

# MANAGEMENT OF THE PSEUDOBLBAR AFFECT (PBA) IN KABUKI SYNDROME COMBINED DEXTROMETHORPHAN-FLUOXETINE TREATMENT AS AN ALTERNATIVE TO DEXTROMETHORPHAN/QUINIDINE

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## ABSTRACT

A case report of a patient with pseudo bulbar affect previous treatments included haloperidol (10mg), *Inosina pranobex* (600mg), clozapine (600mg), olanzapine (20mg), carbamazepine (200mg), paroxetine (20mg), phenobarbital (100mg) and topiramate (50mg), all suspended at August 2016, with current use of quetiapine (700mg) Chlorpromazine (600mg) (+ 200mg on demand of aggression), clonazepam (4 mg), valproate 2500 mg, propranolol (40mg). that was successful treated with off label treatment (dextromethorphan plus quinidine). Previous Brief Psychiatric Rating Scale and Clinical Global Impression-Improvement was applied after and before treatment with dextromethorphan (20mg) plus fluoxetine (20 mg, further increased to 40 mg). Previous Brief Psychiatric Rating Scale BPRS score 56 points and Clinical Global Impression-Severity (CGI-S) Score was 6 (severely ill). The addition of dextromethorphan (20mg) and fluoxetine (20 mg, further increased to 40 mg), allowed clear improvement of pathological crying and outbursts, with BPRS decrease of 8 points and Clinical Global Impression-Improvement (CGI-I) 2 (much improved) – especially pertaining to PBA related symptoms and aggressive behavior. There were no noticeable side-effects. This case report shown an interesting clinical response. It's could be a great alternative in treatment of pseudobulbar affect symptoms. Even though an only case and a great clinical study be necessary.

**Keywords:** *Neurology; genetic syndrome; off label medicine; behavior*

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## INTRODUCTION

Kabuki syndrome (KS) is a rare condition characterized by intellectual disability, congenital anomalies and behavioral abnormalities, including repetitive behavior. Patients with KS tend to have a peculiar facial gestalt, short stature, and skeletal, visceral, cardiac and immunological abnormalities<sup>1</sup>. These individuals also exhibit characteristic vocalizations and/or crying associated with the presence of pseudobulbar affect (PBA)<sup>2</sup>. KS is caused by *de novo* dominant pathogenic variants in the KMT2D and KDM6A genes<sup>3</sup>, each associated with a different subtype of KS. KS1 (MIM#147920) is associated with a KMT2D gene mutation (MIM# 602113), which is present in 43-76% of all patients, while KS2 (MIM#300867) is associated with a mutation in the KDM6A gene (MIM#300128), and accounts for 1-6% of all cases<sup>4,5</sup>. PBA is a neuropsychiatric syndrome observed in different neurological disorders, such as multiple sclerosis (MS) and Alzheimer disease (AD)<sup>2</sup>. It is characterized by uncontrollable episodes of laughing or crying incongruent with the underlying emotional state<sup>1</sup>. Recent neuroimaging studies of PBA support the role of cortico-pontine-cerebellar network dysfunction in context-inappropriate emotional responses<sup>6</sup>. Parvizi and Schiffer described the case of a 70-year-old man with exaggerated crying and tremor with a cerebellar cyst<sup>7</sup>. Different interventions have been attempted to improve symptom control in these patients<sup>2</sup>. Recently, the combination of quinidine and dextromethorphan (Nuedexta) received FDA approval for the treatment of PBA<sup>8</sup>. An ultralow dose of quinidine increases serum levels of dextromethorphan, reducing mood symptoms but increasing the risk of serotonergic syndrome and dextromethorphan-related adverse events

(eg, agitation, confusion, tremor, insomnia, diarrhea and respiratory depression)<sup>9</sup>. Dextromethorphan is a low-affinity, noncompetitive N-methyl-d-aspartate glutamate receptor antagonist and a sigma-receptor agonist with a short half-life, while quinidine is a potent cytochrome P450 2D6 inhibitor that also promotes the metabolism of dextromethorphan<sup>10</sup>. The usual dosage is dextromethorphan/quinidine 30/10 mg twice daily<sup>9</sup>. Since quinidine therapy is no longer recommended by medical guidelines or government approved protocols in some countries, including Brazil<sup>11</sup>, some authors have proposed alternative drug combinations to inhibit cytochrome P450 2D6 and increase plasma levels of dextromethorphan. Selective serotonin and serotonin-noradrenalin reuptake inhibitors (SSRIs/SNRIs) are known to inhibit cytochrome P450 2D6, as described in the case of a 53-year-old woman with MS treated with fluoxetine<sup>12</sup>.

## CASE REPORT

Herein we report the case of a 24-year-old male diagnosed with KS at age 10, by the Genetics Service of the Hospital de Clínicas de Porto Alegre, Brazil. The patient was followed for over 20 years, and displayed frequent tantrums and crying episodes, fulfilling the diagnostic criteria for multidrug- and ECT-resistant PBA<sup>13</sup>. Mental status examination showed below-average intelligence, self-centered behavior, anxiety, articulation difficulties, no perceptual impairment, mood-congruent affect, friendliness, slow logical reasoning, and impairments in insight and critical judgment. Electroencephalography (EEG) data registered with the patient awake and under drug-induced sleep revealed diffuse slow and irregular background activity that was slightly asymmetrical, with intermittent theta activity in the right parasagittal region, and no epileptic paroxysm, suggesting nonspecific diffuse cerebral dysfunction with unclear etiology. The diagnosis of KS1 was based on phenotypic characteristics (high arched eyebrows, upslanted palpebral fissures and low set of ears)<sup>3</sup> and confirmed by the Genetics Service of the *Hospital de Clínicas de Porto Alegre*. PBA was identified using the Center for Neurologic Study-Lability Scale (CNS-LS)<sup>8</sup>. Global psychopathology was examined using the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI), completed before and after add-on treatment. Previous treatments included haloperidol (10 mg), *Inosina pranobex* (600 mg), clozapine (600 mg), olanzapine (20 mg), carbamazepine (200 mg),

paroxetine (20 mg), phenobarbital (100 mg) and topiramate (50 mg), all suspended as of August 2016. At the time of the study, the patient was treated with quetiapine (700 mg), chlorpromazine (600 mg + 200 mg if aggressive behavior was observed), clonazepam (4 mg), valproate (2500 mg), and propranolol (40 mg). The addition of dextromethorphan (20 mg) and fluoxetine (20 mg initially, increased to 40 mg after a month) treatments was associated with a marginal decrease (5%) in BPRS scores (from 56 to 48) and a marked and sustained reduction in CGI severity scores - from 6 (severely ill) to 2 (borderline mentally ill), without noticeable side effects. The observed effects were very similar to those reported by Butler and Williams<sup>12</sup>. To our knowledge, this is the first report of combined treatment with dextromethorphan/fluoxetine (DMTPH/FLUOX)<sup>3</sup> for KS with PBA.

## DISCUSSION

DMTPH/FLUOX (20/40) led to clear clinical improvement in pathological crying and outbursts, with an 8-point decrease in BPRS scores (from 56 to 48). The patient received maximum scores on all observable items (3, 4, 6, 7, 13, 14, 16, 17 and 18). The patient's level of intellectual disability prevented the assessment of all but one subjective item in the scale (item 10, hostility). After treatment, a major improvement in CGI severity scores from 6 to 2 was also observed, largely due to a decrease in PBA-related symptoms and aggressive behavior. There were no noticeable side effects. The difference between the changes observed in the two scales after treatment may be explained by the fact that the CGI is a more general measure than the BPRS. The latter may not have been sensitive to small improvements in the patient's condition due to potential ceiling effects caused by the severity of their symptoms.

A significant improvement in PBA was observed during the 1-month period of add-on treatment with DMTPH/FLUOX. Improvements persisted for two additional weeks, with subsequent reduction in family burden. This treatment is nearly 60 times less expensive than the alternative and has a good safety and tolerability profile. Additional studies with larger samples and analysis of serum fluoxetine levels are needed to confirm the efficacy and safety of this treatment in other cases of PBA.

## Conflicts of Interest

The authors declare no conflicts of interest.

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