

# CHALLENGES IN THE MANAGEMENT OF DELIRIUM: A CASE OF AUGMENTATION WITH DONEPEZIL FOLLOWING INADEQUATE RESPONSE AND ADVERSE EFFECTS WITH RISPERIDONE

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## INTRODUCTION

Delirium is a common complication in the course of hospitalization characterized by disturbances of awareness and attention, cognition and psychomotor behavior. Further characteristics include an abrupt onset, fluctuating course, as well as an underlying etiology causing this syndrome (APA 2000). In particular, in the intensive care (ICU) setting delirium is very common and the occurrence reaches up to 80%. The standard management approach includes the elimination and treatment of underlying etiologies, which in many instances cannot be achieved to completeness, supportive interventions such as providing a safe environment, structure, and reorientation, as well as pharmacological interventions such as the administration of antipsychotics in order to manage the symptoms of delirium (Trzepacz et al. 1999). A few years ago, following the paradigm of a final pathway of dopamine-acetylcholine imbalance (Trzepacz 2000) with the contribution of various other neurotransmitters (Maldonado 2008), cholinesterase inhibitors (ChEI) were studied in the management of hypoactive delirium with limited evidence (Moretti et al. 2004, Overshott et al. 2008, Gamberini et al. 2009). This approach has not been followed since then, in part, due to the superior results in management with antipsychotics. However, ChEI merit consideration as an augmentation strategy as illustrated in the following case.

## CASE REPORT

Mr D is a 54-year-old Caucasian male with a past psychiatric history of alcohol dependence which led to major duodeno-pancreatic surgery six weeks prior to the current event. Mr D was set on fire due to an explosion which occurred when fumes ignited while he was distilling alcohol in his garden shed. He then jumped into a water-filled rain barrel outside the shed. His daughter witnessed the incident, helped to smother the fire and alerted emergency services. As a consequence, the patient suffered II°a to III°-burns of 42.5% of the body surface including the face, neck, arms, and legs.

On arrival of the emergency medical service, the patient was conscious and cooperative. Subsequently, he was transferred to the University Hospital Zurich and his lesions were managed according to standard procedure on the burn unit. After initial sedation with propofol and ketamine, Mr D developed a severe delirium, meeting the DSM-V diagnostic criteria of mixed delirium with rapidly developing and fluctuating impairments of awareness and attention, as well as cognition such as severe disorientation, severe hallucinations and delusions, affective flattening, psychomotor behavior switching from retardation to restlessness, and lack of cooperation which interfered with management at the burn unit. The delirium as measured with the ICDSC (Intensive Care Delirium Screening Scale) was severe and reached scores of 8 on diagnosis of delirium and averaged 5.5 the following days.

Upon first consultation by the consultation-liaison (C-L) psychiatry service, laboratory results revealed a discrete hypernatremia (150mmol/l (135-147)) and a moderate hyperchloremia (118mmol/l (95-105)), normal renal and hepatic function, a moderate rise of inflammation markers such as c-reactive protein (CRP) (43mg/l (<5mg/l)), procalcitonin (PCT) of 0.48ug/l (<0.1ug/l), and leucocytes at 10.5G/l, in addition to a normocytic, normochromic anemia (hemoglobin at 70g/l). The electrocardiogram (ECG) performed after the onset of delirium management displayed a discrete tachycardia (102bpm), an unspecific lowering of the ST-segment in the inferior leads and normal QT-interval (QTc). An electroencephalography (EEG) did not reveal any potentials characteristic of epilepsy or status epilepticus. Neuroimaging was not performed during his hospitalization, as the patient had not suffered craniocerebral injury and did not display signs or symptoms of an intracranial ischemia or hemorrhagia.

The initial management of delirium included risperidone 0.5mg per os (po) at night. A temporary improvement was noted as Mr D's disturbances of attention and awareness, cognition, delusions and perception showed improvement. However, myoclonic jerks and rigidity indicating EPS developed. Then, pipamperone, a low-potency antipsychotic with close to none propensity to

cause EPS, which primarily acts through serotonin (5HT)-2A antagonism as well as through an antagonism of dopamine (D2) and  $\alpha$ -1 receptors to a lesser degree, was added at 20mg per os at night as part of the University Hospital Zurich delirium management schedule. However, the patient's mental and neurological status further deteriorated, delirium and myoclonic jerks worsened, and pipamperone was subsequently discontinued. In order to counteract the EPS, biperidene 5mg was administered intravenously causing an even more pronounced worsening of delirium. Due to this worsening, the neurologic service was involved postulating a central anticholinergic syndrome, and a single dose of physostigmine 2mg intravenously was administered. Within minutes the patient's mental status improved and there was no evidence of disturbances of attention and awareness, cognition and psychomotor behavior. As indicated by the response to one-time administration of physostigmine, augmentative management with donepezil was initiated at 2.5mg po at night and adjusted to 5mg po at night and the drastic improvement after the administration of physostigmine was maintained. As a consequence of the administration of risperidone and donepezil, Mr D remained free of delirium, was able to cooperate with further management and was eventually transferred to a rehabilitation facility.

## DISCUSSION

Although knowledge about the etiopathogenesis of delirium has evolved over the last years, this syndrome still remains elusive and not well understood in many instances. As a severely burned patient, Mr D suffered from an impaired electrolyte and energy metabolism and high infectious risk due to the damaged skin barrier function and to likely medication-induced neutropenia; as a consequence of the latter, a ventilation-associated pneumonia and septic shock developed. Analgesia included fentanyl, and intermittent sedation propofol and ketamine. With a number of etiologies contributing, the delirium was considered to be etiologically multifactorial. During the course of hospitalization, no signs and symptoms of alcohol withdrawal occurred, thus, delirium tremens as another etiology was ruled out.

In this case, the administration of low doses of antipsychotics improved the cognitive function but caused EPS, which responded poorly to the administration of biperidene. The worsening of delirium after the administration of biperidene was not surprising, as the prototypical delirium is characterized by the administration of anticholinergics (Trzepacz 1996), and the etiopathological model posits an imbalance between dopamine and acetylcholine (Trzepacz 2000), however the administration was deemed necessary at the time in order to counteract EPS.

In this case, the assumption of a hypo-cholinergic state was made. The interactions of dopamine and

acetylcholine have been described early on, and discrete dopamine antagonism increases the release of acetylcholine (Vizi et al. 1977). Nonetheless, this effect was not sufficient and with the administration of donepezil, acetylcholine was replenished and this delirium remitted.

Studies of ChEI in the management of delirium have not revealed a conclusive role. Whereas earlier studies indicated their benefit (Moretti et al. 2004, Gamberini et al. 2009), a systematic review did not find sufficient evidence (Overshott et al. 2008), even more, a detrimental effect was documented later (van Eijk et al. 2010).

Nonetheless, in patients with hypo-dopaminergic states such as Parkinson's disease or hypo-cholinergic states such as dementias, in particular Lewy body's disease or a central anticholinergic syndrome, adverse effects such as EPS often occur in the context of dopamine (D2) antagonism. In these instances, challenges arise in the management of delirium. In this case, the choice of a ChEI was predetermined by the response to the one-time administration of physostigmine. However, this approach might extend beyond this unique case and merits further investigation as an augmentation strategy in challenging cases with delirium. In particular, in those with hypo-cholinergic or hypo-dopaminergic states ChEI could be a beneficial approach.

In retrospective, alternative approaches such as using antipsychotics with a more favorable profile on dopamine (D2) binding could have achieved an equal result, nonetheless, predetermined by the response to physostigmine, considering donepezil was the best choice.

## CONCLUSION

The case of Mr D illustrates the challenge in the management of delirium caused by dopamine (D2) antagonism causing myoclonic jerks and subsequent failure to achieve symptom control.

The current approach in the management of delirium comprises the removal of underlying etiologies, supportive and pharmacological interventions, foremost the administration of antipsychotics. Notwithstanding, as evidenced in this case, the use of antipsychotics carries the risk of causing EPS with subsequent failure to achieve symptom control. In particular, in those patients with low baseline cholinergic or dopaminergic states, the management of delirium can be challenging. In those instances, another strategy, the augmentation with cholinesterase inhibitors in the hypoactive subtype of delirium, could be a beneficial management approach which merits further evaluation.

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