

Bilateral adrenal haemorrhage in the post-operative setting

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Voelker first recorded a case of acute bilateral adrenal haemorrhage in 1894. Since then Waterhouse-Freiderichsen syndrome, usually due to overwhelming bacterial meningococcal sepsis leading to massive haemorrhage into one or (usually) both adrenal glands has been described, with patients showing features of low blood pressure and shock, disseminated intravascular coagulation (DIC) with widespread purpura, and rapidly developing adrenocortical insufficiency. We report two interesting cases of bilateral adrenal haemorrhage in the post-operative setting who presented within two weeks of each other.

An 82-year-old male ten days post right hemicolectomy for caecal malignancy and recent abdominal aortic aneurysm repair, and a 77-year-old female fourteen days after total hip replacement presented similarly with non-specific abdominal pain and lethargy. Aside from iron-deficiency anaemia in the male and previous tuberculosis in the female there was no significant past medical history. On examination, both patients were pyrexial, slightly confused, and had soft, non-distended abdomens with generalized tenderness and slight guarding. They both underwent routine blood tests and radiological investigation.

Blood samples from both patients revealed an increase in inflammatory markers (CRP, WCC), and urea, and a decrease in haemoglobin compared with the preoperative figures (see box below).

	CRP	WCC	Urea	Hb
Male pre op	168	14.2	3.8	10
post op	298	22.1	5.9	8.5
Female pre op	139	11.6	5.5	10.7
post op	243	15.4	7.7	9.2

Although inflammatory markers were raised,

there was no obvious source of sepsis. He underwent a chest and abdominal x-ray which showed prominent loops of bowel most likely to be paralytic ileus, while she had an ultrasound scan which revealed no major pathology. Both were then investigated with a computerised tomography (CT) scan of the abdomen and pelvis, which revealed the presence of bilateral acute adrenal haemorrhage (figures 1 & 2).



Figure 1 Post contrast CT of the female patient showing bilateral smooth adrenal enlargement consistent with adrenal haemorrhage.



Figure 2 Post contrast CT of the male patient similarly showing smooth bilateral adrenal enlargement consistent with haemorrhage.

A biochemical review for signs of hypoadrenalism was then performed in

each patient, which only revealed a slightly decreased sodium level in the female (Na: 128). A short synacthen test in the male then confirmed adrenal insufficiency [basal cortisol: 95nmol/L (3.42µg/dL), cortisol 30 min post-synacthen: 104nmol/L (3.74µg/dL), cortisol 60 min post-synacthen: 120 nmol/L (4.32µg/dL)], while a random serum cortisol measurement in the female produced a result of 405 nmol/L (14.58 µg/dL). An antibody screen to check for the presence of antiphospholipid syndrome (disease which can predispose patients to adrenal haemorrhage) was then performed in the female, which only revealed the presence of anti-nuclear and smooth muscle antibodies.

Treatment for both patients began with discontinuation of the anticoagulation treatment and commencement of intravenous hydrocortisone which was later switched to oral prednisolone. Both patients responded well to treatment and following consultation with an endocrinologist, were discharged home on steroids. Blood results from both patients on discharge demonstrated a trend back towards normal limits. Unfortunately, the male patient was readmitted to hospital six months later with metastatic disease and died shortly afterwards. A random serum cortisol measurement on that admission returned a value of 491nmol/L (17.68 µg/dL).

Discussion:

Two cases of postoperative, bilateral adrenal haemorrhage found serendipitously on CT scan are reported here. Adrenal haemorrhage, which is classically associated with the Waterhouse-Friderichsen syndrome of meningococcal septicaemia usually presents with signs of hemodynamic compromise (e.g. increased cardiac output, low systemic resistance and hypotension)². However, this uncommon disorder has also been described in the postoperative period^{2,4}, in trauma⁵, in coagulopathies³, in pregnancy⁵, and

spontaneously⁶. It can also exhibit physical findings such as low-grade fever, poorly localized abdominal pain¹, and changes in mental state² (e.g. lethargy, delirium).

The actual incidence of bilateral adrenal haemorrhage in the post-operative setting is unknown as in the past many cases went undiagnosed, however it is quite a rare phenomenon, with only four reports being published before 1975^{15,16,17,18}. It was first described by Taylor in 1930 reporting the case of a 54-year-old operated on for duodenal obstruction. Since then, mostly due to the advent of computerized tomography, the number of reported cases has risen, with approximately 50 published reports being listed on Medline.

The incidence of adrenal insufficiency of any etiology in the general population is quite low at <0.01%⁸, although this rises to approximately 30% in critically ill patients¹². In the past it has been reported that the incidence of adrenal hemorrhage (unassociated with adrenal tumor or Waterhouse-Friderichsen syndrome) in post – mortem examinations ranges from 0.14% - 0.69%¹⁹.

Risks factors that have been suggested in the literature for developing adrenal haemorrhage in surgical patients include increased age (>55yrs), type of surgery (emergency vs. elective), and treatment with anticoagulants or steroids^{2,19}. However, a recent report which systematically tested risk factors using analytical studies showed that thrombocytopenia, heparin therapy - of any type or route - for greater than three days, and sepsis had the greatest link to patients developing bilateral massive adrenal haemorrhage²⁶. Both of the patients we presented were aged greater than 55, and receiving a prophylactic dose of low molecular weight heparin.

The most common cause of acute adrenal insufficiency in critically ill patients is sepsis and the SIRS (systemic inflammatory response

syndrome). Although the exact pathogenic explanation is likely to involve many mechanisms, numerous studies have shown that cytokines (TNF- α , IL-6) released during severe stress can suppress the hypothalamic – pituitary – adrenal axis,^{20,21,22} along with causing activation of the coagulation cascade, inhibition of fibrinolysis, and endothelial damage which could cause adrenal haemorrhage²³. However, it has also been shown as in our case, that stress (i.e. surgery) increases corticotropin secretion, which will give a rise in adrenal blood flow^{29,30}. This increase in blood flow into the adrenal gland, which comes from roughly fifty smaller branches of the three suprarenal arteries, is only drained by a few venules. This anatomical structure of the gland, which has been described as a “vascular dam,”²⁸ makes it very susceptible to haemorrhage. Along with this anatomic predisposition, animal models have shown that focal necrosis occurs in the adrenal gland when it is chronically stimulated with corticotropin³¹.

Adrenal insufficiency is frequently linked to the classical signs of hyponatremia and hyperkalemia, however according to one study of 141 patients with diagnosed adrenal haemorrhage, hyponatremia (sodium concentration <130 mEq/L) only occurred in 13 (9%) of all patients, while hyperkalemia (potassium concentration >5 mEq/L) only occurred in 23 (16%) of all patients¹. These abnormalities usually take days to develop, whereas hypotension that is refractory to fluid treatment and requires vasopressors is the most common feature of adrenal insufficiency²⁴. Other acute signs include confusion, fever, agitation, and lethargy, as well as leukocytosis, and increase in blood urea nitrogen,¹⁹ most of which our patients exhibited. These symptoms and signs can usually be attributable to the post-operative state, and thus the eventual diagnosis is often delayed.

During times of severe physiological stress,

cortisol production rises a great deal, and a serum cortisol level of more than 18 μ g/dL is often used to exclude adrenal insufficiency in these situations¹. However, this criterion is usually based on the result of a short synacthen test, which was developed and based on non-stressed, non-critically ill patients^{13,14}. The literature suggests that during times of severe stress serum cortisol levels rise in relation to the severity of the stressor, and that the higher values correlate with higher mortality rates¹⁰. Chernow et al¹¹ reported a mean cortisol level of 32 μ g/dL 1 h after cholecystectomy and 52 μ g/dL 1 h after subtotal colectomy, and Rothwell and Lawler¹⁰ showed that ICU admission mean cortisol levels were 27 μ g/dL in survivors compared to 47 μ g/dL in the nonsurvivors. Based on this evidence it has been suggested that the use of a threshold random serum cortisol of 25 μ g/dL be used to determine adequate adrenal response to severe illness¹². As in our case both patients had random serum cortisol measurements below 18 μ g/dL (male: 3.42 μ g/dL, female: 14.58 μ g/dL).

Alongside biochemical studies, radiological assessment of the adrenal glands should be performed, with abdominal CT being probably the most reliable and widely available method for detecting AH⁷, although one report has shown recently that MRI provides the most accurate diagnoses in the investigation of adrenal diseases⁹. Ultrasound scan (method of choice in neonates) is less reliable in the adult patient as it is a challenge to image a small suprarenal mass. Although radiological assessment is key to confirming a diagnosis, we feel that steroid treatment should not be delayed if there is a suspicion of adrenal haemorrhage.

The treatment of adrenal insufficiency involves the replacement of corticosteroids (usually IV hydrocortisone), which should be instituted as soon as possible. McKee and Finlay²⁵ have shown that glucocorticoid treatment of

critically ill patients with adrenal insufficiency improves mortality when compared to placebo (13% mortality on glucocorticoid treatment versus 90% mortality with placebo).

In a review published in 1989 of over 150 cases of bilateral massive adrenal haemorrhage (BMAH) Rao, Vagnucci, and Amico created an algorithm for the diagnosis and management of BMAH, which is in accordance with the initiation of steroid treatment when there is a high index of suspicion for adrenal haemorrhage²⁷.

Previous reports have shown that elderly, critically ill patients in the post operative setting are at a greater risk of developing acute adrenal haemorrhage. Although hypotension, pyrexia, and abdominal pain are frequently seen in the early post-operative stages, we feel the diagnosis of adrenal haemorrhage should be considered in any patient where hypovolemia, sepsis and cardiovascular causes have been ruled out - particularly, in the elderly (over 55 years of age) and those receiving any type of prolonged heparin therapy. Random serum cortisol levels are easily available, usually require less time for testing, and as the above data show are quite good predictors of adrenal insufficiency in critically ill patients. Further diagnostic testing involving CT scanning and short synacthen testing can also be implemented, however this should not delay the prompt initiation of corticosteroid treatment.

Conclusion

In the management of severely ill, hypotensive patients, the diagnosis of adrenal insufficiency should not be overlooked, and random serum cortisol measurements along with prompt steroid treatment can allow for quicker management and ultimately decreased mortality of these patients.

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