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Case report

DISTINGUISHING BETWEEN NEUROLEPTIC MALIGNANT SYNDROME AND SEROTONIN SYNDROME IN POLYPHARMACY: AN OVERVIEW WITH A CASE REPORT

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INTRODUCTION

The incidence rate of neuroleptic malignant syndrome in patients taking antipsychotics varies between 0.02 and 2.4% (Ananth et al. 2004), however the incidence of serotonin syndrome is largely unknown, because especially mild cases are frequently overlooked. Serotonin syndrome is considered to be a consequence of serotonin excess and presents serotonin toxicity. NMS results from excessive dopamine receptor blockade or genetically reduced function of dopamine receptor D2 (Mihara 2003). There is considerable overlap of symptoms in NMS and serotonin syndrome and both conditions are still considered relatively rare. Therefore, it comes as no surprise that many clinicians find it challenging to recognize and treat them, especially when polypharmacy is used. Publishing case reports of patients on polypharmacy may be helpful in distinguishing between the two syndromes and perhaps even in preventing them in the future. The important role of predisposing genetic factors that influence drug metabolism and neurotransmitter receptor functioning is also increasingly recognized. Genetic testing and therapeutic drug monitoring are becoming important parts of serious side effects prevention and optimal patient management in general, which is a goal of personalized medicine after all.

CASE REPORT

Patient A.K., now 54 years old, was diagnosed with schizophrenia when he was 28 years old. During his late twenties and thirties, he was treated with various first and second-generation antipsychotics. He experienced akathisia and mild parkinsonism approximately five times, mostly when taking first-generation antipsychotics or a combination of drugs, such as haloperidol or fluphenazine combined with risperidone, olanzapine or amisulpride. By the time he was 38 years old he became treatment resistant and was put on clozapine. During the course of his illness, he was hospitalized 25 times and his medication adherence was often poor. In his forties he was also prescribed with various antidepressants and benzodiazepines, sometimes in attempt to alleviate his persistent negative symptoms and anxiety. At one point, he was taking 900 mg of clozapine while hospitalized, the dose of which was subsequently lowered to around 500 mg, when it became clear that the patient continued to show positive and negative symptoms despite confirmed adherence to the high clozapine dose. Because he also proved to be clozapine resistant, he was almost always prescribed additional antipsychotics.

At the age of 53, he was admitted to the ER with GCS 9, rigidity, fever (39°C), sweating, tremor, muscular spasms, hypersalivation, spitting and face flushing. He had his eyes opened, was verbally unresponsive and restless at the same time, most likely delirious. A week before that, he came to our psychiatric clinic for an unscheduled emergency psychiatric check-up, because he was feeling nervous and described an uneasy feeling of weakness in his legs. At the time, he was supposed to be taking the following daily drug regimen: clozapine 450 mg, amisulpride 200 mg, venlafaxine 150 mg, lorazepam 4 mg, gabapentin 1200 mg and lamotrigine 100 mg. His blood pressure was 135/81 mmHg, pulse 120/min and SpO2 99%. ECG showed no abnormalities. Initial abnormal laboratory results were as follows: leucocytes 18.5 10^9/L, urea 20.0 mmol/L, creatinine 295 µmol/L, sodium 158 mmol/L, chloride 123 mmol/L, CRP 12 mg/L, creatinine kinase 758.9 µkat/L, AST 13.34 µkat/L, ALT 3.33 µkat/L, LDH 14.29 µkat/L, myoglobin 266184.7 ng/ml, procalcitonin 36.01 ng/ml, eGFR 20, Troponin I Ultra 0.861 µg/L. Arterial blood analysis showed metabolic acidosis. Urine analysis showed proteinuria and hemoglobinuria (probably myoglobinuria, since the laboratory machine couldn't distinguish between the two). The above laboratory findings were indicative of rhabdomyolysis with subsequent acute kidney failure. Since creatinine kinase, myoglobin and leucocyte count were elevated as well, a diagnosis of neuroleptic malignant syndrome was made. In the ER, the patient received diazepam, lorazepam and i.v. hydration and was then admitted to ICU.

In the ICU, the patient was sedated, intubated and mechanically ventilated in order to alleviate muscular spasms and rigidity and subsequently prevent further kidney damage. During his treatment in ICU he received benzodiazepines midazolam, heparine, furosemide, vasoactive support with noradrenaline, 0.45% NaCl infusions and parenteral nutrition. He also received hemodyalisis regularly. On the second day of treatment creatinine kinase elevated to 1395.52 µkat/L, while myoglobin levels fell rapidly from 93409.47 ng/ml on day two to

19232.93 ng/ml on day four. Liver enzymes were also on the rise, up to the following values: LDH 28.94 µkat/L, AST 15.21 µkat/L, ALT 8.41 µkat/L. By day three CRP rose to 71 mg/L, so piperacillin/tazobactam was started. The patient was extubated on day four and transferred to a half-intensive unit, where he continued treatment with clonazepam and supportive measures. Inflammation markers continued to fall, while creatinine and urea were still on the rise - the maximum values were measured on day 15: urea 40.2 mmol/L, creatinine 1111 µmol/L, eGFR 4. By day 15 he also developed normocytic anemia (Hb 89 g/L) and thrombocytopenia (throbocytes 497x10⁹/L). Myoglobin and creatinine kinase fell steadily from day 7 to day 22: creatinine kinase from 44.50 to 0.99 µkat/L and myoglobin from 4381.6 to 295.9 ng/ml. During this time, he was still verbally unresponsive, but clearly conscious, so psychosis was suspected and the patient was transferred to a psychiatric clinic.

Clozapine was restarted immediately and titrated very slowly and cautiously. During the first week, he remained passive and mutacistic and there was still a trace of elevated muscular tonus in the extremities. He spoke for the first time after more than a month since NMS had commenced. He required hemodialysis for another week (about six weeks in total) and by that time urea and creatinine fell to 18.1 mmol/L and 175 µmol/L respectively. He was discharged after additional two months of psychiatric treatment and continued taking clozapine 400 mg daily and lorazepam 4 mg daily. Eventually, all of his laboratory parameters returned back to normal and he didn't suffer any long-term consequences of NMS.

NEUROLEPTIC MALIGNANT SYNDROME VERSUS SEROTONIN SYNDROME

Neuroleptic malignant syndrome and serotonin syndrome are on each other's differential diagnosis and especially in polypharmacy they are often mistaken for one another. Serotonergic and dopaminergic pathways in the brain interact extensively, so it is possible that similar mechanisms are involved in pathophysiology of both conditions. To complicate matters even further, second-generation antipsychotics are also known to have serotonergic properties (Stahl 2013). Both conditions share some important characteristics, such as alterations in mental status, vital signs instability, increased temperature, sweating, hypersalivation, tremor and rigidity. In NMS however, the rigidity is typically "lead pipe" and there are laboratory findings suggestive of subsequent rhabdomyolysis (elevated myoglobin and creatinine kinase). In serotonin syndrome there is also increased muscle tone, especially in lower extremities, but myoclonus and hyperreflexia should be more pronounced (Nisijima et al. 2007). Body temperature is usually higher in NMS than in serotonin syndrome, but in both instances it is usually 38.5°C or higher. In serotonin syndrome mental status changes involve irritability, confusion, agitation, hypomania and coma, whereas in NMS, patients are usually closer to akinetic mutism or stupor. Defining feature of serotonin syndrome is gastrointestinal upset, manifested as diarrhea and vomiting, which is not typical for NMS (Keaton 2013).

Treatment of both conditions consists largely of immediate discontinuation of the offending agent and supportive measures, such as adequate hydration, infection prevention, antipyretics and hypercoagulable state management. In severe cases, such as our patient, it is vital to distinguish between NMS and serotonin syndrome, since this has important acute treatment implications. Serotonin syndrome responds to antiserotonergic agents, such as cyproheptadine, and NMS can sometimes be treated with bromocriptine and amantadine. Benzodiazepines may be used in both conditions to treat muscle stiffness (Keaton 2013). In NMS, dantrolene, a muscle relaxant, can be used, but it is not recommended in serotonin syndrome, since it was reported, that it can sometimes exacerbate serotonin toxicity (Gillman 2006, Nisijima 1993). ECT can be used in severe cases of NMS, while there are cases of ECT precipitated serotonin syndrome in patients on antidepressants (Herrington et al. 2018).

THE ROLE OF PERSONALIZED MEDICINE IN PREVENTION OF NMS AND SEROTONIN SYNDROME

Susceptibility to NMS and serotonin syndrome may be higher in genetically predisposed individuals, particularly in those with dysfunctional alleles for cytochromal P450 (CYP) enzymes, which are crucial in metabolism of most psychotropic drugs. Any dysfunctions of CYP enzymes are probably even more consequential in patients on polypharmacy. It has already been shown that poor CYP2D6 metabolizers have an increased risk of developing extrapyramidal side effects, when taking antipsychotics (Brandl et al. 2014). Polymorphisms in dopamine D2 receptor (DRD2) genes may also play an important role. Studies conducted in Japan have found that carriers of −141°C Del allele coding for DRD2 are more predisposed to developing NMS (Kishida et al. 2004). Serotonin syndrome is thought to result from overstimulation of 5-HT2A receptors, so genetic differences in 5-HT2A receptor sensitivity could play a role in serotonin syndrome development (Francescagneli et al. 2019). Genetic testing may prove useful in explaining, why NMS or serotonin syndrome has occurred in a particular patient and the results can be used in future drug regiment planning. Therapeutic drug monitoring (TDM) could prove invaluable in NMS and serotonin syndrome prevention, since both conditions are precipitated by elevated plasma drug concentrations. TDM of clozapine has already entered common clinical practice in many countries, as it enables dose

correction in patients with CYP function abnormalities. TDM presents an important part of personalized medicine and should be dutifully employed in patients that have experienced serious side effects, such as NMS or serotonin syndrome (Hiemke 2017).

DISCUSSION

Concomitant use of both second-generation antipsychotics and antidepressants has become common practice in treatment of many psychiatric disorders, so it appears to be of increasing importance for clinicians to be able to better differentiate between NMS and serotonin syndrome. In polypharmacy pharmacokinetic interactions are very likely. Our patient was taking clozapine, which is primarily metabolized via CYP1A2 and CYP3A4, and amisulpride, which is eliminated by the kidneys mostly unchanged. He was also taking venlafaxine, which is a weak CYP2D6 inhibitor and does not inhibit CYP1A2 or CYP3A4. Lamotrigine is known to cause very little drug interactions and gabapentin does not induce CYP enzymes, so these two drugs are unlikely to have contributed to NMS development in this patient. Lorazepam is metabolized by glucuronidation, so it is also an unlikely causative agent in possible pharmacokinetic interactions (Stahl 2013). It remains unexplained why exactly our patient experienced NMS and it may well be that he has unfavorable genes for drug metabolism or receptor variants. In light of increasing emphasis on personalized medicine, the choice of further psychopharmacological treatment for patients who have experienced either NMS or serotonin syndrome, warrants extreme caution, especially if polypharmacy is required. The most useful tool in future care for our patient would probably be therapeutic drug monitoring of clozapine, even if it is an unlikely culprit of NMS. It could also prove useful to test for possible polymorphisms in dopamine D2 receptor genes in this patient, but for now this technology is still out of reach for most clinical practices. Psychiatry is heading towards a more personalized approach to patient care and we remain hopeful that genetic testing will become part of common clinical practice in the future.

Contribution of individual authors:

Tana Debeljak: manuscript writing, literature research.
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