Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Apomorphine-Induced Immune Hemolytic Anemia

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Since the first description of drug-induced immune hemolytic anemia (DIIHA),[1] more than 130 drugs have been reported to cause this adverse hematologic effect.[2] L-dopa was the first dopaminergic drug to be directly related to DIIHA.[3–6] The involvement of other dopaminergic drugs has been suggested, including the dopamine agonists cabergoline and apomorphine, although very few confirmed cases have been published.[7–9]

Case Report

A 56-year-old woman was diagnosed with idiopathic Parkinson's disease (PD) in 2006. She was first treated with L-dopa/benserazide (up to 500 mg/day), rotigotine (up to 8 mg/day), and amantadine (200 mg/day), and she responded positively for the first 5 years. In time, however, the patient developed motor complications including motor fluctuations, gait freezing, and dopa-related dyskinesias. In 2011 (age 61 years), she began receiving intermittent subcutaneous injections of apomorphine and then, in April 2013 (age 63 years), continuous infusion of apomorphine, and she showed good tolerability and functional improvement. As of April 2013, her medication included apomorphine infusion (4.9 mg/h during 15 h; total daily apomorphine: 75 mg), L-dopa/benserazide (400 mg/day), and rotigotine 8 mg at night. The results of a peripheral blood test performed before the apomorphine infusion (April 2013) were within the normal range (Table 1). The patient had no other conditions, such as autoimmune diseases (eg, systemic lupus erythematosus), neoplastic disease (eg, Hodgkin's lymphoma, chronic lymphoid leukemia), or tumors (eg, thymoma, ovarian dermoid cyst), and she was not taking any other drugs.

The patient presented to the emergency department in October 2013 with subacute symptomatology of 3 days' duration, including central chest pain, dyspnea, diarrhea, vomiting, and paresthesias. No evidence of fever or other symptoms of infection were detected. Clinical examination showed hypotension (blood pressure 90/60 mm Hg), a heart rate of 76 bpm, and baseline oxygen saturation at 96%. Jaundice, systolic heart murmur, edemas, and choluria (dark or brown urine) were also observed. Urgent radiologic imaging tests, including aortic, pulmonary, and coronary studies, were normal. A peripheral blood test showed severe anemia suggestive of hemolysis (see Table 1), after which a direct Coombs test was requested. The results at 37°C were positive at a high titer (1/2048, with IgG component at a titer of 1/512; the rest of the subunits were negative, ie, IgA, IgM, and complement), thus supporting an immune origin of the condition. The patient was admitted for treatment and for the completion of the diagnosis. Fluid support was administered first, and prednisone 1 mg/kg/24 h was started. No blood transfusion was undertaken. A complete peripheral blood test was performed to rule out other potential etiologies (see Table 1).

Suspecting apomorphine involvement, the drug was immediately withdrawn, the dose of L-dopa was increased, and trihexyphenidyl was added to control morning dystonia. Seven days later, the patient was discharged in good clinical condition. Hemoglobin levels were 8.3 g/dl, and a decrease in hemolytic parameters was observed. Corticosteroids were discontinued 7 days after discharge. At the time of writing (3 years of follow-up), clinical and hematological remission remains complete.

Discussion

The first documented case of DIIHA appeared in 1953 and was attributed to mephenytoin.[1] Since then, DIIHA has been reported in reaction to more than 130 drugs. The most widely known are alpha-methyldopa and antibiotics such as cephalosporin and penicillin.[1,2,10] L-dopa-induced DIIHA was first described in 1972, and since then several reports have been published[3–6]; among the drugs reported, dopamine agonists, including cabergoline and apomorphine, have been associated

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TABLE 1 Peripheral Blood Test

Parameter (Normal Range)	April 2013 (Baseline)	October 2013
Hemoglobin (12–15 g/dl)	11.4	5.8
Hematocrit (36–43%)	33.8	16
Mean corpuscular volume (80–100 ff)	85	90
Reticulocyte count (0.5–1.5%)	0	29.35
Platelet count (150–450 × 10^3/mm^3)	180 × 10^3	200 × 10^3
White cell count (15–450 × 10^3/mm^3)	7 × 10^3	6 × 10^3
Blood smear findings	Normal	Anisocytosis +++ Spherocytosis ++
Creatinine (0.5–1.1 mg/dl)	0.6	0.6
Aspartate aminotransferase (0–34 U/L)	17	25
Total bilirubin (0.3–1.2 mg/dl)	0.5	2.8
Unconjugated bilirubin (0–1 mg/dl)	0	2.7
Lactate dehydrogenase (LDH 230–460 UI/dl)	426	715
Haptoglobin (mg/dl)	1.5	<1
Serum Iron (50–170 µg/dl)	60	60
Transferrin (200–380 mg/mL)	278	94
Ferritin (30–120 mg/mL)	80	213
Transferrin saturation (>16%)	28	35
Antinuclear antibodies titer (<1/80)	<1/80	<1/80
Beta-2 glycoprotein	—	Negative
Anticardiolipin antibodies	—	Negative
IgA, IgG, and IgM immunoglobulin	—	Normal range
Serum electrophoresis	—	Normal range
Beta-2 microglobulin (0.6–2.4 mg/L)	—	2.16
Rheumatoid factor (0–14 UI/mL)	7	2
B12 vitamin (223– 915 pg/mL)	545	715

with DIIHA.[7,8] Apomorphine has many associated adverse effects, although most are mild and transient, including vegetative (eg, orthostatic hypotension, nausea, vomiting, bradycardia, salivation, sweating), neuropsychiatric, and local reactions (eg, subcutaneous or skin nodules, abscesses, necrosis), in addition to leg edema and livedo reticularis. Hematologic reactions are less common and, although very rare, some events may be life threatening, including DIIHA.[11–13]

Drugs are responsible for 12% of all cases of immune hemolytic anemia (IHA).[10] However, DIIHA incidence is probably underestimated.[10,14,15] Mild cases may go undetected, with only the most severe cases receiving proper study.[10]

The mechanism behind DIIHA is not well understood and may be different for each drug. Drugs sometimes cause an alteration in the antigens of red blood cells, which produces antibodies that cross-react with the original antigens in the cell (as occurs with L-dopa, methyldopa, procainamide, and apomorphine).[14] Other times, it is the drug that associates directly with cell structures, acting as an antigen in a haptenic reaction (as in penicillin, cefotetan, ceftriaxone, and NSAIDs). In both cases, the antibody attached to the red blood cell can be detected by a direct Coombs test. Also, the subclass of the antibody involved (IgG, IgM, or complement-mediated hemolysis) can be identified to assess its clinical impact.[16]

There are some controversial aspects about how frequently a basic peripheral blood test should be performed (including complete blood count and hemolytic parameters) to monitor the treatment with apomophine. Six monthly intervals are suggested, but this may be excessively long, and we recommend 3 monthly intervals to detect subclinical cases. However, despite this measure, the anemia may develop suddenly when it is least expected, and it is therefore important to improve education about the symptoms of anemia to improve early detection. Patients may present pallor, dyspnea, jaundice, and easy fatigability, although the severity of symptoms is closely related to the rate of hemolysis. It is important to note that the results of a direct Coombs test may be positive for weeks or months after discontinuing the drug.

In DIIHA, the primary treatment—and often the only treatment necessary—is to discontinue taking the drug. To date, no published studies have documented reintroduction of the drug following withdrawal. It is thought that further exposure may induce a stronger immune response, leading to poor outcome, as has been described with L-dopa.[6] The use of steroids in the acute phase of DIIHA is controversial. Steroid administration has been demonstrated as a useful first-line treatment, with 60 to 80% of patients entering remission.[15] Nonresponders or patients needing high-dose corticoids throughout long periods of time are candidates for splenectomy or immunomodulatory or immunosuppressive treatment.[14,15]

In this case report, clinical symptoms appeared after several months of good clinical response to a modest dose of apomorphine (4.4 mg/h). The results of the urgent blood test suggested an IHA, as anemia, elevated reticulocytes, and a positive direct Coombs test are hallmarks of IHA. The reticulocytes increased in a fashion that appeared to express bone marrow hyperactivity. Other parameters such as elevated lactate dehydrogenase (LDH) and elevation in unconjugated bilirubin are common findings in IHA.[16] Diagnosis of DIIHA was based primarily on clinical suspicion and positive response following apomorphine withdrawal, in addition to the results of immunohematological tests. Other potential causes of IHA such as autoimmune,

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neoplastic, and infectious diseases were ruled out based on the findings of serologic testing and imaging studies. Also, a positive direct Coombs test at 37°C served to rule out cold agglutinin disease such as Donath-Landsteiner hemolytic anemia, among others.

Because DIIHA can be associated with several dopaminergic drugs,[3,6–8] the combination of these drugs (L-dopa plus apomorphine plus an oral/transcutaneous dopamine agonist) might increase the risk of this adverse effect. Our patient was taking L-dopa and rotigotine at the time and had developed no relevant hematologic problems. A short course of steroids would not have sufficed to treat secondary IHA. Therefore, apomorphine seems to have been directly responsible for IHA.

Summary

DIIHA is an infrequent but threatening adverse effect of several drugs, including apomorphine, therefore past medical history should be reviewed carefully. Strong clinical suspicion is needed to perform a proper immunohematological test. Clinical scenario and the temporal relationship between apomorphine administration, apomorphine withdrawal, and the decrease in hemolytic parameters and the time of clinical recovery support suspicion of DIIHA. In this case, the offending drug, apomorphine, must be withdrawn. Shorter intervals of serial blood tests are suggested to improve early DIIHA diagnosis, thus preventing serious adverse effects.

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

B.V.P.: 1A, 1B, 1C, 3A
M.S.S.F.: 3B
C.F.F.: 1A, 1C
T.A.P.: 3B
J.d.V.F.: 1A, 3B
P.J.G.-R.: 1A, 1B, 1C, 3B

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