

# Treatment of Pathological Crying with Citalopram<sup>1</sup>

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Pathological laughing and/or crying may occur as a concomitant symptom of various diseases of the central nervous system. No known anatomical basis for any of these disorders exists at present. However, references to a disturbance in central serotonergic neurotransmission have become frequent in the literature, implicating this as an important etiological factor. In the present communication three cases of successful treatment of pathological crying using the SSRI citalopram are reported. Besides the response of pathological crying in cerebral ischemia to SSRIs, which has already been described in earlier publications, this is the first report on the successful administration of citalopram for treating pathological crying in Parkinson's disease. Onset of response was very rapid in all cases.

## Introduction

Pathological laughing and/or crying has been observed as a concomitant symptom in a large number of neurological conditions with varying backgrounds. This occurs especially frequently in amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) or vascular lesion [2,9,11,12,17,19]. Rarer manifestations have been described, such as in tumors with compression of structures of the brain stem [7,16,21], vascular malformations [4], Parkinson's disease [8,13], and closed craniocerebral trauma [31].

Poock defined the following characteristics for pathological laughing and crying [22,23]:

- Sudden, frequently occurring loss of emotional control with laughing, crying or both;
- Manifestation after non-specific, often emotionally neutral stimuli;
- No connection with prevailing mood.

Up to now, no unequivocal anatomical substratum responsible for pathological laughing and crying could be identified. It is probable that the uncoupling of cranial motor nerve nuclei and supranuclear integrative centers from their cortical control is of crucial importance [30]. Ross drew attention to the important distinction between pathological laughing and crying with and without pseudobulbar paralysis [25]. In manifestations without pseudobulbar paralysis, in particular lesions of the basal forebrain (unilateral or bilateral), of the medial temporal

region, of the diencephalon and the tegmentum have been found [4,25]. In functional terms, the impairment of central serotonergic neurotransmission appears to play a key role [2].

The most extensive experience in treating pathological laughing and crying has been gathered in the treatment of vascular lesions (for a review, see Andersen [3]). Favorable results have been reported under treatment with levodopa and amantadine [29], with tricyclic antidepressants (TCA) [24,26] and with the selective serotonin reuptake inhibitors (SSRI) sertraline [6,20], paroxetine [9], fluoxetine [18], and citalopram [1].

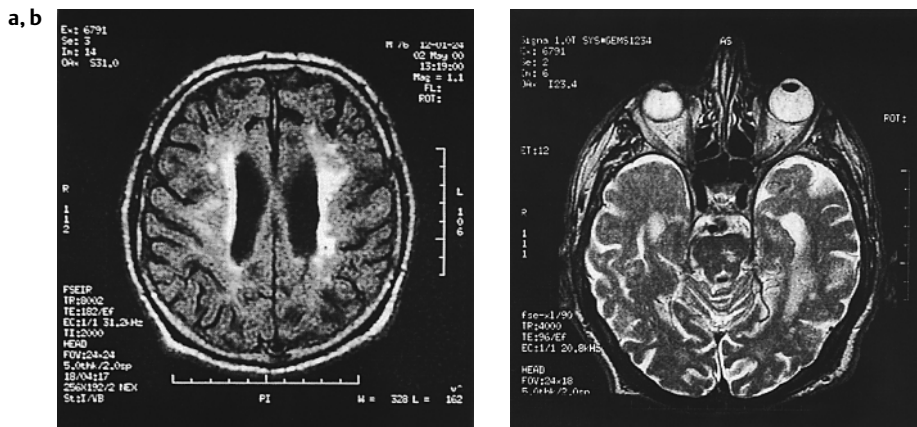
Placebo-controlled, double-blind studies have been performed using amitriptyline (Schiffer et al. [26], 12 patients included), nortriptyline (Robinson et al. [24], 28 patients included), and citalopram (Andersen et al. [1], 16 patients included). In all treatment groups, there was a statistically significant improvement of pathological crying compared to placebo. However, in a few patients suffering from ALS, pathological crying was replaced by pathological laughter or preexisting pathological laughter was accentuated during antidepressant treatment [18].

In the present communication, we will report on a case of Parkinson's disease and two cases of cerebral ischemia (one case of brain stem ischemia and one case with left hemispheric ischemia) with pathological crying. Here, practically complete disappearance of the pathological crying could be attained under treatment with citalopram.

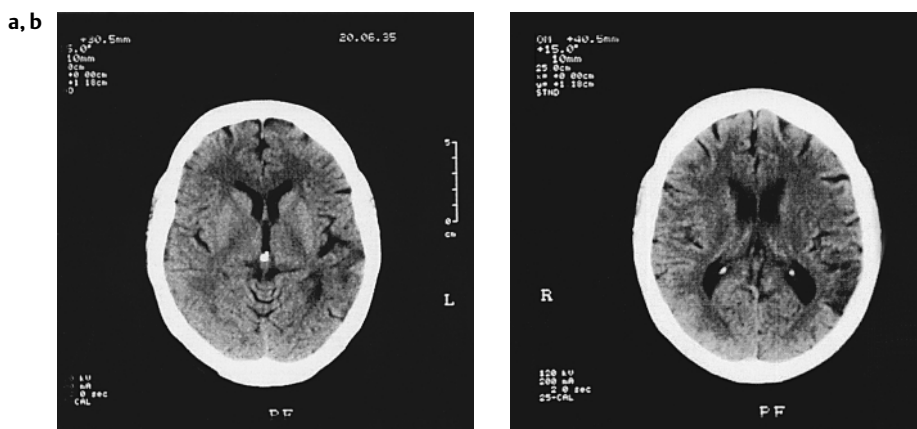
## Case 1

The 66-year-old patient (G.E.) had been suffering from idiopathic parkinsonian syndrome since 1989. Symptoms were resting tremor, tetra-rigidity that was more severe on the right side, hypomimia, rare blinking (more pronounced on the left than the right), small-step gait as well as reduced concomitant movement of the arms and start inhibition which was difficult to control therapeutically.

<sup>1</sup> Essential parts of this communication have been presented on the occasion of the 1st International Forum on Mood and Anxiety Disorders, Monte-Carlo, Monaco, November 29 – December 2, 2000



**Fig. 1** Brain MRI of case 2 showing multiple white matter lesions both supratentorially (a) and in the left pontine region of the brainstem (b).



**Fig. 2** Cranial CT of case 3 showing hypodensities in the brain areas supplied by the parieto-occipital branch of the left middle cerebral artery (a) and (b).

Extracranial Doppler sonography of the vessels of the neck carried out in 1995 suggested a stenosis of the left vertebral artery, which was differentially diagnosed as hypoplasia of the left vertebral artery.

Duplex sonography revealed occasional hyperechoic plaques on both sides near the carotid bifurcation. Transcranial Doppler sonography showed normal arteries at the base of the brain; transnuchally, there was also a suspicion of distal vertebral arterial stenosis, differentially diagnosed as hypoplasia of the left vertebral artery.

The EEG carried out in 1995 revealed a slight general change and focal findings in the left temporal lobe and left temporo-basal lobe with grouped focal dysrhythmias.

The cranial CT performed in November 2000 showed a small infarction lateral of the left anterior ventricle.

Under outpatient treatment with the COMT inhibitor, tolcapon (3 × 100 mg), plus 300 mg levodopa (with decarboxylase inhibitor) and selegilin (2 × 5 mg) in our hospital's neurology department, he reported frequent pathological crying (average frequency: 12 times per hour) in June 1998. Attempted treatment with the St. John's wort preparation Spilan® 425 at a dosage of 2 × 1 capsule per day did not result in any improvement. In August 1999, a consultative psychiatric

examination was therefore carried out with the following findings: cooperative patient with clear consciousness as well as complete orientation in space and time and in relation to persons, speaking with a relatively unmodulated low voice. Mood was indifferent; drive and affective modulation were somewhat reduced. From a formal point of view, thinking was slowed down and rambling. Thought content was focussed on the physical symptoms. Attention and concentration still appeared appropriate to age in the investigation situation. Capacity to remember and recall was reduced. Recording the case history, examination, and exploration all lasted about one hour. During this time, the patient cried suddenly and unexpectedly in a manner that was not adequate to the situation on 13 occasions. This was mostly a reaction to being spoken to on emotionally neutral topics. Above and beyond the known parkinsonian syndrome, an organic brain syndrome with pathological crying was diagnosed, and the recommendation was made to substitute St. John's wort for citalopram at an initial dosage of 10 mg per day. After two weeks of treatment, a marked improvement in the pathological crying was noted.

In April 2000, the patient reported that the loss of emotional control in terms of pathological crying no longer occurred under continued use of citalopram (10 mg per day). Meanwhile, the absence of this symptomatology has been documented for the last 17 months, and the patient is still taking 10 mg of citalopram per day.

## Case 2

The 76-year-old patient (Z.K.) was admitted as an inpatient to our neurology department in April 2000, as his wife had noticed that he was increasingly confused and weepy three days previously. Moreover, there was uncertain gait with dragging behind of one leg and the left corner of the mouth drooped. He frequently started to choke on his food, and there was coughing and slurred speech.

Known previous illnesses were a condition after amputation of the right thigh and amputation of the left lower leg in 1945 with recurring phantom-limb pain. In 1994, cerebral ischemia had developed on the left with subsequent symptomatic (secondarily generalized) tonic clonic convulsions that ceased under carbamazepine at 300 mg. The known risk factors were arterial hypertension and hyperlipidemia.

The neurological investigation on admission showed a weakness of the oral branch of the left facial nerve. Hearing was reduced on both sides. The retching reflex was weak, and there was hypoglossal paresis on the left-hand side. There was discrete pronation and a tendency to fall in postural tests on the left-hand side, but otherwise no latent or manifest pareses. As far as they could be tested after amputation, monosynaptic reflexes were more pronounced on the left. The execution of the finger-nose test on both sides was rather unsteady. There was bradydysdiadochokinesis on the left. Sensitivity was normal.

According to the psychiatric findings, the patient was lucid, with clear consciousness (even though he was tired) and unimpaired orientation both in space and time and in relation to other people. His mood appeared to be indifferent. Drive and affective modulation were reduced. In the course of the investigation, intellectual grasp and ability to concentrate corresponded to his age, as did formal thinking. Without emotional stimuli, the patient cried suddenly in a manner inappropriate to the situation, frequently just on being spoken to. These episodes occurred eight times per hour on average.

In supplementary diagnostics, the laboratory investigations revealed hypercholesterolemia of 278 mg/dl, HDL at 51 mg/dl, LDL at 156 mg/dl. Serum homocysteine was raised (19.8  $\mu$ mol/l). The CSF findings, including borrelia diagnostics and oligoclonal IgG screening, were normal.

The brain NMRI showed extensive multiple infarction with detection of supratentorial as well as infratentorial multiple white matter lesions, especially in the left pontine region. Moreover, there was marked medullary and cortical atrophy.

Extracranial color-coded duplex ultrasonography showed discrete long thickenings of the wall of the common carotid artery on both sides. Moreover, there were, if anything, hypochoic plaques at the bifurcation on both sides with a degree of stenosis at less than 30% and a pronounced coiling of the left internal carotid artery distally without stenosis. Vertebral artery imaging showed it to be narrower on the right than on the left, with greater pulsatility on the right than on the left.

In transcranial Doppler and color-coded duplex ultrasonography, the vertebral artery was imaged transnuchally on both sides and the basilar artery was imaged at a depth of up to

100 mm. There was a low flow rate (less than 30 cm per second) and high pulsatility. This is consistent with microangiopathy. Transtemporally, the finding was normal.

We diagnosed brain stem ischemia with hemiparesis on the left, pathological crying and hypoglossal paresis on the left, dysarthria and dysphagia within a multiple infarction process (risk factors: arterial hypertension, hypercholesterolemia).

With regard to the pathological crying, treatment with citalopram at 20 mg per day was started. The frequency of episodes of pathological crying decreased under this treatment during the three-week stay in hospital from an initial rate averaging eight per hour to an average of one to two per day.

This improvement was maintained for a period of nine months, continuously taking citalopram at 20 mg per day. The patient then developed increasing cognitive deficits corresponding to a state of multiple infarction dementia.

## Case 3

In August 2000, the 65-year-old female patient (S.M.) was admitted for the third time as an inpatient at our neurology department. She was suffering from exhaustion depression after the death of her husband, who had required nursing for many years, as well as increasing overstrain from nursing her daughter who had multiple sclerosis. In particular, there was a rising incidence of disturbed impulse control in the last eight weeks as well as very frequent, sudden and unmotivated bouts of pathological crying. This greatly burdened her, especially in dealing with other people. In addition, speech disorders, which had occurred subsequent to a left parieto-occipital infarction of the middle cerebral artery from April 1996, had gotten worse.

A moderately severe amnesic aphasia (diagnosed using the Aachen Aphasia Test) with a disorder in recalling words and slight disturbances in the ability to remember and recall in undisturbed attention and concentration were detected in the neuropsychiatric investigation. The patient was cooperative, had clear consciousness, and complete orientation in relation to space, time and other individuals. Affective modulation was present, drive was somewhat reduced, the mood was depressive and the patient appeared exhausted. Other findings were slight bradydiadochokinesis and fine motor disorder of the right arm and deficient innervation of the oral branch of the facial nerve, slight ungainliness in the Romberg test, but otherwise, findings were normal.

In conversation, sudden crying occurred several times although emotionally stressful topics had not been addressed. She reported a frequency of crying of six to ten times in the course of a normal day.

The patient scored 22 points in total on the Hamilton depression rating scale (21 items) and 19 points on the Beck depression inventory.

Supplementary investigations revealed a discrete wedge-shaped hypodensity in the areas supplied by the parieto-occipital branch of the left middle cerebral artery in the cranial CT.

Extracranial color-coded duplex ultrasonography revealed moderate residual stenosis in the left subclavian artery after performance of balloon dilatation (June 1996), with very high-grade subclavian arterial stenosis with subclavian syndrome prevailing at that time. Tests also revealed hypoechoic plaques with stenosis at around 30% near the carotid bifurcation. Transcranial Doppler sonography was normal. According to the EEG, there was a regular 11/s alpha rhythm with a discrete focal finding in the left temporal lobe.

The very comprehensive search for risk factors, which included CSF diagnostics, made in 1996 in investigating cerebral ischemia only revealed moderate hypercholesterolemia. The cholesterol value was 255mg/dl in the present investigation.

The diagnosis was exhaustion depression with pathological crying and slight organic brain syndrome with amnesic aphasia and very discrete hemisymptoms on the right hand side after infarction of the middle cerebral artery located in the left parieto-occipital lobe.

The SSRI citalopram was chosen, especially with the pathological crying in mind. The initial dose of 10 mg was increased to 20 mg after seven days. There was already a marked decrease in pathological crying after ten days, and crying disappeared almost completely after 20 days with an overall improvement in the depressive mood.

On a follow-up inquiry by telephone, this improvement was reported to have remained stable up to January 2001.

## Discussion

The good therapeutic response of pathological crying to medication was common to the selective serotonin reuptake inhibitor (SSRI) citalopram in all three cases described, despite the total difference in diagnosis and functional morphology between each case. We could therefore confirm the observations of Andersen et al. in stroke patients and extend these to a patient with Parkinsonism [1]. Moreover, we could support the assumption of a disorder of central serotonergic innervation originating from the dorsal and medial raphe nuclei of the brainstem [2] as an important etiological factor.

However, it would seem conceivable that other neurotransmitter and/or neuromodulator systems could also play a role in this symptomatology.

Interestingly, a syndrome resembling pathological crying in some respect, but comprising depressed mood and despair has been observed during deep brain stimulation, a new treatment for Parkinson's disease [5,14].

Whereas Udaka et al. found that L-dopa and amantadine were effective in treating pathological laughing and crying in patients with cerebrovascular processes and craniocerebral trauma [29], pathological crying developed under ongoing parkinsonism therapy with L-dopa in one of our patients (case 1).

In our first case, we could not find any definite indications regarding damage actually causing the pathological crying. On the other hand, analogous observations made by other authors

strongly imply that ischemic damage to the brain stem (specifically, the pons) was centrally involved in the pathological crying etiology in our second case [2,4,7,16,21].

As demonstrated in experimental investigations, pharmacological elimination of the right hemisphere (Wada test) results in dysphoric reactions ranging to sudden crying, whereas elimination of the right hemisphere tends to lead to unmotivated laughing [8,10,15,28]. This might correspond to our observation that the pathological crying occurred in our third case after an infarction of the middle cerebral artery located in the left parieto-occipital lobe.

The correlation between pathological laughing and crying with parathymia, as typically occurs in schizophrenic illnesses, appears to be of particular interest from a pathophysiological and therapeutic point of view, but also in terms of psychopathological criteria. It would be beyond the scope of the present case report to discuss this problem in detail. However, it is doubtless a challenge for future research.

In summary, our observations show that citalopram is an effective treatment for pathological crying with varying etiologies; indeed, its effectiveness is possibly independent of etiology. In agreement with the observations by Andersen et al. [1], a rapid onset of action can be expected.

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