Dopamine dilemma: case report of treating psychosis in patient with retinitis pigmentosa

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ABSTRACT
Retinitis Pigmentosa is a rare inherited degenerative eye disease affecting the retinal pigment epithelium (RPE), in which mutation of rhodopsin leads to severe visual impairment, and legal blindness. The D4 receptors are abundant within the rods of the retina and dopamine release is the primary feedback mechanism preventing retinal degeneration by the unopposed action of melatonin. Here, we present a 50-year-old female patient with schizophrenia and retinitis pigmentosa who was admitted to an inpatient unit for an acute psychotic exacerbation with agitation and persecutory delusions. Patient initially was administered IM haloperidol since she refused oral form, but she eventually was compliant to oral Haloperidol with eventual reduction in daily dose to 5mg/d with treatment response and good tolerability including no change in visual acuity. The treatment of psychosis in patients with retinitis pigmentosa is challenging and requires consideration of the potential D4 receptor effects associated with an antipsychotic medication to prevent further retinal damage.

Introduction
A 50-year-old Hispanic female with a past psychiatric history of schizophrenia and retinitis pigmentosa, and no prior admissions to our inpatient unit, brought in involuntarily by police for acute psychotic exacerbation with agitation, persecutory delusions and disorganized behaviour.

Patient has been deteriorating and non-compliant with home psychiatric medication for the past few months. She reportedly has been paranoid about people coming into her house and has called 911 numerous times claiming that someone is in her home. Moreover, the patient has called her daughter repeatedly reporting that the daughter’s father is trying to kill her, despite the fact that he actually no longer lives with her. Per the report, 911 was called by store employees where the patient had a “mental breakdown”. The patient was seen wandering around busy intersections multiple times despite being legally blind. Also per the report, the patient was not sleeping or eating well, and she thinks that someone is poisoning her. She stated, “The world will end if you don’t believe in God” and said that God has told her what his plans are. She was reportedly hostile and aggressive towards police officers.

Upon interview at our inpatient setting, the patient presented with flat affect and fair grooming/hygiene. She was calm, minimally cooperative with the interview, very evasive, guarded, lose, disorganized and selectively mute. The patient appeared internally pre-occupied at times and displayed speech latency to many questions. The patient minimized her symptoms and completely denied all intake information. When asked about the numerous calls to police, the patient said that she “accidentally hit buttons on the phone” and dialled the police, relating this to her inability to see well. She asserted that she did not do it on purpose and denied concerns about people being in her house. The patient denied all psychiatric symptoms or any recent stressors and mentioned normal energy levels, concentration and motivation. She also denied having a mental or medical illness and dismissed the need to be on medication. The patient also denied substance, alcohol or tobacco use. Later after the interview, the patient started screaming, yelling, was very disruptive, severely agitated, refused all oral medication, received emergency medication Haloperidol 5 mg IM and diphenhydramine 50 mg IM.

Based on her of schizophrenia and the current presenting symptoms in addition to her non-compliance to treatment, the diagnosis of relapse was considered the most likely diagnosis. However, the possibility of a general medical condition or medications causing her symptoms could not be totally ruled out based solely on her denial. This warranted further investigation to rule out other possible etiologies before this diagnosis could be assigned. Another consideration was her retinitis pigmentosa diagnosis that she had...
since early in her life, which warranted further investigation.

Patient spoke Spanish and English, and interviews were conducted with the presence of interpretation services at the hospital. Her medical history and lab investigations were negative for medical issues except being legally blind due to retinitis pigmentosa and a previous cataract surgery 5 years earlier. Due to her worsening condition and being non-compliant to the prescribed oral medications, court-ordered medication petition was granted and she was started on haloperidol 5 mg qam&qhs for psychosis and diphenhydramine 25 mg qam&qhs for EPS prevention. Subsequently, after the first few injections, she became compliant with oral medications. She then reported that she lives at her home with her niece. She denied auditory and visual hallucinations, suicidal or homicidal ideations. She, however, consistently denied the need for any medications and stated that she used to refuse to take her medications because they worsen her already impaired vision.

The choice of a specific antipsychotic medication was complicated by the patient’s retinitis pigmentosa as well as her history of non-compliance to medication on an outpatient basis. It was not an easy decision given the fact of scarce data in the literature and the yet to be fully elucidated underlying mechanisms.

Quetiapine and aripiprazole have a relatively low affinity for the D4 receptor [1] (Table 1) but no IM and/or depot formulations were available at the inpatient facility. Risperidone depot – in addition to not being available in our facility – was disregarded as an option due to its multiple retinal side effects reported in the literature. Haloperidol was subsequently selected based on its relatively similar D4 affinity to the remaining atypical antipsychotic medication, and also since it was available in an IM and depot formulations. The patient was initially given IM haloperidol since she refused the oral form, but she eventually was compliant to oral haloperidol with eventual reduction in daily dose to 5 mg/day with good treatment response and good tolerability including no change in visual acuity. At discharge, patient psychosis symptoms improved. She had good sleep and appetite. She did not report side effects of worsening vision after adjusting her medication doses.

**Discussion**

Ocular side effects in the advent of antipsychotics administration are a well-known problem despite the relative rarity of its wide-scale studies in the literature [2]. As early as 1956, Goar and Fletcher published the first study conducted on 34 psychiatric patients treated with chlorpromazine, 28 of them developed retinopathies of various degrees [3]. Since then, reports were published linking retinopathy to different types of antipsychotics use such as thioridazine [4], phenothiazines [5–8], chlorpromazine [9], haloperidol [10] and clozapine [11]. Risperidone was linked to retinal artery occlusion in one case report [12], central retinal vein occlusion in another [13] and macular edema in a more recent report [14].

In 1992, Cohen et al. detected high-density D4 (D2-like) receptors located in the retina, particularly the photoreceptor cells, more than elsewhere in the brain [15]. In 2002, Nir et al. in their study on D4 knockout mice showed that the D4 receptors functionally couple with adenylyl cyclase, and the loss of these receptors in the retina results in changes in the response to light [16].

Fujieda et al. showed that melatonin receptors 1 and 2 (MT1 & MT2) are located in the rod photoreceptors [17]. Interestingly, melatonin was previously shown to exert its effects through G-protein family coupled receptors (GPCRs) that are negatively coupled with adenylyl cyclase [18]. Doyle et al. showed that in mice retina dopamine is released from amacrine and interplexiform retinal cells in response to light and acts on D4 receptors on the photoreceptor cells to further suppress cyclic AMP synthesis and Ca2+ levels, thus inhibiting melatonin biosynthesis [19].

Tosini et al. formulated for the first time in the literature a feedback mechanism between melatonin and dopamine levels in mammalian retina. In their model, melatonin release induces dopamine release from amacrine D4 cells, which in turn acts through a negative feedback loop suppressing cyclic AMP synthesis and Ca2+, ultimately leading to control melatonin levels, by keeping them in what they called “physiological levels” to the eye, and they stated that any disruption in that negative feedback mechanism will lead to unopposed action of melatonin that will be increased to “pathological” levels to the retina leading to its degeneration [20] (Figure 1).

**Table 1. Relative binding affinity of selected antipsychotics on dopamine D4 receptors.**

| Antipsychotic medication | D4 receptors |
|--------------------------|-------------|
| Aripiprazole              | ++          |
| Quetiapine               | ++          |
| Ziprasidone              | +++         |
| Clozapine                | +++         |
| Olanzapine               | +++         |
| Ziprasidone              | +++         |
| Quetiapine               | ++          |
| Aripiprazole             | ++          |
| Haloperidol              | ++++        |
| Chlorpromazine            | ++++        |

Note: Based on published data in the literature from Kusumi et al. [1].

**Conclusion**

Antipsychotics with high D4 affinity alter this physiological feedback mechanism by blocking the D4 receptors dopaminergic action, thus leading to melatonin release from under control and subsequent retinal toxicity. The treatment of psychosis in patients with retinitis pigmentosa is not only challenging but requires
the consideration of the potential D4 receptor effects associated with an antipsychotic medication. Otherwise, further retinal damage may occur. Since there is little data available concerning this rare but important issue, this case report provides some guidelines for psychosis management in such patients.

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