Acute adrenal insufficiency following arthroplasty: a case report and review of the literature

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Abstract

Background: Acute adrenal insufficiency is a potentially lethal condition rarely caused by bilateral adrenal haemorrhage due to heparin use. Most of the times, it is difficult to establish the diagnosis, as symptoms are not specific. Few cases have been reported in the literature.

Case presentation: A 52-year-old Caucasian woman presented with abdominal pain, vomiting and weakness nine days after arthroplasty and heparin use. Hyperkalemia, low cortisol and high adrenocorticotropic hormone levels were found, indicating adrenal insufficiency. Magnetic resonance imaging of the upper abdomen was compatible with preceding adrenal haemorrhage. Hydrocortisone and fludrocortisone were administered. Review of the literature revealed 36 cases of postoperative adrenal haemorrhage which are presented briefly.

Conclusion: Postoperative acute adrenal insufficiency due to haemorrhage is a rare condition. If patients are treated based on clinical suspicion, they have good chances to survive. Hydrocortisone is given permanently in the majority of the patients.

Keywords: Adrenal insufficiency, Arthroplasty, Heparin

Background

Acute adrenal failure (AAF) is a potentially life-threatening complication presenting with non-specific symptoms as abdominal pain, nausea, fever, tachycardia, hypotension and lethargy [1]. However, hyponatremia and hyperkalemia as indicators of adrenal insufficiency should be evaluated very thoroughly [2].

AAF may occur in patients with previously undiagnosed primary adrenal insufficiency and sometimes after bilateral adrenal infarction or postoperative haemorrhage in otherwise healthy individuals [1]. The postoperative period carries a high risk for haemorrhage, as platelet consumption may lead to bleeding in vital organs, independently of anticoagulant administration. Additionally, the use of heparin represents an independent risk factor that predisposes to haemorrhage [3]. Injuries during procedures such as extracorporeal shock-wave lithotripsy or electroconvulsive therapy [4,5] or use of certain materials and techniques may also predispose to coagulopathy and haemorrhage [6].

Moreover, hypothermia itself may play an important role in bleeding [6]. As signs and symptoms are not specific, they may easily lead to wrong diagnosis, such as postoperative septic shock or inflammation.

Total hip arthroplasty is a common surgical procedure associated with deep venous thrombosis and pulmonary embolism that are prevented by the use of anticoagulants [7,8]. The extensive use of anticoagulants in these operations explains the fact that bilateral adrenal haemorrhage is more often observed after knee or hip arthroplasty. However, orthopaedic surgery is probably associated with risk factors (other than anticoagulants) which lead to haemorrhage [9].

The use of low molecular weight heparin (LMWH) to avoid postoperative thromboembolic events can induce thrombocytopenia (heparin-induced thrombocytopenia [HIT]) and may lead to bilateral adrenal haemorrhage [2]. A pre-test clinical score (including thrombocytopenia, timing of platelet count fall, thrombosis, presence of other causes for thrombocytopenia, the so-called 4 T's) has been developed to establish the clinical suspicion of HIT [10], while heparin-platelet factor 4-immunoglobulin G (IgG)
(PF4-IgG) antibodies and 14C-serotonin release assay are useful diagnostic tests [2].

The incidence of bilateral adrenal haemorrhage is estimated to be around 4.7–6.2 cases per million inhabitants in developed countries, but the prevalence is much higher in hospitalized patients, rising to 1.1% of them [11,12]. There are difficulties in establishing an early diagnosis of the disease [13] and adrenal haemorrhage is usually a post-mortem finding during autopsy performed to unravel the cause of death.

In addition to the elusive clinical presentation, imaging may also be deceiving: the enlarged haemorrhagic adrenals may be misdiagnosed as neoplastic masses, with irregular margins, though maintain their adreniform shape. Acute and subacute adrenal haemorrhage show high attenuation (50–90 HU) at unenhanced computed tomography (CT), without enhancement following intravenous (IV) contrast. In doubtful cases, decreased density and size of the adrenals during follow-up as well as the presence of calcifications may be extremely useful to confirm the diagnosis. Magnetic resonance imaging (MRI) is the most sensitive and specific imaging modality to confirm adrenal haemorrhage. Like CT, the appearance of adrenal haemorrhage on MRI also depends on the progression of the bleeding. The most characteristic sign on MRI is the low signal ring on T2 sequences during the chronic phase [14].

The aim of the present work was a) to present a case of acute adrenal insufficiency caused by bilateral adrenal haemorrhage observed after arthroplasty and b) to summarize the published data regarding this rare and interesting clinical entity.

Computerized literature search was performed in the PubMed electronic database. The original query provided 71 possibly relevant articles. Furthermore, 10 articles were retrieved after searching the “Related Articles” link and the references. Of these, 34 were finally selected (including 36 case reports), whereas the remaining 47 articles were excluded for the following reasons: spontaneous bilateral adrenal haemorrhage without apparent cause (n=9); concurrent diseases (n=7); bilateral adrenal haemorrhage due to heparin for other reasons, not postoperatively (n=27); article in Japanese (n=1); reviews and letters to the editor (n=3).

In summary, 36 cases of postoperative bilateral adrenal haemorrhage have been documented. Mean age of patients during haemorrhage was 65.2 years (range 44–83) and there was no particular sex distribution. Abdominal pain, fever, vomiting and hypotension were the main symptoms at presentation, usually occurring between first and second week after surgery. Hyponatremia and hyperkalemia were the most common laboratory findings. In 27 out of 36 patients, diagnosis was made by CT scan, in two by abdominal ultrasound and in one by exploratory laparotomy. In four patients the diagnosis was confirmed after their death during autopsy and in two cases the imaging was not described. Nine patients succumbed to adrenal insufficiency.

Patients’ clinical characteristics and diagnostic methods are summarized in Tables 1 and 2. Reported cases are divided into two groups: the first includes 21 patients with adrenal insufficiency after orthopaedic surgery (Table 1) and the second reports 15 patients with adrenal insufficiency after any other surgery (Table 2).

Case presentation
Patients’ history
A 52-year-old Caucasian woman, mother of two children, underwent right hip arthroplasty and was administered LMWH (enoxaparin 8,000 IU per day) for seven days in order to prevent thromboembolic events. Arthroplasty was successfully completed without intraoperative or early postoperative complications, except for a fall in platelet count from 214,000/μL to 116,000/μL. Haemoglobin and white blood cell count were normal. The patient was discharged from the hospital in good condition without any sign or symptom of haemorrhage, thromboembolism or infection.

9th postoperative day, emergency department
On postoperative day 9, she presented in the emergency department complaining of abdominal pain, vomiting and weakness. She was dehydrated and tachycardic (105 beats per minute). Decreased skin turgor and low blood pressure (90/60mm Hg) were observed. Biochemical exams indicated hyponatremia (128mmol/L, normal range 136–145) and hyperkalemia (5.97mmol/L, normal range 3.5–5.1), normal serum glucose levels, as well as normal kidney and liver function. The patient was afebrile and the wound healed satisfactory. The administration of isotonic solutions was decided but the patient responded poorly. Intravenous use of dopamine was added thereafter, resulting in slight improvement of clinical symptoms, mainly vomiting and arterial blood pressure. As the abdominal pain was persistent, the patient underwent abdominal CT which was indicative of “bilateral adrenal adenomas”. Due to this finding, the patient was referred to our department for further evaluation.

Referral to the endocrinology department
Considering the clinical signs of dehydration and the presence of hyperkalemia (5.72mmol/L, normal range 3.5–5.1) and hyponatremia (130mmol/L, normal range 136–145), adrenal insufficiency was suspected. Cortisol levels were measured and found to be very low (cortisol 40nmol/l, normal range 70–250nmol/l). A 250-μg adrenocorticotropic hormone (ACTH) stimulation test (Synacthen test) was performed for further evaluation; no increase in cortisol was observed confirming the diagnosis of primary adrenal
| Cases | Author                          | Country   | Age | Sex | Type of surgery | Diagnosis | Symptoms                                                                 | Biochemical exams                                                                 |
|-------|--------------------------------|-----------|-----|-----|-----------------|-----------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 1     | Findling et al., 1987 [15]     | USA       | 44  | M   | unspecified     | CT        | abdominal pain, vomiting, hypotension                                    | hyponatremia, hyperkalemia                                                        |
| 2     | Delhumeau et al., 1989 [16]    | France    | 76  | F   | total hip arthroplasty | abdominal ultrasound | abdominal pain, fever, hypotension, altered consciousness                | hyponatremia, natriuresis, thrombocytopenia                                        |
| 3     |                                 |           | 74  | M   | tibial osteosynthesis | not done  | abdominal pain, fever, hypotension, shock, altered consciousness         | hyponatremia, thrombocytopenia                                                    |
| 4     |                                 |           | 62  | M   | tibial osteosynthesis | CT        | abdominal pain, asthenia, nausea                                        | hyponatremia, thrombocytopenia                                                    |
| 5     | Ernest and Fischer, 1991 [17]  | Australia | 68  | F   | total hip arthroplasty | CT        | fever, hypotension                                                       | hyponatremia, hyperkalemia                                                        |
| 6     | Souied et al., 1991 [18]       | France    | 63  | F   | total hip arthroplasty | CT        | fever, hypotension                                                       | hyponatremia, hyperkalemia                                                        |
| 7     | Bleasel et al., 1992 [19]      | Australia | 69  | F   | total knee arthroplasty | CT        | fever, nausea, vomiting, abdominal pain, hypotension                   | hyponatremia, hyperkalemia                                                        |
| 8     | Hardwicke and Kisly, 1992 [20] | USA       | 63  | F   | bilateral total knee arthroplasty | CT        | fever, nausea, anorexia, vomiting, abdominal pain, confusion, feeling of illness, hypotension | anemia, hyponatremia, hyperkalemia                                               |
| 9     | Delhumeau et al., 1993 [21]    | France    | 74  | M   | total hip arthroplasty, thrombectomy of both limbs due to bilateral arterial thrombosis | CT        | abdominal pain, fever, hypotension, abdominal tenderness                | hyponatremia, hyperkalemia                                                        |
| 10    | Santonastaso et al., 1993 [22] | Italy     | not reported | F | osteotomy | CT | somnolence, asthenia, hypotension | not reported |
| 11    | Ries et al., 1994 [23]         | USA       | 61  | F   | bilateral total knee arthroplasty | autopsy   | abdominal discomfort, nausea, collapse                                  | none                                                                              |
| 12    | Cozzolino et al., 1997 [24]    | USA       | 66  | F   | total knee arthroplasty | CT        | nausea, anorexia, emesis, lethargy                                      | hyponatremia, hyperkalemia, anemia, azotemia                                      |
| 13    | Rowland et al., 1999 [25]      | Australia | 50  | M   | unspecified     | CT        | fever, abdominal pain, dizziness, hypotension                            | hyponatremia                                                                      |
| 14    | Caubet et al., 1999 [26]       | France    | 63  | F   | tibial osteosynthesis | CT        | fever, hypotension, tachypnea                                           | thrombocytopenia, hyponatremia, hyperkalemia                                      |
| 15    | Scheffold et al., 2001 [27]    | Germany   | 63  | M   | intracondylar nail-extension       | abdominal ultrasound | abdominal pain, fever                                                   | leukocytosis                                                                       |
| 16    | LaBan et al., 2003 [28]        | USA       | 82  | F   | bilateral knee arthroplasty       | CT        | abdominal pain, nausea                                                  | elevated INR, hyponatremia                                                        |
| 17    | Schuchmann et al., 2005 [8]    | USA       | 83  | F   | bilateral total knee arthroplasty | autopsy   | anxiety, hypertension, midback pain, shortness of breath, shock         | hyponatremia, hyperchloremia, leukocytosis, anemia, elevated INR                   |
| 18    | Kurtz and Yang, 2007 [29]      | USA       | 54  | F   | total hip arthroplasty            | CT        | fever, abdominal pain, orthostatic syncope                               | not reported                                                                      |
| 19    | Mongardon et al., 2007 [30]    | France    | 64  | M   | total hip arthroplasty            | CT        | fever, abdominal pain, confusion, hypotension                            | thrombocytopenia, high urinary sodium                                              |
| 20    | Thota et al., 2012 [31]        | USA       | 68  | M   | bilateral total knee arthroplasty | CT        | fever, abdominal discomfort, anorexia, fatigue, hypertension, tachycardia, altered mental status | hyperglycemia, increased INR                                                        |
| 21    | Chow et al., 2012 [32]         | USA       | 44  | M   | bilateral total knee arthroplasty | CT        | hypotension, abdominal pain, tachycardia, fever                          | leukocytosis, D-dimers elevation, hyponatremia, thrombocytopenia                   |
| Cases | Author | Country | Age | Sex | Type of surgery | Diagnosis | Symptoms | Lab results |
|-------|--------|---------|-----|-----|-----------------|-----------|----------|-------------|
| 1     | Steer and Fromm, 1980 [33] | USA | 71 | M | cholecystectomy | not done | abdominal pain, fever, vomiting, anorexia, weakness, hypotension | eosinophilia, hyponatremia, hyperkalemia, prothrombin time elevation |
| 2     | Jacobson et al., 1986 [34] | USA | 55 | M | retropubic prostatectomy | CT | fever, tachycardia, hypotension, dyspnea, abdominal pain, nausea, vomiting, diarrhea, ileus | hyponatremia, hyperkalemia |
| 3     | Miller et al., 1986 [35] | USA | 81 | F | aorto-iliac aneurysmectomy | CT | fever, nausea, vomiting, abdominal pain, lethargy | hyponatremia, hyperkalemia, leukocytosis |
| 4     | Homcy and Southern, 1989 [36] | USA | 71 | M | colectomy | autopsy | confusion, hypotension | hyponatremia |
| 5     | Ting et al., 1992 [37] | USA | 62 | M | coronary bypass grafting | CT | left flank pain, fever, tachypnea, tachycardia, tired, hypotension | leukocytosis, hyponatremia, hyperkalemia |
| 6     | Leschi et al., 1994 [38] | France | 63 | M | aortofemoral bypass graft | autopsy | confusion | hyponatremia, hyperkalemia |
| 7     | Belmore and Walters, 1995 [39] | USA | 53 | M | laparoscopic cholecystectomy | CT | abdominal pain, anorexia, fatigue, hypotension, dehydration | hyponatremia, hyperkalemia, hyperamylasemia, partial thromboplastin time prolonged |
| 8     | Scheiwiller et al., 2002 [40] | Switzerland | 71 | M | low anterior rectum resection | CT | anorexia, abdominal pain, fever, hypotension | hyponatremia |
| 9     | Sousa Escandon et al., 2002 [41] | Spain | 82 | M | partial nephrectomy for renal adenocarcinoma | CT | abdominal pain, nausea, fever, hypotension, severe respiratory distress | hyponatremia, azotemia, anemia, leukocytosis, thrombocytosis |
| 10    | Bakaeen et al., 2005 [42] | USA | 51 | M | coronary artery bypass graft | CT | fever, abdominal pain, diarrhea, orthostatic hypotension, tachycardia | thrombocytopenia |
| 11    | Gutenberg et al., 2007 [43] | Germany | 69 | M | intracranial tumor surgery | exploratory laparotomy | hypotension, abdomen tense | not reported |
| 12    | Munoz Corsini et al., 2008 [44] | Spain | 63 | M | right hemicolectomy | CT | disorientation, difficulty in breathing, tachycardia, fever | leukocytosis, anemia, increase in fibrinogen, |
| 13    | Peel and Whitelaw, 2011 [45] | USA | 60 | M | right hemicolectomy | CT | backache, fever, hypotension, agitation, confusion | hyponatremia, thrombocytopenia, leukocytosis |
| 14    | Rosenberger et al., 2011 [2] | USA | 69 | M | gastrectomy, esophagectomy, cholecystectomy | CT | abdominal and flank pain, tachypnea, tachycardia, hypotension, oliguria, myocardial infarction | oliguric renal failure |
| 15    | Balsach Sole et al., 2012 [46] | Spain | 70 | M | cephalic duodenopancreatectomy | CT | lethargy, hypotension | hyponatremia, hypoglycemia |
insufficiency (basal cortisol equal to 32.9nmol/l, 30 and 60 min after Synacthen equal to 34nmol/l and 32.1nmol/l respectively, normal range 70-250nmol/l). ACTH levels were very high (1763.4pg/ml, normal range 9–52). MRI of the upper abdomen showed the presence of bilateral adrenal “lesions” with greatest dimension 2.3cm on the right and 2.5cm on the left. On T2 weighted-images the above mentioned findings had high signal intensity with a low signal intensity ring along the periphery compatible with the presence of haemosiderin consequence of previous haemorrhage and chronic hematomas (Figure 1). No signal drop-off on in- and out- of phase images and no significant enhancement following iv contrast was depicted.

Diagnostic evaluation and therapy
Considering the variety of causes that could trigger bilateral adrenal haemorrhage in accordance with the medical history of the patient, traumatic injury, burns or pregnancy were ruled out [13]. Furthermore, she was afebrile without any clinical signs of septic shock. Antiphospholipid syndrome was excluded due to the absence of vascular thrombosis and the history of two normal deliveries. Based on the fact that the patient had received LMWH postoperatively, haemorrhage was considered to be the cause of adrenal failure. Heparin-PF4-IgG antibodies (measured by enzyme-linked immunosorbent assay [ELISA]) were negative. Moreover, the low pretest clinical score for HIT (total 2 points, 1 point from thrombocytopenia and 1 point from surgery) in the patient was correlated with high- negative predictive value for heparin induced adrenal haemorrhage [10].

Replacement therapy with hydrocortisone and fludrocortisone was started. Three months later, ACTH levels fell to 397pg/ml. Adrenal MRI showed that the lesions had decreased in size and had homogeneous low

Figure 1 Abdominal magnetic resonance imaging obtained 15 days after surgery. Axial (A) T2 weighted image with fat suppression, coronal (B) T2 weighted image, in and out of phase axial (C, D) T1 images, axial (E, F) T1 weighted images with fat saturation before and after contrast administration, coronal (G) T2-weighted image. Bilateral adrenal lesions showing high signal both on T1-weighted (E) and on T2-weighted images (A, B), and low signal rim on T2-weighted images (A, B), representing haemosiderin. The lesions do not show any signal drop-off on T1 in- (C) and out- of phase images (D) After intravenous contrast administration (F) no enhancement is depicted. These findings are consistent with chronic adrenal hematomas. Note the signal void in the right pelvis due to the presence of a metallic right hip prosthesis.
signal on T2 weighted images, findings consistent with the evolution of hematomas (Figure 2). The oral replacement with hydrocortisone and fludrocortisone remains until the present time.

Conclusions
Bilateral adrenal haemorrhage is a rare disease which can follow major surgical operations. It should be suspected in patients presenting with fever, abdominal pain, confusion and hemodynamic collapse not responding to standard medical treatment [31]. The increased incidence after orthopaedic surgery, the association with anticoagulants use and the great mortality in misdiagnosed cases should keep physicians alerted.

Consent
Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
AAF: Acute adrenal failure; LMWH: Low molecular weight heparin; HIT: Heparin induced thrombocytopenia; IgG: Immunoglobulin G; PF4-IgG: Platelet factor 4- immunoglobulin G; CT: Computed tomography; IV: Intravenous; MRI: Magnetic resonance imaging; ACTH: Adrenocorticotropic hormone; ELISA: Enzyme-linked immunosorbent assay.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SM and MB reviewed the literature and prepared the draft. KX performed and discussed imaging. EM collected patients’ clinical data. SG performed the immunoassay. AC and KPP conceived the idea and made the amendments of the manuscript. All authors read and approved the final manuscript.

Disclosure statement
The authors have nothing to disclose.

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