and 9 clinical MSA-c	Pathological changes confined to cerebellum, basilar pons and olives	cerebellum and brainstem connections
Chattha et al. (60)	PD with STN-DBS	PBA	1 PBA+	Laughter with DBS stimulation of sub-thalamic nuclei	Basal ganglia: STN
Saini et al. (61)	CPM	PBA	1 PBA+	Basilar pons demyelination	CPC tracts: Pons
Martin et al. (62)	Anti-Yo cerebellar degeneration	PBA	1 PBA+	Breast cancer presenting as uncontrollable crying and motor cerebellar syndrome	Cerebellum
McCullagh et al. (20)	ALS	PCL	10 PCL + 8 PCL- 10 HC	Executive dysfunction in PCL+	Pre-motor frontal cortex
Palmieri et al. (45)	ALS	EL	29 EL+	Correlations: (1) bulbar disease and EL (2) bulbar disease and executive impairment. However, no correlation between PCL and cognitive changes	Extra-motor frontal lobe
Olney et al. (13)	ALS	PCL	21 PCL+, 14 PCL–	Laboratory study: PCL+ had impaired regulation of facial expression	Frontal cortex
Hübers et al. (63)	ALS	PCL	10 PCL+, 10 HC	PCL+ more susceptible to mood-incongruent stimuli than controls, PCL associated with emotional lability/suggestibility	Frontal cortex
NEUROSURGICAL CASES					
Krack et al. (64)	PD with STN-DBS	Mirthful laugh	2 PL+	Associated with DBS stimulation of bilateral STN in one patient and right STN in other	Basal ganglia: STN
Okun et al. (65)	PD post-thalamotomy	PBA	1 PBA+	Post-thalamotomy pathological laughing	Basal ganglia
Okun et al. (66)	PD with STN-DBS	PC	1 PC+	Pathological crying with DBS stimulation of left sub-thalamic nucleus	Basal ganglia: STN
Famularo et al. (67)	Cerebellar ependymoma	PL	1 PL+	PC as sole presenting feature of cerebellar vermis tumor abutting the floor of the fourth ventricle	Cerebellum (vermis)
Low et al. (68)	PD with STN-DBS	PC	1 PC+	Pathological crying with DBS stimulation in region of caudal internal capsule (without signs of PBP)	Internal capsule (caudal)
Wolf et al. (69)	PD with STN-DBS	PC	1 PC+	Pathological crying with DBS stimulation of sub-thalamic nuclei	Basal ganglia: STN

CPC, cortico-ponto-cerebellar pathways; CPM, Central Pontine Myelinolysis; Dx, Diagnosis; HC, Healthy control; MSA-C, Multiple system atrophy, cerebellar type; n, sample size; PBP,Pseudobulbar Palsy; PC, Pathological crying; PL, pathological laughing; PM, Post-mortem/Autopsy; SERT, Serotonin transporter; STN-DBS, Subthalamic nucleus, deep brain stimulation; UMN, Upper motor neuron; WM, White matter.

availability of serotonin at synapses in corticolimbic and cerebellar circuits (32).

A SPECT study found reduced brainstem serotonin receptor (SERT) densities in post-stroke PCL (71), providing further evidence of the role of serotonergic transmission in PCL. Serotonergic neurons from the raphe nuclei have widespread projections from the paramedian brainstem to cortical, subcortical, and cerebellar targets (76, 77). Also consistent with the serotonin hypothesis, lesions involving these nuclei and their projections are frequently associated with PCL (70). An MRI study of PBA in MS patients showed an association between symptoms and lesions in key regions: brainstem, bilateral inferior parietal, and medial frontal regions (23).

There is increasing recognition of the role of sensory deafferentation of the cerebellum in PCL (78). Evidence from neurophysiological studies in PCL suggests that the cerebellum

may filter emotional output through a "gate-control" mechanism (79). At a cellular level, cerebellar Golgi cells may play a crucial role in gate-control. It has been demonstrated that Golgi cells, when activated from various peripheral inputs, show decreased firing rate, thereby reducing inhibition of granule cells (80). This finding, suggests, that rather than providing "gain-control," Golgi cells may act as a "context-specific gate" on transmission through the mossy fiber–granule cell pathway. A study of PCL in MSA-cerebellar type found a prevalence of 36% in this condition, in which clinically-significant cerebellar dysfunction is apparent (59).This prevalence estimate exceeds those of studies in idiopathic Parkinson's disease (5), suggesting that cerebellar pathology is linked to PCL in Parkinsonian disorders. Several neurological and neurosurgical case-reports have linked PCL to cerebellar pathology, especially in association with vermis pathology (3, 62, 67, 81). These studies support the cerebellar

TABLE 2 | Anatomical conclusions of neuroimaging studies in PCL.

References	Neurological condition	Terminology	n	Main study findings	Anatomical localization
Andersen et al. (70)	Stroke	PC	12 PC+	Isolated, bilateral pontine lesions in most severe cases; bilateral basal ganglia lesions in intermediate group; unilateral subcortical lesions in milder	Pons (raphe nuclei), Basal ganglia, Subcortical WM
Murai et al. (71)	Stroke	PC	6 PC+ 9 PC−	Reduced SERT binding ratios in midbrain/pons in PC	Brainstem (raphe nuclei)
Tateno et al. (72)	TBI	PCL	92 PCL+	PLC associated with traumatic frontal lobe lesions, particularly lateral left frontal lobe	Frontal lobes (esp. left lateral)
Ghaffar et al. (23)	MS	PBA	14 PBA+ 14 PBA−	Greater lesion volume in PBA subjects in brainstem; bilateral inferior parietal and medial inferior frontal; right medial superior frontal	Brainstem; Parietal lobes (bilateral inferior); frontal; basal ganglia
Floeter et al. (10)	ALS	PBA	22 PBA+ 25 PBA− 28 HC	PBA+ (vs. PBA-): reduced FA underlying left motor cortex, Increased MD underlying the frontotemporal cortex, the transverse pontine fibers, and MCP. IC pathology in both groups	widespread disruption of CPC tracts in PBA
Wang et al. (21)	Stroke	PCL	56 PCL+, 56 PCL−	PCL associated with pontine infarcts, particularly paramedian lesions	Pons
Christidi et al. (73)	ALS	PCL	28 PCL+ 28 PCL− 25 HC	PCL+ vs. PCL-: Reduced GM volume: left orbitofrontal cortex, frontal operculum, putamen; and bilateral frontal poles. WM pathology: decreased FA in left cingulum bundle, posterior corona radiata	Frontal cortex: left orbitofrontal; and operculum Cingulate WM

CPC, cortico-ponto-cerebellar pathways; CPM, Central Pontine Myelinolysis; Dx, Diagnosis; HC, Healthy control; MSA-C, Multiple system atrophy, cerebellar type; n, sample size; PBP, Pseudobulbar Palsy; PC, Pathological crying; PL, pathological laughing; PM, Post-mortem/Autopsy; SERT, Serotonin transporter; IC, Internal Capsule; STN-DBS, Subthalamic nucleus, deep brain stimulation; UMN, Upper motor neuron; WM, White matter.

gate-control theory of emotional expression, indicating that the disruption to cortico-ponto-cerebellar emotional circuitry may underlie this disorder.

Insights From PCL Studies in Motor Neuron Disease

Corticobulbar tract dysfunction in ALS has been linked to cognitive impairment, and in particular to executive dysfunction (82). A study of PCL in ALS found an association between PCL and poor performance in executive tasks, implicating pre-frontal cortical areas in the disorder (20). Other studies, in contrast have found no such associations (8, 45). Systematic studies of social cognition in patients with PCL are lacking. Despite the conflicting findings, evidence from imaging and neurophysiology studies support the involvement of frontal cortical dysfunction in PCL (73, 79).

Advanced neuroimaging techniques enable the characterization of symptom-specific structural (83, 84), and functional (85, 86) alterations, providing insights into disease mechanisms (87, 88). Given the high prevalence of PCL in MND, it provides unique opportunities to explore PCL-specific network alterations (58). Floeter et al. used MRI diffusion methods to explore the white matter signature of PCL in ALS and PLS (10). Both ALS and PLS patients exhibited considerable white matter pathology in the corticospinal tracts and the corpus callosum. PCL-associated white matter changes were identified in frontotemporal regions, transverse pontine fibers and the middle cerebellar peduncles. A recent multimodal MRI study by Christidi et al. used the CNS-LS to divide a large group of ALS patients into PCL-positive and PCL-negative groups (73). The PCL-positive group showed significant gray and white matter changes compared with the PCL-negative group. The gray matter assessment found reduced volume of left orbitofrontal cortex, operculum, putamen, and of bilateral frontal poles. White matter analyses revealed diffusion abnormalities in the left cingulum, the posterior corona radiata and in the left middle and bilateral inferior cerebellar peduncles. The finding of cerebellar involvement in PCL in ALS again implicates cerebellar dysfunction in the pathophysiology of PCL, across a range of neurological diseases. While it is challenging to detect cerebellar signs clinically in the presence of pyramidal and lower motor neuron degeneration in ALS, imaging studies suggest that cerebellar degeneration is an important feature of ALS pathology, which is likely to contribute to PCL (89–91).

THERAPEUTIC OPTIONS

Antidepressant Medication in the Management of PCL

Divergent pharmacological strategies have been explored in the management of PCL. SSRIs and TCAs are the most frequently used off-label medications (75). Surprisingly, we did

not identify any placebo-controlled trial of any antidepressants for PCL in ALS. In the absence of robust clinical trial data in ALS, evidence from other neurological conditions, most-commonly stroke, is used to guide treatment. There have been positive results in small placebo-controlled trials of SSRIs including citalopram (92), fluoxetine, (31) sertraline (93) and of the TCA nortriptyline (38), in post-stroke PCL. Case-reports and uncontrolled trials reported symptom improvement with amitriptyline (94) and duloxetine (95) in ALS; memantine in AD (96); and mirtazapine in post-stoke PCL (97). A 2010 Cochrane review of treatments for "emotionalism" after stroke concluded that there is "suggestive but not definitive" evidence that antidepressants reduce frequency of symptoms, although it highlighted "several methodological deficiencies" in available studies (98).

Management of PCL in Motor Neuron Disease

In 2010, dextromethorphan/quinidine (Dx/Q) became the first FDA-approved treatment for PCL, following more than a decade of research into the potential benefits of the commonly-used anti-tussive for this indication (99). Dextromethorphan acts as a non-competitive glutamate antagonist on NMDA-receptors and as an agonist on sigma receptors (100). When administered alone, it is rapidly metabolized by first-pass metabolism through the cytochrome P450-2D6 system. The addition of the CYP-2D6 inhibitor, quinidine, dramatically increases the bioavailability of dextromethorphan (101). In 2004, a randomized, double-blinded study compared treatment with Dx/Q (30/30 mg twice daily) with dextromethorphan alone in ALS patients with PBA, defined by a CNS-LS score ≥ 13 (43). The combination not only reduced CNS-LS scores and episode frequency but also led to improvements in quality-of-life measures. Treatment-related side effects including nausea, dizziness, somnolence, and loose stools were relatively common however; about one quarter of patients withdrew from treatment, the majority within 1 week (102). A follow-up study in 2010 assessed whether a lower quinidine dose would reduce adverse effects relative to the earlier trial, while maintaining efficacy (42, 103) The study randomized ALS ($n = 197$) and MS ($n = 129$) patients with PBA to Dx/Q 30/10 mg BID, Dx/Q 20/10 mg BID or placebo BID. Both Dx/Q doses were found to reduce episode frequency, CNS-LS scores and to improve the likelihood of symptom remission compared to placebo. There was a lower discontinuation rate than in the earlier trial. It is interesting to note the considerable placebo response rate across efficacy endpoints in both trials. It must also be pointed-out that CYP450 2D6-poor metabolizers (104) were excluded from the efficacy and safety analyses raising questions about the requirement to screen for this phenotype prior to prescribing (105). Efficacy outcomes were also maintained in a 12-week open label extension study (106). A 52-week open-label study in 553 patients, including 199 patients with ALS, reported no serious drug-related adverse effects (75). However, clinicians must be cognizant of underlying cardiac conditions as quinidine can cause serious QT-interval prolongation (107).

Limitations of Currently Available Treatments

While the emergence of the first FDA-approved drug for PCL is an important advancement, the effective treatment of PCL remains challenging. Unfortunately, there have been no head-to-head trials of Dx/Q and any commonly used antidepressant. This knowledge-gap is particularly problematic given the current cost of Dx/Q, which may be prohibitive. Not only is the price of the approved combination product higher than alternative options, it is dramatically more expensive than the combined cost of its individual components (108). Finally, although Dx/Q was granted approval by the European Medicines Agency (EMA) in 2013, it was subsequently withdrawn by the manufacturer in 2016, on commercial grounds. (109, 110) A 2017 Cochrane review of "symptomatic treatments" in ALS highlighted emotional lability, as a symptom for which there is a "significant gap" in studies regarding the effectiveness of available treatments (111). There is a pressing and unmet need for robust clinical trials of antidepressants in the management of PCL. Finally, there is evidence that ALS patients and carers, lack awareness of the association between PCL and their underlying neurological condition (112), highlighting the importance of enquiring about PCL symptoms in patients with high-risk conditions, such as ALS.

CONCLUSIONS

Pathological crying and laughing is a shared symptom of many neurological conditions across infective, vascular, inflammatory, and neurodegenerative etiologies. Various terminologies have been used to encompass the heterogeneity of symptoms, which vary in severity, emotional congruity, frequency, and degree of control. After centuries of insightful observations, lesion studies and case reports, neuroimaging methods now provide long-awaited *in-vivo* insights into the specific pathophysiological mechanisms underlying the disorder. Patho-anatomical correlations indicate, that irrespective of the pathology (i.e., neurodegeneration, stroke, demyelination, TBI), the disorder occurs due to disruption in circuits involved in the initiation and modulation of emotional output. Key components of the network include sensori-motor cortical regions and their pontine and cerebellar connections. Further research is needed to elucidate the specific role of individual components within the network and their interactions. Effective symptomatic treatments are available; however, further studies are needed to establish individualized treatment strategies for patients experiencing impaired social or occupational functioning.

AUTHOR CONTRIBUTIONS

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