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Clozapine-induced agranulocytosis and thrombopenia in a patient with dopaminergic psychosis

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Summary. In patients with Parkinson' disease and dopaminergic psychosis, clozapine treatment is recommended as the drug is free from extrapyramidal side effects and does not worsen motor symptoms of the underlying disease. The use of clozapine, however, is limited due to its hematotoxic side effects. For treatment of clozapine-induced agranulocytosis, granulocyte colony-stimulating factors (G-CSF) are recommended. We report the case of a 72-years-old male patient with clozapine-induced agranulocytosis and thrombopenia. Neutropenia was successfully treated with G-CSF, but thrombopenia persisted and resolved spontaneously after 14 days. Bone marrow toxicity of clozapine is not restricted to white cell maturation, but may also impair thrombocytopoesis.

Keywords: Agranulocytosis, clozapine, dopaminergic psychosis, granulocyte colony-stimulating factor, neutropenia, Parkinson's disease

Introduction

Drug-induced psychiatric states frequently occur in Parkinson's disease (PD). In the pre-levodopa era, psychiatric disorders were described in PD, but in untreated patients psychosis was rare. Since the development of levodopa and other dopaminergic drugs for treatment of PD, psychotic symptoms became more common and affect up to 50% of patients suffering from PD. Psychosis in PD has been associated with all antiparkinson drugs. The most common features are vivid visual hallucinations (optic hallucinosis) occurring on a background of clear sensorium that are in a minority of patients (10–15%) accompanied by paranoid delusions, confusion and clouding of consciousness (Factor et al., 1995). The emergence of psychosis reduces the patient's functional capacities and increases caregiver burden. It also poses a therapeutic dilemma as effective treatment of psychosis may result in worsening of the motor symptoms of PD and vice versa. Atypical neuroleptics such as clozapine have been successfully applied in the treatment of PD-associated psychiatric states. Yet, due to a relatively high incidence of disturbances in

hematopoesis, the use of clozapine is limited to strictly selected patients. While agranulocytosis is well known to be caused by clozapine, there is only scarce information on disturbances of platelet function due to clozapine treatment (e.g. Durst et al., 1993).

We report the case of a 72 years-old patient that developed both agranulocytosis and thrombopenia under clozapine treatment for psychosis in PD.

Case report

The 72 years-old male patient had been suffering for four years from Parkinson's disease (Hoehn and Yahr stage IV, Webster Score 24 of 30 points). Under a combined therapy of 100 mg L-DOPA qid, Selegilin 5 mg bid, Biperiden 2 mg tid and Amantadin 100 mg tid, he developed an acute delirious state with visual and acustic hallucinations, vivid delusions, paranoia and aggressive eruptions. The daily dose of dopamine agonists was gradually reduced. As psychotic symtoms persisted, the patient was put on a symptomatic treatment with typical neuroleptics (Haloperidol 1 mg qid). However, psychotic symptoms did not respond and concomitantly, extrapyramidal symptoms worsened and the patient became bedridden. The patient was admitted to hospital and antipsychotic therapy was changed to clozapine starting with a daily dose of 12.5 mg that was gradually increased to 37.5 mg per day. Psychotic symptoms ameliorated, and the patient was able to sit in a wheelchair and walk for a few meters with assistance. Three weeks after the initiation of clozapine therapy, the patient developed pneumonia caused by *klebsiella pneumoniae* that rapidly developed into a bacterial sepsis. With the onset of sepsis, symptoms of disseminated intravascular coagulation (DIC) were observed with a fall of thrombocytes from 297.000/µl to 111.000/µl and INR rise from 1.2 to 2.9 associated with spontaneous gingival bleeding. However, instead of suspected leucocytosis, a severe leucopenia was found in white blood cell count (2.500/µl, 24% neutrophils, 18% eosinophils and 58% lymphocytes). Due to progressive respiratory insufficiency and septic shock, the patient was intubated and mechanically ventilated. Clozapine therapy was discontinued immediately. Upon admission to the ICU the patient's body temperature was 39°C. Maximum body temperature on the following day was 38°C and remained stable at this level for the following days. INR was 2.9. upon admission. After immediate substitution of fresh frozen plasma, INR was 1.6 on the second day and was between 1.4 and 1.7 at daily measurements during the following week without further plasma substitution. Fibrinogen level upon admission was 600 mg/dl, 627 mg/dl on the second and 452 mg/dl on the fourth day. Sepsis was successfully treated within 24 hours, and symptoms of the DIC vanished. During the following days, there were neither clinical nor laboratory findings compatible with the assumption of ongoing sepsis and DIC. Platelet counts were stable with values above 100.000/µl, but severe leucopenia persisted. Examinination of sternal bone marrow aspirate showed considerable eosinophilia, a markedly reduced granulocytopoesis with a shift to the left and a moderate decrease in the number of megacaryocytes. Toxic bone marrow dysfunction was assumed and a therapy with the recombinant granulocyte-colony stimulating factor (G-CSF) filgrastim (Neupogen^{R}) was started in a daily dose of 10 µg/kg body weight. From the second day of G-CSF treatment, a rise in neutrophils was found in peripheral white blood cell count and therapy with G-CSF was terminated after four days. Daily white blood cell counts documented the persistence of normalisation. In the following four days however, thrombocyte number gradually decreased. In the absence of signs of systemic infection (normothermia, leucocytes 7.000/µl, INR 1.4, fibrinogen 500 mg/dl), thrombocytopenia could not be attributed to septic or infectious processes. Five days after admission to the ICU, and with platelet counts below 40.000/µl (nadir of thrombocytes under substitution: 35.000/µl), spontaneous bleeding from nasal (epistaxis) and oral mucosa was observed. As with agranulocytosis, a toxic effect of clozapine therapy was assumed as bone marrow aspirate had already demonstrated a disturbance in

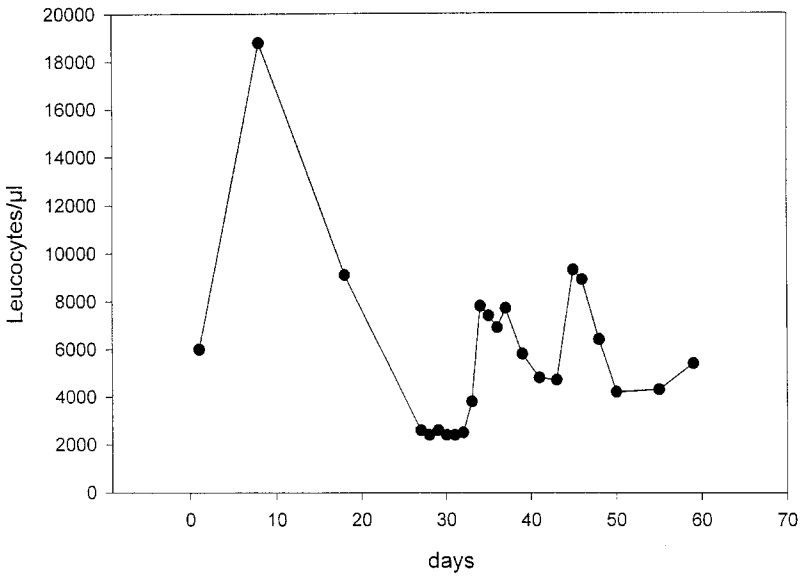

Fig. 1. Synopsis of leucocyte counts

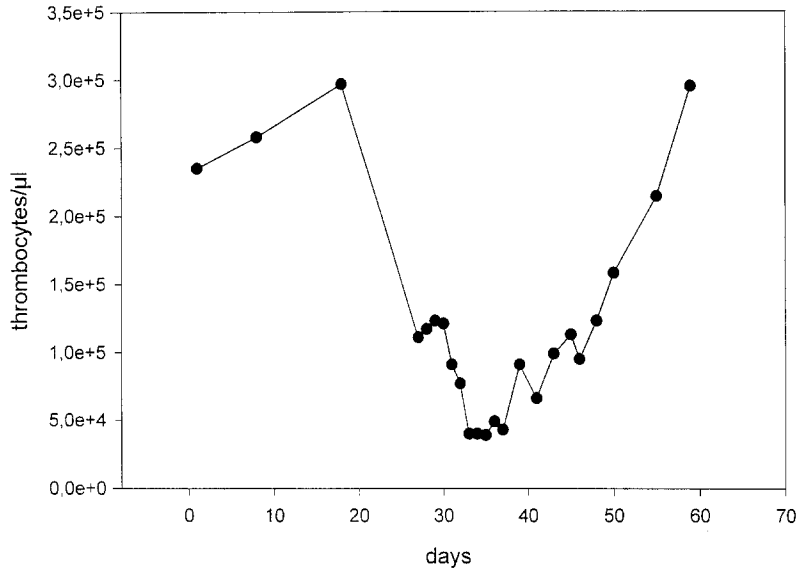

Fig. 2. Synopsis of platelet counts

thrombocytopoesis. Repeated transfusion of thrombocytes was performed to keep platelet counts above 40.000/µl in order to control the bleeding disorder until spontaneous restitution of thrombocytopoesis was observed after one week. The patient was successfully weaned from the respirator and dismissed from the ICU six weeks after admission. Due to the patient's age and general medical condition and for intercurrent complications independent from the initial septic syndrome and its sequela, weaning from the ventilator

turned out to be extremely difficult and was complicated e.g. by a second pneumonia from pseudomonas aeruginosa. Parkinson's disease remained a therapeutic problem with recurrence of psychotic symptoms following dosage adjustmemt of dopaminergic drugs. Severe akinesis and rigor made mobilisation difficult and prolonged the stay at the ICU. Thus, the entire duration of patient's six-weeks stay in the ICU was not due to the initial sepsis only, but also to factors independent from that condition.

Retrospectively, no other reason for agranulocytosis and delayed thrombocytopenia except for clozapine treatment could be found, as the patient had not received concomitant medication with possible hematotoxic side effects and sepsis had been successfully treated at several days before thrombocytopenia became clinically significant.

A graphic synopsis of white blood cell and platelet counts during the observation period is given in Figs. 1 and 2.

Discussion

First reports of psychotic symptoms in Parkinson's disease (PD) date from the pre-levodopa era, but in untreated patients psychosis was rare. Since the development of levodopa and other dopaminergic drugs for treatment of PD, psychotic symptoms became more common (Overview: Factor and Brown, 1992). Psychosis in PD has been associated with all antiparkinson drugs and affects about 20% of all patients on levodopa medication (Goodwin, 1971). This percentage rises to more than 30% if dopamine agonists are used as adjunctive therapy (Factor et al., 1988).

The emergence of psychosis poses a therapeutic problem as effective treatment of psychotic symptoms may result in worsening of the motor symptoms of PD and vice versa. Reduction of antiparkinson medication ("drug holiday") usally leads to increasing parkinsonian disability (Marsden and Fahn, 1981). Classical neuroleptics are utilized with mixed results, as they ameliorate psychotic symptoms, but concomitantly worsen extrapyramidal manifestations (Rondot et al., 1984).

Atypical neuroleptics such as clozapine have been successfully applied in the treatment of PD-associated psychiatric states (Pfeiffer and Wagner, 1994; Factor et al., 1994; Rabey et al., 1995). The exact mechanisms of the antipsychotic effect of clozapine in PD are still controversial. Clozapine is a dibenzo-diazepine derivate with high affinity to the dopamine D4-receptor. It also blocks dopamine D1-receptor sites in the limbic system sparing striatal locations and has potent antiserotoninergic, antiadrenergic, antimuscarinergic and antihistaminic effects, as interactions of the drug with dopamine (D_3, D_4) and serotonin (5-HT_{2a}, 5-HT_3, 5-HT_6) receptors were described (Meltzer, 1995). The alleviation of dopaminergic psychosis in PD after administration of the 5-HT_3 serotonin receptor antagonist ondansetron supports the notion that dopamine causes mental disturbances in PD by interacting with serotonin in the mesolimbic and mesocortical systems (see summary of the topic by Rabey et al., 1995 and Meltzer, 1995). As low plasma levels of clozapine are sufficient to obtain an effective blockade of D_4 and 5-HT_{2a} receptors, low daily doses of clozapine (less than 50 mg/d) are adequate to alleviate psychotic symptoms in PD (Pfeiffer and Wagner, 1994; Meltzer et al., 1995). However, continuous therapy is often necessary to prevent recurrence of psychotic symptoms (Pinter and Helscher, 1993; Rabey et al., 1995). Because of its potentially life-

threatening implications, bone marrow toxicity is the most important side effect that restricts the application of clozapine. In approximately 3% of patients treated with clozapine, it results in granulocytopenia, and in approximately 0.6% in agranulocytosis (Alvir et al., 1993; Lieberman and Alvir, 1992; Atkin et al., 1996). The mechanisms of bone marrow toxicity from clozapine are still under debate. Toxic damage from clozapine or its metabolites (Veys et al., 1992) and immunological reactions (Pisciotta et al., 1992) are discussed. Recent studies demonstrate that clozapine probably impairs two stages of hematopoesis: damage to myeloblasts results in persisting agranulocytosis, toxic effects to late stages of granulocyte maturation result in granulocytopenia (Veys et al., 1992). While in the latter case white blood cell counts quickly return to normal values after discontinuation of clozapine, agranulocytosis from toxic myeloblast damage persists. These patients are at high risk for septic complications with high mortality rates. Early use of granulocyte-colony-stimulating factors (G-CSF) may shorten the duration of agranulocytosis from a mean of 16 days and reduces the morbidity of these patients (see the review by Gerson, 1994). Toxic bone marrow dysfunction was documented in our patient by sternal bone marrow aspirate. Peripheral blood and bone marrow smears showed a considerable eosinophilia. This phenomenon is often seen under these circumstances, its etiology, however, is obscure (Veys et al., 1992).

The positive effect of G-CSF was also demonstrated in our patient: the duration of agranulocytosis was reduced to 3 days, and sepsis was successfully treated. However, in spite of successful treatment of the infectious disorder, platelet counts continued to drop to a nadir of 35.000/μl four days later. Thrombocytopenia was followed by symptomatic mucosal bleedings. The time course of thrombopenia was not influenced by G-CSF treatment.

Reports on disturbances of platelet function due to clozapine treatment are rare, and their existence is being disputed (Klimke and Klieser, 1995). Durst an co-workers (1993) reported a case of thrombocytopenia cessating spontaneously after discontinuation of clozapine treatment. Thrombocytopenia with platelet counts around 40.000/μl was present from the fifth day after admission to the ICU, i.e. at least three days after sepsis had been controlled. As thrombocytopenia in sepsis usually occurs during the acute phase as a symptom of DIC, the delayed thrombocytopenia in our patient was a symptom independent from sepsis. At the time INR was 2.9 during the acute phase of the sepsis, platelet counts were 111.000/μl, and at thrombocyte nadir – five days later – INR was 1.6. Thus, a common reason for thrombopenia and INR rise – e.g. ongoing DIC from sepsis – seems improbable. Furthermore, if thrombocytopenia in our patient had been the result of sepsis-related DIC, immediate amelioration would have been observed after successful treatment of the infection. The nadir of thrombocyte counts was 35.000/μl – under platelet substitution, however. Lower values might have escaped detection, because thrombocyte substitution was started as soon as spontaneous bleeding occurred. Therefore, we assume that thrombocytopenia was the consequence of clozapine-induced toxic bone marrow dysfunction. Our conclusion is backed by the results of bone marrow aspirate showing

both disturbances of granulocytopoesis and thrombopoesis at a point where platelet counts still revealed normal values. Lifetime of platelets (approximately 5–7 days) is longer than that of granulocytes (circulating half-time 6–7 hrs, cf. Gallin, 1988). Therefore, after toxic damage to both neutrophile stem cells and megacaryocytes, the drop in white blood cell counts will preceed the declining platelet counts by up to 5 days. This corresponds to the observations in our patient.

Before the introduction of colony-stimulating factors, clozapine-induced agranulocytosis subsided within two weeks after onset if patients survived the infectious complication (Gerson, 1994). Given the data from our patient (see table 2), the same seems to be true for toxic thrombopenia due to clozapine treatment: spontaneous normalization of platelet counts may be expected 10–14 days after symptom onset. Until then, bleeding complications have to be treated with substitution of thrombocytes. Cytokine therapy of toxic thrombocytopenia was not available in 1993, when our patient was treated. Parallel to the experiences in toxic agranulocytosis, a positive effect of recombinant megacaryocyte colony-stimulating factors may be expected. This should be considered in the treatment of toxic thrombopenia, a rare complication of clozapine therapy.

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