Neuroleptic Malignant Syndrome and Severe Thrombocytopenia: Case Report and Literature Review

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We report an unusual case of thrombocytopenia associated with neuroleptic malignant syndrome (NMS). A 31-year-old Black male with a history of hypertension, partial seizures, and schizophrenia developed acute rigidity closely followed by severe hyperpyrexia (temperature 102°F), tachypnea, and tachycardia. His home medications at the time of presentation included propanolol 10 mg tid, haloperidol 10 mg bid, sodium valproate 500 mg bid, benztropine 1 mg bid, and haloperidol decanoate 100 mg i.m. every 3 weeks, from another psychiatric facility. Despite vigorous therapy for the hyperthermia, he rapidly developed significant hypoxia requiring mechanical ventilation. A diagnosis of neuroleptic malignant syndrome was made and the patient continued to receive aggressive supportive care. On hospital day 2 his platelet count dropped to 47,000/μl and bottomed out at 36,000/μl by day 3 with other blood cell counts remaining within normal limits. Over the next few days he showed rapid clinical improvement with normalization of his blood chemistries and he was discharged home after 5 days of hospitalization in good condition.

KEY WORDS: neuroleptic malignant syndrome; thrombocytopenia; neuroleptics.

INTRODUCTION

Blood dyscrasias occur as a frequent side effect of neuroleptic (NL) administration, the most serious being agranulocytosis and, of less concern, granulocytopenia. NL-induced thrombocytopenia is fairly uncommon and usually occurs concomitantly with leukopenia. Indeed, in a 6-year course study, the largest reported series in the world literature, by Rosebush and Stewart (1), elevated platelet count rather than thrombocytopenia was the most frequent finding.

Two fatal cases of coexistent leukopenia and thrombocytopenia were reported in the past; one was a 28-year-old female patient receiving chlorpromazine (2) and the other secondary to jaundice, agranulocytosis, and thrombocytopenia associated with prochlorperazine administration in 1963 (3). Isolated NL-induced thrombocytopenia is a more rare occurrence, but it has been reported three times during the last decade and a half (4–6).

However, in a study encompassing one entire year of observations no clinical differences were found between NL-treated and untreated schizophrenics. Yet, there was a suggestion of a trend, as three of the NL-treated patients had platelet counts of less than 150,000/μl. It is unkown whether the development of neuroleptic malignant syndrome (NMS) increases the risk of agranulocytosis, leukopenia, thrombocytopenia, or a combination of these blood abnormalities. But it appears that isolated thrombocytopenia associated with NMS is also uncommon. Indeed, no cases were reported throughout a time span of almost two decades, beginning in 1976 (7), and only three cases during the last 3–4 years despite awareness of the NMS since it was first reported in 1968 (8). It is not known whether thrombocytopenia was reported in conjunction with NMS between 1968 and 1976, and also since the introduction

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of NL agents for the treatment of psychosis in France in the early 1950s. It would be informative to know whether such cases were ever reported. This would reinforce the cause–effect connection or at least the correlation between NMS and thrombocytopenia, which at this stage cannot go beyond the level of high suspicion. It is intriguing that all the four cases so far reported were patients in their early to middle 30s including the lethal case reported by Lenler-Peterson *et al.* (9). These authors had already pointed out that NMS is overrepresented in young patients.

CASE REPORT

A 31-year-old black Male with a history of hypertension, partial seizure disorder, and schizophrenia was admitted to a local county hospital with acute onset of severe rigidity and unresponsiveness. His home medications included propranolol 10 mg three times a day, haloperidol 10 mg twice a day, valproic acid 500 mg twice a day, benztropine 1 mg three times a day, and haloperidol decanoate 100 mg intramuscularly every 2–3 weeks. He had received the most recent injection of haloperidol decanoate 2 days prior to presentation. According to the patient's family, he had been in his usual state of health 1 day prior to hospitalization when he started to develop agitation with increasing body stiffness. He began to breathe at a rapid rate with a decreasing level of consciousness.

Upon arrival at the local hospital he was found to be unresponsive and extremely rigid, with a core temperature of 108.7°F. His heart rate was 120 beats/min, his blood pressure was 160/70 mm Hg, and his respiratory rate was 20/min. His skin was hot and dry. The remainder of the physical exam was unremarkable. A diagnosis of neuroleptic malignant syndrome was made and the patient received one dose of dantrolene 2 mg/kg intravenously. He received vigorous therapy for his hyperthermia with cooling blankets, ice packs, and gastric lavage with iced normal saline. While in the emergency room he started to become bradypneic with a falling oxygen saturation, was intubated, and was placed on artificial ventilation. Within a few hours his temperature decreased to 102.8°F and he was transferred to the University Hospital.

Upon arrival he was minimally responsive to painful stimuli. His vital signs showed a blood pressure of 118/74 mm Hg, a heart rate of 75/min, and a temperature of 97.2°F. Physical examination was positive for minimal muscular rigidity. A CT scan of the brain, a lumbar puncture, and an EKG were done and were found to be unremarkable. Laboratory data from the local county hospital showed the following findings from blood drawn at the time the patient was initially brought to them. A WBC count of 148,000/μl, platelets at 211,000/μl (with no abnormalities on peripheral smear), a serum sodium of 129 mEq/L, a potassium of 4.4 meq/L, a BUN of 9 mg/dl, and a creatinine of 2.2 mg/dl. CPK was 973 U/L. He was admitted to the ICU and received supportive care. On hospital day 2 his platelet counts acutely dropped to 47,000/μl, but with no signs of active bleeding. On day 3 his platelets further dropped to 36,000/μl. He had a minimal nosebleed. The next day his platelets increased to 46,000/μl. Prothrombin time was increased to 15.7 sec (*N:* 10.7–14.3) on day 1 and 14.7 on day 3, which was marginally high, but the partial thromboplastin time was normal throughout this period (Table 1).

He began to wake up on day 2 and was extubated the same day. He remained afebrile and improved rapidly over the next 2 days with his mental status reverting to baseline. His platelet count increase paralleled his symptomatic improvement and on the day of discharge the platelet count was 86,000/μl. His peak CPK levels reached 1324 U/L by day 3 and then dropped to 387 U/L by day 5 prior to discharge (Table 1). No evidence of renal insufficiency was noted during his stay. A drug and alcohol screen was negative. Initially his differential diagnosis included an infectious process, specifically meningitis, but the blood and spinal fluid cultures remained negative during hospitalization.

DISCUSSION

A hypothesis has been proposed by Yao *et al.* (10) to explain the concomitance of thrombocytopenia and NMS. It is based on their findings that thrombin-induced platelet production of inositol

Table 1. Laboratory Data

	On Admission	Day 3	Day 5
WBC ($10^3/\mu$l)	12.7	7.9	6.8
Hemoglobin (mg/dl)	13.2	11.7	12.0
Hematocrit (%)	39.7	35.2	35.8
Platelets ($10^3/\mu$l)	211	36	86
CPK (U/L)	973	1324	387
PT (sec)	15.7	14.7	12.9
PTT (sec)	30	30	21

phosphates (IP) is higher in haloperidol-treated as well as untreated schizophrenics. This means that schizophrenics may produce higher levels of IP than nonschizophrenics and that the source of the extra-IP may reside in the platelets. On the other hand, NL-induced blockage of dopamine also contributes to a serum increase in IP levels, which would in turn potentiate activation of protein kinase C (11). These findings suggest that there may be an increased signal transduction in schizophrenia and that this state may be mediated through neuroleptic-regulated IP hydrolysis (10).

However, understanding of the mechanisms responsible for IP synthesis, breakdown, and regulation in schizophrenia in NL-treated and untreated patients is still very rudimentary. It is intriguing to consider that platelets are comparable to catecholaminergic neurons (12) and as such they may represent an acceptable model of a neurosecretory cell to investigate membrane-dependent functions such as signal transduction in schizophrenic disorders (10). Thrombin is a potent agonist leading to the activation of phospholipases C and A2, protein kinases, IP, and Ca^{2+} mobilization. All of these factors are involved in platelet adhesion to endothelial membranes and aggregation with each other. Adhesion and aggregation are two important processes of platelet function. The result of these enzymatic reactions is generation of diacylglycerol (DAG) and inositol triphosphate (IP3), which are the second messengers activating protein kinase C and mobilizing calcium (Ca^{2+}) from intracellular stores. With these transduction mechanisms there is a built-in regulation of phospholipase C (PLC)-induced hydrolysis of IP3 and ion channels. These early biochemical breakdowns are responsible for the signal transduction to move from the membrane surface receptor to the cell interior. This formation of IP3 is significantly higher in haloperidol-treated schizophrenics than in drug-naive schizophrenics or normal controls (13). This increased production of IPs appears, therefore, to be the result of NL treatment. Furthermore, such drug effect may often endure for 4 months after NL withdrawal (13). Subsequent biochemical products of IP metabolism are conversion of IPs to DAG and phosphatidic acid (PA). It has been claimed that schizophrenics with abnormal IP turnover would have a better outcome than those without it, meaning that accumulation of DAG in schizophrenia may be a marker of good prognosis (14), but this would require confirmation. We do know that the accumulation of DAG in the platelets of acute schizophrenics following thrombin stimulation of their platelet membranes persists for at least 2 months even after acute psychotic symptoms have disappeared (14).

Accumulation of DAG and reduction of AC-cAMP function have been demonstrated in platelets of schizophrenic patients. These changes in turn are thought to cause inhibition of the IP3/Ca^{2+} pathway, lowering IP turnover, increased activation of protein kinase C, and reduction in protein kinase A activity and calmodulin-dependent protein kinase. Since neurons respond in ways similar to platelets, it is thought that such a cascade of events may not be restricted to platelets, but may also involve the brain, causing a distorted balance of protein activation via phosphorylation in neurons and further deficits of schizophrenia (11) compounded with NMS. Ray (7) entertained the possibility that these mechanisms might trigger a cascade of events leading to further platelet activation and aggregation, as expected under normal circumstances. Ray (7) went on to postulate that a hyperdynamic pathway may thus be opened that would lead to thrombocytopenia. Ray realized, however, that this postulate fails to explain why no clinical evidence of microvessal thrombosis has yet been observed or reported.

However, the rapidly progressing lethal case reported by Lenler-Peterson *et al.* (9) was complicated by disseminated intravascular coagulation. No definitive answers to the questions posed above are available at this point, but clinicians need to be aware of the possible cooccurrence of NMS and thrombocytopenia. It might be possible to explain the causation of thrombocytopenia by other mechanisms. For example, large groups of patients on tricyclic antidepressants, carbamazepine, and valproate have been studied for their proclivity to develop blood dyscrasias (15,16). According to Tohen *et al.* (16), severe blood dyscrasias, specifically leukopenia, are uncommon in psychiatric patients treated with valproate, just as they are with carbamazepine, imipramine, or desipramine. Blood dyscrasias are also most likely to follow within the first 45 days of treatment. The study by Loiseau (15) is more relevant to our discussion because here the focus was valproate as a cause of platelet dysfunction. The conclusion of this study was that valproate can provoke, infrequently, a thrombocytopenia which does not appear to have much clinical significance except in surgical patients, obviously because of the risk of hemorrhage. The authors recommendation was that valproate doses of 40 mg/kg/day should not be exceeded. Our patient was maintained at 500 mg twice daily, which is close to the

maximum dose recommended by Loiseau (15), who felt that the risk of hematological abnormalities is often dose-related. Vadney (17) also reported in 1992 an association between valproate administration, viral infection, particularly varicella, and thrombocytopenia, a correlation which would be clinically useful to keep in mind.

No reason to suspect viral infection was found during our patient's laboratory work-up. For the reasons mentioned above (rarity of cooccurrence, usually during the first 45 days of treatment, and our patient's relatively low dose of valproate), we do not feel that the probability of valproate being the cause of our patient's thrombocytopenia is very high, but we have no way to rule this out with certainty.

Even though dantrolene has been used for quite some time in the treatment of NMS, there is no evidence that it alters the course of this disease in any way (1). There are anecdotal case reports similar to ours that may suggest a possible effect on NMS, but there is insufficient evidence to recommend dantrolene as a standard treatment.

We were concerned with the risk of spontaneous bleeding in our patient, but a review of the literature was reassuring, as other authors had reported no evidence of bleeding and that bleeding may occur only after platelet counts fall below 19,000/μl (4). This study, although it did not involve a picture of NMS, nevertheless concluded, based on a spleen scan to rule out an inordinate amount of spleen sequestering platelets, that platelets were breaking down at a rate that was significantly greater than normal and this finding further suggested that there may be something faulty about the platelets themselves. A subsequent nonspecific antibody study revealed that "some antibody in both the patient's plasma and attached to his platelets was capable of destroying donor platelets, suggesting that antibodies were being produced in response to a non specific antigen" (4). These authors believed that the antigen substance is usually a drug, which in their case was narrowed down to chlorpromazine. Their literature survey concluded that phenothiazines with an aliphatic side chain, such as chlorpromazine, or with a piperadine side chain, such as thioridazine, have been reported to cause thrombocytopenia; haloperidol was also suggested as a possible cause at least for the initial platelet decline in their patient.

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