

## THE ROLE OF CYP2D6 AND TAQI A POLYMORPHISMS IN MALIGNANT NEUROLEPTIC SYNDROME: TWO CASE REPORTS WITH THREE EPISODES

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### SUMMARY

Malignant neuroleptic syndrome (MNS) is a serious and potentially fatal side-effect of neuroleptic treatment. Beside antipsychotic drugs, other psychotropic drugs such as antidepressants and lithium carbonate can cause this life threatening side-effect. Underlying mechanism of this side-effect is still unknown and debated. So far some risk factors have been identified, with clinical observations and recent pharmacogenetic research suggesting (with inconsistent findings) correlation between genetic mechanisms and predisposition to MNS. Polymorphisms of CYP2D6 enzyme through which most psychotropic drugs are metabolized and TaqIA DRD2 which is target for antipsychotic drugs could be the link between pharmacogenetic factors and potential for development of MNS.

In this paper we present two case reports with clinical presentation of three consecutive MNS. One patient developed MNS while he was taking combination of drugs: first time haloperidol, promazine and fluphenazine, second time fluphenazine and perazine and third time clozapine, promazine and valproic acid consecutively. The other patient developed MNS while taking following combination of drugs: first time haloperidol and lithium carbonate, second time risperidone and third time clozapine consecutively. Pharmacogenetic analysis for CYP2D6 and TaqI A DRD2 polymorphisms for both patients was done. Genotyping of CYP2D6\*1\*3\*4\*5\*6 in both patients showed no evidence of poor metabolizer phenotype. On the other hand, first patient was heterozygous for CYP2D6\*4 (genotype \*1/\*4). CYP2D6 polymorphisms could have clinical significance because may lead to toxicity and unwanted side-effects in standard usual antipsychotic dose ranges. Analysis TaqI A DRD2 polymorphism for first patient showed that he is heterozygous for A1 allele (genotype A1A2) which is commonly associated with predisposition to MNS.

According to our literature three consecutive MNS are rarely described, and incidence of MNS generally is too low to perform clinical research. Many pathophysiological mechanisms may probably underlie this complex and potentially fatal syndrome, still unknown etiology. But, genetic mechanisms could be significant. Further pharmacogenetic research, findings and analysis in patients who develop single or repeated MNS are strongly recommended. In long term, pharmacogenetic analysis, implemented in daily clinical practice, could help in prevention of this extremely serious side-effect.

**Key words:** malignant neuroleptic syndrome (MNS) - CYP2D6 polymorphism - TaqI A DRD2 polymorphism - antipsychotic drugs

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### INTRODUCTION

Malignant neuroleptic syndrome (MNS) is considerably rare complication (0.02-2.0%) during antipsychotic treatment with high mortality rates (20-30%) (Wilkaitis et al. 2004). Besides with antipsychotic drugs, MNS can be caused with other psychotropic drugs such as antidepressants and lithium. Real mechanism of this extremely serious adverse event is yet unclear. So far what we know is that dehydration, malnutrition, exhaustion, infection and/or organic brain disease might be potential risk factors for development of MNS (Itoh et al. 1977, Keck et al. 1989, Sachdev et al. 1997, Berardi et al. 1998, Caroff et al. 1998). Additional suspected risk factors are: high doses of typical antipsychotic drugs with high affinity for D2 receptors, rapid dose titration, numerous intramuscular injections as well as psychomotor agitation (Itoh et al. 1977, Keck et al. 1989).

Furthermore, catatony as motor dysfunction is also considered to be the risk factor for development of MNS (Paparrigopoulos et al. 2009). On the other hand, catatony shares many common symptoms and treatment approaches with MNS so we can speculate whether both syndromes are actually two variants of the same disorder spectrum.

Research findings suggest that among others, genetic mechanisms play important role in predisposition to MNS (Otani et al. 1991, Deuschl et al. 1987, Hosty 1992). Genetic polymorphisms of CYP2D6 are involved in metabolism of various antipsychotic drugs such as haloperidol, fluphenazine, risperidone (Michalets 1998), as well as in metabolism of many other psychotropic drugs. Gene for CYP2D6 is highly polymorphic and consists of more than 70 variants, all resulting in four different phenotypes: extensive (EMs), intermediate (IMs), poor (PMs) and ultra rapid (UMs) metabolizers (Foster et al. 2007). Differences

between phenotypes are based on functionality / non-functionality of certain alleles with consequent different intensity of substrate metabolized through CYP2D6, all resulting in development of toxic side effects or poor therapeutic response.

It is considered that gene polymorphisms of dopamine receptor type 2 (DRD2) which is target of many antipsychotic drugs can play important role in MNS development, specifically the DRD2 TaqI A polymorphism. According to some authors carriers of A1 allele have higher predisposition for development of MNS (Suzuki et al. 2001), while other studies did not confirm such findings (Kishida et al. 2003).

In this paper we present two case reports both of which developed three consecutive MNS. The analysis of CYP2D6 and DRD2 TaqI A, two significant gene polymorphisms commonly associated with potential for MNS development, was done.

## CASE A

In case report A, we describe a 36 years old man, in the 17 years psychiatric treatment due to bipolar affective disorder. He was treated in intensive care unit within a psychiatric ward with clinical presentation of mania with psychotic features. He took clozapine 200mg per day, valproic acid 1000 mg per day and intermittently 50 mg of promazine or 10 mg diazepam intramuscularly when agitated. Third day into his treatment, the patient became febrile up to 39,5 C, somnolent, mutistic, tachycardia was 120 per minute, he had tremor and rigidity of extremities, neck and masticator muscles with consequent dysphagia. He had increased laboratory findings indicating rhabdomyolysis (CPK 5870), hepatic parameters (AST 176, ALT 81, GGT 75) as well as impaired laboratory findings of renal function (creatinine 146) indicating mild initial impairment. Clinical presentation indicated MNS with all major features and that is the reason why we decided to exclude all psychiatric drugs. We initiated intensive symptomatic treatment which included intravenous hydration, body temperature monitoring and monitoring of vital and laboratory parameters (CPK, renal and hepatic parameters). On the seventh day of treatment, the patient's condition improved regarding his consciousness and muscle tone, he was sub febrile (up to 37, 2 C), vital parameters were stabile and CPK decreased to 1365. After vital stabilization he became agitated and psychotic again. For the next ten days he was treated with high doses of diazepam (up to 60 mg

per day oral) which resulted in psychomotoric appeasement. Because of still dominant psychotic symptoms antipsychotic drug was inevitable. Clozapine was carefully titrated and later lithium. The patient was discharged in good condition with 125 mg of clozapine and 900 mg of lithium per day.

Described MNS episode was his third. We looked into his previous medical documentation where we found two well documented previous episodes of MNS. First episode occurred when he was 20, after he took haloperidol, promazine and fluphenazine. As potential antipsychotic drug involved in MNS, haloperidol was suspected. The clinical presentation at the time was described as severe, and among other treatments he was treated with ECT.

Two years later he developed second MNS when he was 22. At the time he took fluphenazine and perazine.

Pharmacogenetic analysis of CYP2D6 and DRD2 TaqI A polymorphisms was done. Genotyping of CYP2D6\*1\*3\*4\*5\*6 showed no evidence of poor metabolizer phenotype. On the other hand the patient was found to be heterozygous for CYP2D6\*4 (genotype \*1/\*4). Analysis for DRD2 TaqI A polymorphisms showed that he is heterozygous for A1 allele (genotype A1A2).

## CASE B

In case report B, we describe 42 years old, male patient in psychiatric treatment for the last 22 years due to schizoaffective disorder, mixed type. He was hospitalized again, only a week after his last discharged. He stopped taking his medicine and he relapsed. After admission we introduced 10 mg per day haloperidol and 900 mg per day of lorazepam when needed, medication which the patient took in the course of previous hospitalization when criteria for remission were fulfilled. On the fourth day of treatment patient became febrile, somnolent, puzzled, tachycardic, with generalized rigidity of skeletal muscles. Laboratory findings were indicating leukocytosis (19) and rhabdomyolysis (CPK 17205). Clinical presentation of MNS was evident and we decided to exclude all psychiatric drugs. We started intensive monitoring of the patient's condition and his vital parameters. He was hydrated intravenously, acquired antipyretics and we monitored laboratory parameters. Tenth days after he was diagnosed with MNS, all laboratory and somatic clinical parameters were normalized. In patient psychic status positive symptoms were dominating with

agitation, motor unrest, dysphoria with destructive ideations and behavior. Because we were aware of intensity and seriousness of early described clinical presentation and potential consequences, next three weeks after we registered increase in CPK, he was treated only with lorazepam. Psychotic symptoms were still evident and we introduced risperidone: first two days 1 mg per day, third day 2 mg per day. Suddenly, the patient again developed MNS with CPK up to 7205.

We excluded all psychiatric drugs, and intensive symptomatic treatment and monitoring was restarted. This time, before introduction of next antipsychotic drug, which was again inevitable because of patient's psychosis, we waited for five weeks. After five weeks during which patient received only diazepam in doses up to 60 mg per day oral, we introduced clozapine (25 per day). On the sixth day of treatment with clozapine, the patient developed third consecutive MNS (CPK-8570, L 20, tax 39,5 C AST 45, ALT 60, GGT 30, creatinine 210). Six weeks after his third MNS patient received only diazepam. At that point we suggested ECT to patient's tutor, but he declined. We decided to slowly introduce quetiapine (25 mg per day) and this time not a single sign or symptom of MNS was observed. Patient met all criteria for full remission with 800mg of quetiapine and 900mg of lithium without any further side effect.

We analyzed genetic polymorphisms for CYP2D6 and DRD2 TaqI A. Genotypisation of CYP2D6\*1\*3\*4\*5\*6 did not confirm poor metabolizer genotype (genotype \*1/\*1). A1 allele in analysis of DRD2 TaqI A polymorphism was not confirmed as well.

## DISCUSSION

MNS was first time described in literature by Delay and Deniker (Delay et al. 1968) at late 60's of the last century. Twenty years later there was a first published report on triple MNS in same patient caused by different typical antipsychotic drugs (Lavie et al. 1986). Later we can find additional case reports on multiple MNS with atypical antipsychotic drugs (Bottlender et al. 2002), but rather rarely.

Clinical presentation can vary from fully developed one (characterized by skeletal muscle rigidity, hyperthermia, alterations in consciousness, autonomic dysfunctions) to masked clinical presentations which can cause many differential diagnostic dilemmas.

That is probably the reason why several diagnostic criteria were proposed (i.e. American Psychiatric Association 1994, Mathews & Aderibigbe 1999). In both presented case reports, clinical presentation was rather typical and confirmed by laboratory findings. Both cases had predisposing factors, especially case A with obvious pharmacological and clinical factors, as well as male gender and age under 40 (Caroff et al. 1980).

Furthermore, it is considered that genetic mechanisms could play important role especially in patients who already experienced MNS. Different gene alterations could be potential risk factors for MNS, especially those in the area of isoenzymes of CYP2D6 and dopamine receptor type 2 (DRD2).

Isoenzyme CYP2D6 plays important role in hepatic metabolism of different psychotropic drugs. Primarily this enzyme metabolizes haloperidol, fluphenazine and risperidone (Michalets, 1998) any of which might have caused MNS in both case reports. For both patients genotypisation was done (CYP2D6\*1\*3\*4\*5\*6) and findings did not confirm poor metabolizer phenotype. On the other hand, case A is heterozygous for CYP2D6\*4 (genotype \*1/\*4), what might suggest certain possibility of compromised enzymatic activity. Several studies suggest correlation between MNS and CYP2D6 polymorphisms as a result of defective activity of CYP2D6 isoenzyme (Iwahashi et al. 1994, Kato et al. 2005, Kato et al. 2007).

Pharmacogenetic research studied the role of DRD2 TaqI A polymorphisms and potential risk for MNS with inconsistent results. Some authors confirm correlation (Suzuki et al. 2001) while others do not (Kishida et al. 2003). Our finding with cases A and B are consistent with findings from literature, with case A being heterozygous for A1 allele (genotype A1A2) and case B not being carrier of A1 allele (genotype A2A2), nevertheless developing three consecutive MNS.

MNS does not represent absolute contra-indication for antipsychotic drugs re-introduction although risk of another MNS exists (Haddad & Dursun 2008).

Earlier it was considered that this serious side effect is related to typical antipsychotic drugs (Pope et al. 1986), but recent findings showed us that atypical antipsychotic drugs can cause MNS (Ananth et al. 2004), as well as other psychotropic drugs. Here presented cases are consistent with described literature. Some authors describe cases of re-introduction of same drug that caused MNS (Cohen 1994, Illing et al. 1996, Huang 2001), as

was done in case A with clozapine without MNS development. Despite the fact that clozapine can cause MNS some authors consider clozapine first line therapy in patients who developed MNS earlier (Weller 1992). Case A, in addition to clozapine, received sporadically typical antipsychotic drugs in intra muscular formulation (promazine) suggesting the possibility that promazine caused MNS. Furthermore, he received valproic acid as additional psychotropic drug. It seems that combinations of psychotropic drugs can increase risk for MNS development. That may explain the fact that when clozapine was rechallenged as a monotherapy in high risk patient who developed MNS, the patient did not develop MNS. As for case B in reintroduction of antipsychotic drug we chose antipsychotic drug from different chemical class and with less affinity for D2 receptors from the original one (Pelonero et al. 1998). Nevertheless, in case B we can observe that even different antipsychotic drugs with different affinity for D2 receptors can cause MNS. Generally, after previous MNS it is extremely difficult to predict outcome of antipsychotic drug rechallenge and it's potential for MNS, as seen in both described cases. Nevertheless, once MNS develops, the risk for second (or third) MNS is increased and with further treatment we must be extremely careful.

Despite all research, etiopathogenesis as well as clinical presentation remains unclear. Genetic mechanisms for sure play important role. The final goal of pharmacogenetics is to help clinicians to choose the best treatment for each individual patient (Mihaljević-Peleš et al. 2008.) Further pharmacogenetic research is necessary as it may at least in one part clarify some of the puzzles related to this syndrome. In long term, pharmacogenetic analysis implemented in every day clinical practice could help in prevention of this extremely serious and potentially fatal side effect.

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