OCULOGYRIC CRISIS DURING TREATMENT WITH ARIPIPRAZOLE

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INTRODUCTION

Objective: We report a case of oculogyric crisis (OGC) occurring in a patient treated with *aripiprazole*, an atypical antipsychotic.

Background: Extrapyramidal symptoms (EPS), such as oculogyric crisis (OGC), are known side effects of neuroleptics, and less commonly other medications, such as carbamazepine, levodopa and tetrabenazine. These complex clinical events, first described by von Economo, are characterized by paroxysmal episodes of fixed eye deviation, thought disorder, and postural and autonomic disturbances. The symptoms rarely occur with newer generation, "atypical" antipsychotics (i.e., *Ablify (aripiprazole)*). *Aripiprazole* has ideal properties for treatment of psychoses, given its partial agonist dopamine D2 and serotonin 5-HT1A receptor actions, and antagonism of serotonin 5-HT2A receptors. Partial agonism refers to its ability to stimulate D2 receptors in a hypodopaminergic environment and to block D2 receptors in a hyperdopamine environment. Crises of any cause can be terminated by treatment with anticholinergics.

METHODS

Design/Methods: Case presentation, including video, and review of literature. Pathophysiologic (i.e., dopaminergic) OGC mechanism will be discussed.

Case Discussion: A 26 year-old female with a history of schizophrenia has experienced frequent attacks (1-4 weekly) with uncontrolled eye-blinking, followed by eccentric eye deviation, left and upwards. Episodes are preceded by intense anxiety, and accompanied by decreased vision, eye/facial pain, photophobia, as well as an overheated sensation and sweating. Attacks occur in the early afternoon, then can recur until bedtime. She takes *aripiprazole* with effective relief of her psychosis symptoms. Reducing her dose of *Abilify* from 20 to 15 mg did not decrease the spasms. To treat OGC she was taking *Cogentin (benztropine)*, without significant relief. Examination is remarkable for normal visual acuity with correction and normal color perception by AOHRR color plates OU. Visual fields were full to finger counting before, but not during an attack. No afferent pupillary defect was present. Optic discs were normal. When testing eye movements by OKN strip, the patient frequent blinked, suddenly became anxious, then assumed a dystonic neck posture, with her eyes deviated up and to the left (see photos, right). She became extremely warm and diaphoretic. She had no trouble answering questions while her eyes remained deviated. She could bring them back to midline with great difficulty, but then her eyes spontaneously resumed their eccentric position. Her symptoms resolved within 15 minutes after oral administration of *diphenhydramine*, 100 mg and did not recur for the remainder of the day.

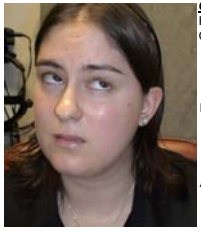
Twelve days after our initial evaluation the patient experienced another attack during a day when she omitted her morning dose of *Cogentin*. The attack responded partially to *Benadryl* 50 mg PO. She was instructed to take *Benadryl* 75 mg if she had another attack. Following her first treatment with *Benadryl*, the patient had a symptom-free hiatus of about 11 days before her next attack.

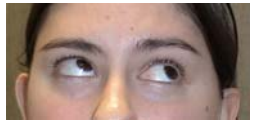
Six days later, the patient had another attack during the evening after a long day of traveling, followed by watching a film in the afternoon. The spasm occurred without warning after a few minutes of eye blinking, and was severe enough that she could not ambulate due to her inability look downwards and to see well. She took 100 mg of *Benadryl* PO, and within 30 minutes the spasm resolved. She was able to eat her evening meal, but had lost some of her appetite due to back cramps which occur when she has an attack. She was then prescribed IM *Benadryl,* which she could self-administer for faster resolution of her spasms.

Five months later the patient had been on a prophylactic regimen of Benadryl 50 mg p.o. each morning for almost two months, and reported a decreased incidence of attacks to at most one per week.

RESULTS

The following photographs and the accompanying video recording convey the clinical phenomenology of this patient's oculogyric crises:





Clinical Features of Oculogyric Crises (Leigh et al. 1987, Schiff et al. 1999):

Four elements of OGC: ocular, motor, autonomic, ideational.

Ocular
- -Eyes usually ⇧, sometimes ⇨ + ⇧, rarely ⇩
- -Eyes usually directed away from posturing
- -Eyes are fixed in crisis; voluntary ⇩ gaze is possible, but painful.
- -Voluntary saccades are full within a restricted field

Motor
- -Increase in parkinsonism
- -Dystonic posturing of the limbs, usually worse contralateral to direction of eye movement
- -neck held in retrocollic posture

Autonomic
- -sympathetic overflow: ⇧ BP, ⇧ HR.
- -pupillary dilation, facial flushing
- - excessive lacrimation, salivation, sweating
- -respiratory crises: tachypnea, bradypnea, resp. rhythm abnormalities, respiratory tics

Ideational
- -thought 'stickiness', inability to shift attention
- -behavioral excitation, restlessness, anxiety

DISCUSSION

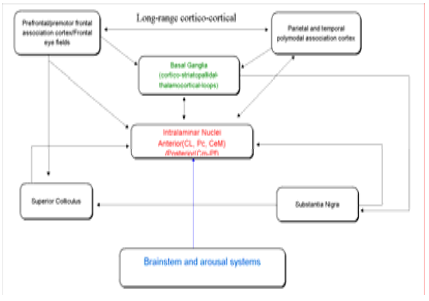


Figure 1 – Projections of the intralaminar-midline thalamic complex (ILN) to the basal ganglia and cortical regions (Schiff et al. 1999).

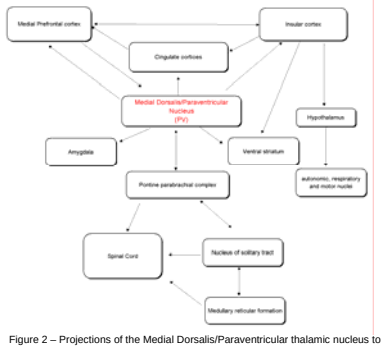


Figure 2 – Projections of the Medial Dorsalis/Paraventricular thalamic nucleus to the cortical, subcortical and brainstem regions (Schiff et al. 1999).

Oculogyric crisis is an acute dystonic reaction of the ocular muscles lasting seconds to hours, most often associated with neuroleptic medications, particularly typical, older generation antipsychotics. However, any medication that antagonizes nigrostriatal dopamine function has the potential to cause dystonic reactions. Dystonic reactions have been reported in 10-60% of patients treated with neuroleptics, occurring more commonly in patients after starting or increasing the dose of this class of medications. Risk factors for acute dystonic reactions include young age, male gender, use of high-potency antipsychotics, high dose, and parenteral administration. Dystonic reactions may also occur more frequently during the afternoon and evening.

The extrapyramidal adverse effects of antipsychotic drugs, such as dystonia and parkinsonian-like symptoms, have been attributed to blockade of striatal D_2 receptors. This hypothesis is supported by a positive correlation that exists between D_2 receptor blockade, antipsychotic potency, and the frequency of acute dystonic reactions.

Schiff et al. (1999) proposed that OGC reflects a dystonia of the intralaminar-midline thalamic complex (ILN), i.e., aberrant synchronization of the ILN-midline complex due to increased cholinergic innervation in the setting of a dopamine deficiency is a physiological mechanism underlying the oculogyric crises.

Support for this economical hypothesis includes:
- The ILN are known to have a unique pattern of projection to basal ganglia, cortical and brainstem that position these nuclei to selectively gate the parallel and segregated cortico-striatopallidal-thalamocortical loops related to ocular, motor, autonomic and cognitive function.
- Brainstem cholinergic afferents from the pedunculopontine nucleus that overlap with thalamostriatal afferents are predominantly located in the midline (PV) and intralaminar nuclei (CL, CM, MD, PF). These input may be overactive in patients with psychotic spectrum disorders (Garcia-Rill et al. 1995)
- The only reported structural lesions causing OGC are of ILN and bilateral globus pallidus (which strongly project to ILN).
- The limbic components of the crisis including anxiety, respiratory and cardiovascular components, can be explained by the role of the paraventricular nucleus and other midline nuclei that project to the ventral striatum and basal-lateral amygdala.
- Disynaptic connections of the different ILN-midline nuclei arise via the nucleus reticularis that could mediate hypersynchrony within this system (Crabtree and Issac 2002).
- Physiological studies of the ILN suggest an attentional gating mechanism in the form of a generalized efference copy including eye movements that may be affected in the dystonia and activated by vestibular stimulation (Purpura and Schiff 1997, Schiff and Pulver 1999).
- The hypothesis provides a unifying mechanism for the observations of VOR like movement pattern during the crisis and early observations that OGC could be reliably induced by caloric stimulation in patients with post-encephalitic parkinsonism (Crow 1949).

CONCLUSIONS

- OGC is a potential complication of treatment antipsychotic agents.
- The occurrence of this side effect with atypical antipsychotics is very rare.
- To our knowledge, there is only one other published report of significant EPS with OGC associated with *aripiprazole* treatment.
- *Aripiprazole* likely acts as a functional D2 antagonist when activity is excessive, and as a D2 agonist when activity is not sufficient.
- A potential mechanism for this very complex clinical entity involves intralaminar and midline thalamic nuclei.
- There is neuroanatomical, neurophysiologic and neuropharmacologic evidence to support aberrant synchronization of the thalamic ILN-midline complex as a mechanism underlying the oculogyric crisis.
- Vulnerability to these events may arise because of underlying (disease based) increased cholinergic innervation to the thalamus unmasked in the setting of pharmacologic dopaminergic blockade.

ACKNOWLEDGEMENTS

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