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A Case of Delayed-Onset, Apomorphine-Induced Haemolytic Anaemia

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Abstract

We present a case of apomorphine-induced haemolytic anaemia in a 72-year-old female patient with Parkinson's disease. Of note, the adverse drug reaction was delayed-onset, occurring three and a half years after commencing the apomorphine infusion. The diagnosis was based on clinical suspicion and supported by immunohaematological testing, including direct Coombs' test, antibody testing and a characteristic blood film. Early recognition and cessation of the drug were critical in the management of the patient. The case highlights the importance of adequate monitoring while on continuous apomorphine to ensure early detection of adverse drug reactions.

Categories: Hematology, Geriatrics, Internal Medicine
Keywords: apomorphine, dopamine agonists, drug-induced haemolytic anaemia, haemolytic anaemia, parkinson's disease (pd)

Introduction

Autoimmune haemolytic anaemia (AIHA) is an autoantibody-driven process resulting in the destruction of red blood cells [1]. It is a rare, yet life-threatening disease categorised into primary and secondary AIHA. The former occurs in the absence of an underlying disorder, whereas secondary AIHA is associated with haematological malignancy, autoimmune diseases, inherited immunodeficiency, infection, or can be drug-induced [1,2]. There are several mechanisms by which it has been suggested that drugs stimulate autoantibody formation: drug-dependent autoantibodies due to either molecular mimicry or an immunoallergic mechanism, or non-specific stimulation of the immune system [3]. Identifying drug-induced immune haemolytic anaemia (DIHA) presents a diagnostic challenge to clinicians, as laboratory findings often mimic those found in AIHA; the key distinction between the two is the resolution of haemolysis after cessation of the suspected culprit [4,5]. Prompt recognition is essential, as left untreated, the haemolysis can result in shock, organ ischaemia, acute respiratory distress syndrome and disseminated intravascular coagulation, ultimately posing the risk of death [6].

In patients with Parkinson's disease, L-Dopa is a known culprit of DIHA, but few incidences of DIHA have also been reported in relation to other dopaminergic drugs such as cabergoline and apomorphine [7-9]. These existing case reports of apomorphine-induced haemolytic anaemia describe haemolysis arising shortly after the initiation of the drug, making this case particularly interesting, as we present a case of probable DIHA secondary to apomorphine occurring three and a half years after initiation of the drug.

Case Presentation

A 72-year-old woman presented to the emergency department (ED) with acute confusion and jaundice. She had a background of cataracts, sciatica, and idiopathic Parkinson's disease, managed with co-careldopa equivalent to 575 mg per day and continuous subcutaneous apomorphine ranging from 2.5 mg to 4.25 mg per hour. Her drug history further included clonazepam, quetiapine, fludrocortisone and macrogol. She required support with some activities of daily living and resided in a care home. She was reported by staff to have normal cognition prior to presentation, though she had a history of periods of hallucinations and REM sleep disorder.

Routine bloods on arrival to the ED identified a significant anaemia and acute kidney injury stage 1 (Table *1*). After discussion with the haematology department, additional panels were sent including iron studies, B12 and folate levels, lactate dehydrogenase (LDH), reticulocytes, haptoglobin, a blood film, conjugated bilirubin, and unconjugated bilirubin. Initial history and examination, including per rectal examination, identified no clear source of bleeding.

Test (Normal Range)	Baseline	November 2025
Haemoglobin (115-165 g/L)	113 g/L	55 g/L

Haematocrit (0.37-0.47)	0.328	0.159
Mean corpuscular volume (80-100 fL)	83 fL	103 fL
Reticulocyte count (40-100 10*9/L)		349.1 10*9/L
Platelets (150-450 10*9/L)	278 10*9/L	315 10*9/L
WCC (4.0-11.0 10*9/L)	5.6 10*9/L	11.2 10*9/L
Blood film		Neutrophil toxic granulation, polychromasia, mild rouleaux formation of red cells, spherocytes
Direct antiglobulin test (DAT)		DAT +ve, anti-human globulin (AHG) 4+, IgG 4+, IgA weak positive
Blood phenotype		C-c+E+e+K-Cw-
Antibody detected		Anti-Kell unassigned antibody autoantibody
Urea (2.5-7.8 mmol/L)	6.8 mmol/L	12.5 mmol/L
Creatinine (49-90 umol/L)	58 umol/L	93 umol/L
Alanine aminotransferase (7-40 u/L)	10 u/L	10 u/L
Total bilirubin (0-20 umol/L)	13 umol/L	55 umol/L
Conjugated bilirubin (0-5 umol/L)		16.1 umol/L
Lactate dehydrogenase (120-246 u/L)		569 u/L
Haptoglobin (0.3-2.0 g/L)		<0.10 g/L
Serum iron (9.0-30.4 umol/L)	12.2 umol/L	10.1 umol/L
Transferrin (2.0-3.6 g/L)	2.21 g/L	
Ferritin (15-291 ug/L)	122 ug/L	
Transferrin saturation (16-45%)	22%	
ANA Ab		Negative
Double-stranded DNA Ab (0.0-9.9 IU/ml)		<1.0 IU/ml
MPO Ab (0.0-0.9 AI)		<0.2 AI
c-ANCA Ab (0.0-0.9 AI)		<0.2 AI
Anti-CCP		Negative
IgA immunoglobulin (0.4-3.5 g/L)		2.24 g/L
IgG immunoglobulin (6.5-16.0 g/L)		9.32 g/L
IgM immunoglobulin (0.5-3.0 g/L)		0.41 g/L
Serum electrophoresis		No abnormality detected
Free Kappa/Lambda ratio (0.3-1.7)		1.00
B12 vitamin (211-911 ng/L)		886 ng/L
Folate (>5.38 ug/L)		>24.0 ug/L
Centromere Ab, SS-A, SSA-52, SSA-60, SS-B, Sm, SmRNP, RNP-68, Scl-70, Jo-1, ribosomal P, chromatin		All negative
Rhinovirus/enterovirus		Detected by PCR

CMV, EBV, hepatitis B, hepatitis C and HIV screen	Negative

TABLE 1: Initial investigation results for the patient on admission, accompanied by the patient's baseline results.

Table 1 demonstrates the values identified on initial screening of the patient on her arrival to the ED, which assisted in the diagnosis of DIHA. Please find the normal ranges for each value as per the Trust in brackets following the test title.

By the time the patient came to be clerked by the medical team, a raised LDH and reticulocyte count had been identified. Examination revealed a labile blood pressure responsive to intravenous fluids and a soft systolic murmur. A urine dipstick had shown pyuria. Considering an acute haemolytic anaemia in the presence of a new murmur, the patient was initially empirically treated for infective endocarditis with broad-spectrum antibiotics and further intravenous fluids. Unfortunately, transfusion of RBCs was not initially possible as the patient had anti-Kell autoantibodies identified, meaning specific cross-matching was required at a specialist site, though this was performed once matched RBCs were available (Table *1*). Additional sets of blood cultures, urine cultures, viral swabs, a procalcitonin and a direct Coombs' test were sent, and the patient was referred to haematology and cardiology for further workup.

Early discussion with the patient's Parkinson's specialist suggested an apomorphine reaction was the cause of AIHA, so the drug was withdrawn. By the second day of admission, after a review of the investigations and clinical picture, haematology agreed that the AIHA was apomorphine-induced, so prednisolone 1 mg/kg was commenced alongside folic acid, a proton-pump inhibitor for gastric protection, and bone protection in the form of calcium carbonate and vitamin D3. DAT testing returned strongly AHG positive and IgG positive, with a weak positive IgA further supporting the diagnosis.

On day 3 of admission, after transfer to the local haematology ward, the patient underwent a transthoracic echocardiogram, which demonstrated a rim of pericardial effusion and normal valves with no vegetations, signifying no evidence of infective endocarditis. She also had a CT thorax, abdomen, and pelvis, which found a normal spleen, no lymphadenopathy and no masses, excluding lymphoproliferative disease. An autoimmune and virology screen was performed, which returned mostly negative, but found a positive rhinovirus/enterovirus result, which was felt to be an incidental finding (Table *1*). The patient responded well to cessation of apomorphine and prednisolone, with a normalising haemoglobin by day 4, so the steroids were tapered by 10 mg every five days. She continued to demonstrate a stable haemoglobin, which gradually improved over the course of her admission, returning to her baseline four weeks after she first presented.

After the apomorphine was ceased, the patient's motor symptoms markedly worsened, resulting in a prolonged admission while her Parkinson's specialist aimed to reduce her symptom burden. She was trialled with a rivastigmine patch, which was not tolerated due to increasing delirium. Ultimately, improved symptom control was gained with up-titration of her co-careldopa.

Following her discharge, the patient was reviewed at just over three weeks and three months post-discharge. No recurrence of haemolysis was noted at either appointment, so she was discharged from haematology services. Further review in the Movement Disorders Clinic was also undertaken, increasing the patient's morning dose of modified-release co-careldopa to achieve better symptom control.

Parkinson's disease background

The patient was diagnosed with idiopathic Parkinson's disease 20 years ago, with left-sided tremor predominance and good initial response to treatment. Early use of ropinirole led to some impulse control issues, so it was ceased. She then had a steady period of several years of good control with Stalevo (levodopa, carbidopa and entacapone), rasagiline, and amantadine. As motor fluctuations became more problematic, ropinirole was reintroduced. In 2019, she tried apomorphine pens for the first time with more effective control of motor fluctuations than with dispersible co-beneldopa. The pens were stopped after a vasculitic rash appeared, though bloods including a vasculitis screen were negative.

Then, in 2021, the patient was admitted to hospital with acute psychosis, so the amantadine and dopamine agonists were reduced. In May 2022, the apomorphine pens were tried again and this time without return of the skin reaction. After discussions around the different appropriate advanced therapies, the patient was commenced on the apomorphine pump at 2.5 mg per hour from 8 am to 10 pm. Over the period of 2023-2025, gradual increases were made to the apomorphine rates and duration of the pump, with noted episodes of impulse control issues and psychosis. She was also on quetiapine throughout this period, which was periodically increased to 75 mg per day by June 2025.

Discussion

Drug-induced immune haemolytic anaemia is a rare phenomenon, though it is suspected that incidences are largely under-reported [9]. It can be attributed to both drug-dependent antibodies, which are only identifiable in the presence of a drug, and less commonly drug-independent antibodies, which do not need to be present to cause in vitro reactions [5]. While drugs like ceftriaxone and piperacillin are associated with drug-dependent antibodies, medications such as methyldopa, levodopa and beta-lactamase inhibitors result in drug-independent antibodies (DIABs) [7,10]. Apomorphine is understood to fall into the same category as alternate Parkinson's medications, causing DIABs that make complexes with red blood cells, inducing haemolysis [6,7]. A similar case has been reported once in association with cabergoline, another dopamine agonist, though apomorphine remains the most notable dopamine agonist associated with DIHA [11].

Drug-independent antibodies are typically associated with a sub-acute presentation of haemolysis that emerges days to weeks after exposure to the drug [6]. This is in keeping with the presentation of our patient, whose symptoms developed three years and six months after the induction of therapy, though unfortunately drug-dependent antibodies were not tested by our laboratory to further support this suggestion. Interestingly, examination of her community health records and previous blood results revealed that her haemoglobin had been gradually declining over the six months prior to her presentation to the ED. Her general practitioner had been investigating possible causes of her new anaemia, including faecal immunochemical testing, and assessing for B12, folate and iron deficiencies but had not identified a cause. Apomorphine monitoring advice, such as that in the British National Formulary [12], suggests monitoring for haemolytic anaemia and thrombocytopenia every six months while on apomorphine with simultaneous levodopa use. This case has international relevance by substantiating the need for continued monitoring of full blood counts in Parkinson's patients on apomorphine and supports ensuring adequate shared care agreements are implemented to identify adverse reactions early. Furthermore, to our knowledge, this case report represents the longest time documented between initiation of apomorphine infusion and onset of haemolytic anaemia from the few existing case reports on apomorphine-induced haemolytic anaemia and the TOLEDO study [7-9].

The challenge posed by drug-independent antibodies in clinical practice is that they are not distinguishable from antibodies that cause warm AIHA [5,13,14]. Often, the only differentiating factor is the subsequent remission after the cessation of a drug in DIHA [5]. Strong clinical suspicion is therefore essential in the early recognition of DIHA, which is ultimately essential to reducing harm to the patient [15].

Discontinuing the culprit drug remains the mainstay of treatment for DIHA [16], which supported the diagnosis in this case as a normalising haemoglobin was observed after cessation of the apomorphine, with no demonstrated recurrence of haemolysis at three weeks and three months. Drug-independent antibodies have equally been demonstrated to be steroid-responsive, with a response rate of up to 96% [3,10], so in such cases, supportive management with corticosteroids is suggested [10].

Conclusions

In this case, the evidence strongly suggests a diagnosis of apomorphine-induced haemolytic anaemia and encourages clinicians to suspect drug-induced haemolysis as a differential in an acutely unwell Parkinson's patient, both shortly after initiation and once long-established on apomorphine. Importantly, this case expands the established timeframe for which we suspect DIHA can occur secondary to apomorphine. Laboratory results cannot be relied upon alone to diagnose DIHA given the similarity in picture to AIHA, and so we are reminded of the importance of strong early clinical suspicion in identifying the diagnosis. Early cessation of a precipitating drug is the mainstay of treatment for DIHA and is essential for improving outcomes; this case adds to the evidence for the use of steroids as supportive management in cases of suspected drug-independent antibodies. This case finally highlights the importance of continuous six-monthly monitoring of full blood counts when using apomorphine to enable early detection of adverse reactions.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sophie C. Bowden, Daniel Logue

Acquisition, analysis, or interpretation of data: Sophie C. Bowden, Daniel Logue

Drafting of the manuscript: Sophie C. Bowden, Daniel Logue

Critical review of the manuscript for important intellectual content: Sophie C. Bowden, Daniel Logue

Supervision: Daniel Logue

Disclosures

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