THE NORTHERN HOSPITAL

ACUTE ADRENAL INSUFFICIENCY

Detail from the so called "Sarcophagus of Stilicho", in marble, Fifth century A.D. Sant'Ambrogio, Milan.

Despite its title, there is no evidence that the identity of the burial is Stilicho, though it clearly belongs to a Fifth century A.D Roman of the very highest rank. Some historians and archaeologists have suggested that it may in fact be the sarcophagus of the last great Roman general Aetius, the only general to have defeated Attila, the Hun in battle. If this is true then this is the only image we have of Aetius one of the "saviours of the Western world" and his wife, Pelagia. The figure is wearing scale armour, depicting the occupant to be a military man, (but then again so was Stilicho). Aetius led a collation of Romans, Goths, Franks and others, which defeated Attila in 451 A.D at the Battle of the Catalaunian fields, near Chalons in modern day France and by so doing saved the "West" - as we know it today - from what surely would have been a very different future.

"....He represented to Theodoric that an ambitious conqueror who aspired to the dominion of the earth could be resisted only by the firm and unanimous alliance of the powers whom he laboured to oppress. The lively eloquence of Avitus inflamed the Gothic warriors by the description of the injuries which their ancestors had suffered from the Huns, whose implacable fury still pursued them from the Danube to the foot of the Pyrenees. He strenuously urged that it was the duty of every Christian to save from sacrilegious violation the churches of God and the relics of the saints; that it was the interest of every barbarian who had acquired a settlement in Gaul to defend the fields and vineyards, which were cultivated for his use, against the desolation of the Scythian shepherds. Theodoric yielded to the evidence of truth, adopted the measure at once the most prudent and the most honourable, and declared that as the faithful ally of Aetius and the Romans he was ready to expose his life and kingdom for the common safety of Gaul. The Visigoths who were at that time in the mature vigour of their fame and power, obeyed with alacrity the signal of war, prepared their arms and horses, and assembled under the standard of their aged king, who was resolved, with his two eldest sons, Torismond and Theodoric, to command in person his numerous and valiant people. The example of the Goths, determined several tribes or nations that seemed to fluctuate between the Huns and the Romans. The indefatigable diligence of the patrician gradually collected the troops of Gaul and Germania, who had formerly acknowledged themselves the subjects or soldiers of the republic, but who now claimed the rewards of voluntary service and the rank of independent allies; the Laeti, the Armoricans, the Bretons, the Saxons, the Burgundians, the Samatians or Alani, the Ripuarians, and the Franks who followed Meroveus as their lawful prince. Such was the various army which, under the conduct of Aetius and Theodoric, advanced by rapid marches to relieve Orleans, and the give battle to the innumerable host of Attila...

The Catalaunian fields spread themselves round Chalons, and extend, according to the vague measurement of Jordanes, to the length of one hundred and fifty, and the breadth of one hundred miles, over the whole province, which is entitled to the appellation of a champagne country. This spacious plane was distinguished, however, by some inequalities of ground; and the importance of an height which commanded the camp of Attila was understood and disputed by the two generals. The young and valiant Torismond first occupied the summit; the Goths rushed with irresistible weight on the Huns, who laboured to ascend from the opposite side: and the possession of this advantageous post inspired both the troops and their leaders with a fair assurance of victory....

Cassiodorus...had familiarly conversed with many Gothic warriors who served in that memorable engagement, "a conflict", as they informed him, "fierce, various, obstinate, and bloody; such as could not be paralleled either in the present or past ages. The number of the slain amounted to one hundred and sixty two thousand, or, according to another account, three hundred thousand persons", and these incredible exaggerations suppose a real and effective loss, sufficient to justify the historian's remark that whole generations may be swept away by the madness of kings in the space of a single hour....The Visigoths, who had been thrown into confusion by the flight or defection of the Alani, gradually restored their order of battle; and the Huns were undoubtedly vanquished, since Attila was compelled to retreat....they retired within the circle of wagons that fortified their camp and the dismounted squadrons prepared themselves for a defence to which neither their arms nor their temper were adapted.....

It was determined in a general council of war to besiege the king of the Huns in his camp....but the impatience of the barbarians soon disdained these cautious and dilatory measures: and the mature policy of Aetius was apprehensive that, after the extirpation of the Huns, the republic would be oppressed by the pride and power of the Gothic nation. The patrician exerted the superior ascendant of authority and reason to calm the passions which the son of Theodoric considered as a duty, represented with seeming affection and real truth, the dangers of absence and delay; and persuaded Torismond to disappoint, by his speedy return, the ambitious designs of his brothers, who might occupy the throne and treasures of Toulouse. After the departure of the Goths, and the separation of the allied army, Attila was surprised at the vast silence that reigned over the plains of Chalons: the suspicion of some hostile stratagem detained him several days within the circle of his wagons, and his retreat beyond the Rhine confessed the last victory which was achieved in the name of the Western Empire....."

Edward Gibbon, The History of the Decline and Fall of the Roman Empire, Volume 3, 1781.

History stood at the crossroads for the West, in A.D 451. The Huns having crossed the Rhine were deep into the territories of the Western Empire, now only a shadow of its former glory - large swathes of it occupied by barbarian tribes only nominally in "alliance" with Rome, but in reality they acted only for their own interests and not for the distant eternal city. But suddenly the game had changed. A terrifying horde of uncertain origin but somewhere from the far distant eastern steppes of Russia, had swarmed across northern Germania conquering all in their path. They were led by a ruthless and invincible king, known as Attila. Attila had never been defeated in open battle, and he had gathered an immense horde including large numbers of the Germanic tribes he had subdued, in addition to his own countrymen. The Western empire had virtually accepted its fate - the end would come swiftly. But it didn't. Rome had one last glorious "swan song" left. Two brilliant individuals, the senator and diplomat Avitus and the last truly great general of the West, Aetius stood in Attila's way. Avitus pleaded with Theodoric, the Gothic king, trying to persuade him that an alliance was essential if Attila was to be defeated. Theodoric had ties with Aetius and saw that his own people were just as much under threat from Attila as were the Romans. Avitus spoke of how his own kin, the Ostrogoths has been disastrously defeated by Attila in the northern Gothic homelands and now were noting but slaves under him. Theodoric agreed - there would have to be a genuine military alliance with Rome, but there was only one general in all of Rome that the Goths and other barbarian tribes within the borders of the empire respected, his name was Aetius. Only Aetius could bring Roman and Goth together as neither trusted each other in any degree. Aetius also knew the Huns. As a young boy he had spent years with them as a hostage during the negotiations of an earlier conflict. No one else in the empire, knew the Huns as did Aetius. Avitus sped back to Rome to announce to the senate that Theodoric had agreed to fight with them. As news of the alliance spread through the west other smaller barbarian tribes, who had been vacillating between Rome and Attila, now saw the distinct possibility of a Roman victory and so also declared for Aetius.

According to Jordanes, Attila's army had been camped in the region of the Catalaunian fields, near Chalons, (champagne country as Gibbon delightfully point outs) when he saw an unexpected and unsettling sight. An immense army approaching from the south. It was

not so much the fact that it appeared to consist of Goths and assorted other tribes, which he was expecting, it was the battle standards that disturbed him - they were well known, ancient and greatly feared - "SPQR"- "The Senate and People of Rome" - this largely barbarian army was fighting under the banner that had subdued the world for centuries past, and it was being led by a Roman general - Attila knew it could only be Aetius. Victory over the West would not be quite so easy as he had thought. He now faced the fiercest barbarian warriors, and they were being led by greatest Roman general of the age. Attila however had never been defeated. The West faced its greatest challenge since Thermopylae almost ten centuries before - this battle, Gibbon wrote, would decide the fate of the West.

The Catalaunian fields held a critical piece of high ground, strategically vital, which Theodoric was quick to see. Hun and Goth clashed over this ground that would decide the outcome of the battle. Cassiodorus tells of a battle on the scale of Cannae. Though Theodoric himself was killed, the Goths pushed the Huns from the high ground and the Romans then took up the chase corralling the remnants of Attila's army in their home camp, settling into a siege. The Huns found themselves surrounded and in unfamiliar circumstances. Aetius then unexpectedly called of the troops. He knew that Attila was utterly defeated, but now he shrewdly understood that the Goths were masters of the field. Theodoric's son Torismond wanted to finish the Huns off to a man, but Aetius persuaded him that the job had been done and Attila was no longer a threat. It would be far better for him to rush back to Toulouse and claim his right to become the new king of the Goths, lest one of his brothers get in before him. Torismond agreed and rushed back to Orleans with news of a great victory. With the Huns defeated and the Goths disbanded, Aetius was left supreme in the field, and undisputed leader of the West. Attila fled back across the Rhine and would not seriously threaten Rome again. Eventually the Huns would be totally crushed at the battle of Nedao, and disappear forever from history. The battle of the Catalaunian fields was the last brilliant military glory in the twilight years of the thousand year history of the Western empire. Gibbon famously observed...."...After the departure of the Goths, and the separation of the allied army, Attila was surprised at the vast silence that reigned over the plains of Chalons: the suspicion of some hostile stratagem detained him several days within the circle of his wagons, and his retreat beyond the Rhine confessed the last victory which was achieved in the name of the Western Empire....."

It was clear that Aetius would be the next emperor - so clear in fact that the emperor of the West, the insipid Valentinian III, ambushed and murdered him! Such was the long, sorry and miserable history of Rome in its eternal inability to achieve a smooth and peaceful succession to the throne. The barbarian tribes were shocked at the news of the assassination of Aetius, a leader who many greatly respected and were willing to follow. Within a generation of Aetius' death the degenerate Western empire finally collapsed - not to the Huns but to those who considered Rome no longer fit to govern the West - the Goths, Franks and others that had formed the main part of the coalition against Attila.

History tell us that great things can achieved by mutual cooperation, the Goths and the Romans at Chalons, being a case in point. And so it is within the biological empire of our own bodies - the catecholamines rule over our "fight or flight" response to stressors of Hunnic dimensions, but they can only do so with the aid of a powerful ally - a tribe known as the glucocorticoids!

ACUTE ADRENAL INSUFFICIENCY

Introduction

The clinical presentation of adrenal insufficiency is variable and non-specific.

A high index of suspicion must therefore be maintained for the condition.

ED presentations can be due to:

- Acute adrenal crises.
- Chronic insufficiency with exacerbation due to a precipitate stress, where diagnosis if not already known, may be far more problematic.

Classic Addisonian **crisis** occurs in patients with primary adrenal insufficiency and is a life-threatening medical emergency.

History

Addison's disease is named after **Thomas Addison**, (1793 - 1860) a graduate of the University of Edinburgh Medical School who first described the condition in 1849.

Pathophysiology

The first evidence of **autoimmune adrenal insufficiency** is usually an increase in plasma renin activity in association with a normal or low serum aldosterone concentration. This fact suggests that the zona glomerulosa is involved in the disease process initially.

Several months to years later, zona fasciculata dysfunction develops, initially by a decreasing serum cortisol response to ACTH stimulation, then later by an increased basal serum ACTH concentration, and finally by a decreasing basal serum cortisol concentration with the consequent development of symptoms.

Causes:

Primary causes:

1. Autoimmune disease:
    - **Addison's disease** (this is the most common cause).
2. Infection:

    Acute:

    - Severe sepsis, (meningococcus in particular).

- ♥ Including Waterhouse-Friedrichsen syndrome (i.e. bilateral adrenal haemorrhages).

Chronic:

- TB
- HIV

3. Malignancy:
   - Metastatic invasion.
   - Lymphoma.
4. Infitrations:
   - Haemochromatosis/ sarcoid/ amyloid.
5. Vascular:
   - Adrenal vein thrombosis.
     - Anti-coagulant therapy, (i.e bilateral adrenal haemorrhages).
6. Adrenalectomised patients:
   - Surgical.
   - Medical e.g. glutethamide therapy.
7. Genetic disorders:

   These are *rare* inherited conditions that present in infancy/ childhood. Examples include:

   - Adrenal leukodystrophy.
   - Adrenal myeloneuropathy.

Secondary causes:

1. Secondary to **pituitary** or **hypothalamic** disease:
   - Note that there is usually no associated mineralot deficiency in these cases.
2. Secondary to steroid suppression:
   - Exogenous glucocorticoid suppression:

- ♥ This is the single most common cause of adrenal insufficiency.

- Exogenous glucocorticoid suppression:
  - ♥ e.g. from tumour production

Precipitants of acute adrenal crisis:

Any patient with adrenal insufficiency or on long term steroids, who:

- Undergoes an acute "stress":
  - ♥ e.g. multi-trauma, severe burns, sepsis, ACS.
- Have their steroid therapy abruptly withdrawn.

Complications of acute adrenal insufficiency:

These principally include:

1. Electrolyte disturbances:
   - **Hyponatraemia** (aldosterone lack).
   - **Hyperkalaemia** (aldosterone lack).
   - Hypocalcaemia (reduced glomerular filtration and increased proximal tubular resorption)
   - Metabolic acidosis (normal anion gap).
2. Hypoglycaemia:
   - Reduced insulin antagonism due to the loss of cortisol.
   - Usually only mild if present.
3. **Circulatory shock:**
   - **The glucocorticoids play an important role in facilitating/ enhancing the actions of endogenous catecholamines.**
4. **Susceptibility to "stressors"**
   - A refractory shock like state can ensue when patients are subjected to stressors, in the form of trauma, surgery or acute medical illness.

Clinical Features

Acute presentations:

Features of the patient who presents in an acute adrenal crisis include:

1. Acutely ill:
    - Non-specific constitutional symptoms are prominent such as lethargy, malaise, weakness.
2. Hypoglycaemia.
3. GIT symptoms:

    These are common:
    - Anorexia, nausea, vomiting.
    - Abdominal pain can also be a feature.
4. **Circulatory shock:**
    - **This is the most serious presentation.**
    - The shock state can be very resistant to fluid loading and inotropic support.
    - **Acute adrenal insufficiency should be considered in patients who present with circulatory shock for whom no apparent cause can be determined.**
5. CNS:
    - Confusion/ altered conscious state.
6. Evidence of a precipitating event:
    - Sepsis, trauma, ACS, burns, or post-surgery.

Chronic Presentations:

Insidious onset of:

1. Non-specific constitutional symptoms:
    - Weakness, lethargy, malaise
2. GIT symptoms:

- Anorexia, weight loss.

3. CVS:

   - Shock state with relatively minor stresses.
   - Unexplained **postural hypotension.**

4. **Pigmentation:**

   Due to a lack of normal ACTH, **MSH** is no longer inhibited.

   Look for hyperpigmentation particularly in:

   - Exposed skin areas and skin creases.
   - Buccal mucosa.
   - Recent scars.

5. Evidence of other autoimmune processes.

6. Females may have reduced body hair due to androgen lack, not usually the case in men due to testicular androgens (unless there is a secondary failure).

7. Water intoxication (inability to excrete a water load, rare)

Note on Secondary Adrenal Insufficiency:

1. Aldosterone levels are not greatly affected, therefore features are primarily of cortisol and androgen loss only, rather than mineralot deficiency.

2. Loss of other pituitary hormones (TSH, GH, Gonadotrophic hormones) will result in other clinical features.

3. Hypoglycaemia may be more severe (due to loss of GH)

4. Hypo (rather than hyper) pigmentation will be seen.

Investigations

Blood tests:

1. FBE

2. CRP

   - Evidence of infection, as a precipitating illness.

3. U&Es/ glucose:

   - **Decreased sodium**
   - **Increased potassium**

   Note that the absence of hyponatremia and hyperkalaemia does not exclude early Addison's disease.

   - **Hypoglycaemia (rarely the presenting symptom)**

4. Calcium:

   - Elevated calcium (uncommonly)
   - This may herald the onset of an Addisonian crisis.

5. Renal function:

   - Increased urea/ creatinine.

6. Blood gases:

   - **Mild metabolic acidosis.**

7. Hormone levels:

   In undiagnosed cases of acute adrenal insufficiency take blood (before any treatment) for:

   - Cortisol levels
   - ACTH levels
   - Renin levels

Making the Diagnosis:

The diagnosis of **primary adrenal insufficiency** is confirmed by the combination of:

- A positive short Synacthen test:

  ♥ An absent (or severely blunted) plasma cortisol response to tetracosactrin 30 - 60 minutes after injection.

  ♥ A baseline or post Synacthen cortisol level > 550 nmol/L is considered normal.

- Elevated adrenocorticotrophic hormone (ACTH) levels.
- Elevated plasma renin:
    - ♥ Measured by direct concentration or by plasma renin activity.

Measuring diurnal (morning and afternoon) plasma or serum cortisol concentrations is *not* useful for evaluating adrenal insufficiency. [1]

CT Scan:

CT scanning is done:

- Of the abdomen to image the adrenal glands or for disseminated malignancy.
- To image the pituitary gland.
- To guide needle biopsy of adrenal tissue.

Management

1. ABC:
    - IV **normal saline** fluid resuscitation will be the immediate priority in most cases.
    - **Note however that patients in acute adrenal crisis will be very resistant to fluid therapy until glucocorticoids have been administered.**
2. Hypoglycaemia:
    - This may be the presenting problem, though it is usually only mild.
    - It should always be looked for and corrected as required.
3. Hyperkalaemia:
    - Potassium levels should be checked urgently and corrected as necessary.
    - Intravenous **sodium bicarbonate**, rather than glucose and insulin, is preferred for emergency treatment of hyperkalaemia if adrenal insufficiency cannot be excluded. This is because patients in adrenal crises have a tendency to hypoglycaemia (due to lack of cortisol antagonism) and these patients are *very sensitive* to the effects of insulin. [1]
4. Hyponatraemia:

- *Severe* hyponatraemia may occur in hypopituitarism, mainly as a consequence of glucocorticoid deficiency. Management is by glucocorticoid replacement and restriction of water intake. [1]

5. Adrenocorticosteroids:

Note that when both adrenal glands atrophy (Addison's disease) or are destroyed or removed, catecholamines do not need to be replaced, but replacement of **glucocorticoids** and **mineralocorticoids** is essential.

The mainstay of treatment for acute adrenal insufficiency is replacement therapy with a glucocorticoid.

Hydrocortisone (cortisol) and cortisone (which is converted to hydrocortisone by the liver) should ideally be avoided in **undiagnosed patients** because both are measured in cortisol radioimmunoassays, which interfere with the interpretation of any subsequent synacthen testing.

Dexamethasone, which is not measured in these assays, is therefore the glucocorticoid of choice in patients in whom a definite diagnosis of adrenal insufficiency has *not* been made.

In known cases of adrenal insufficiency:

In severe cases with hypotension and disturbance of consciousness and/or mental state, urgent treatment with parenteral hydrocortisone should be initiated on the basis of clinical findings, even before laboratory results have become available. [1]

- **Hydrocortisone 100 mg IV, then 50 mg IV 6 hourly until stable.**

  Subsequent dosing depends on initial response, and should be guided by an endocrinologist.

Resolution of clinical features will generally occur over 4 - 6 hours and must be followed by oral replacement therapy

- After initial intravenous therapy and stabilization, it is important to use higher doses than normal of oral glucocorticoid replacement for the next 24 to 48 hours. [1]

  Give cortisone acetate 25 mg orally, 3 times daily, gradually reducing to maintenance dose over 2 to 3 days. [1]

  For cortisone maintenance the dose is 0.3 mg/kg or less daily.

In undiagnosed (but suspected) cases of adrenal insufficiency:

Where initial treatment is required for presumed Addison's disease on clinical grounds alone:

- Dexamethasone 4 mg IV stat, (dexamethasone is not detected in plasma cortisol assays).

Then:

- Dexamethasone 500 micrograms twice daily [1], or after the short Synacthen test - hydrocortisone 50 mg IV, every 6 hours until stable.

6. Mineralot corticoids:

Mineralocorticoid replacement with fludrocortisone may also be required for unwell patients with acute adrenal crisis.

Use:

- **Fludrocortisone 100 micrograms orally, daily and adjust according to response.**

  Acute adjustment of mineralocorticoid therapy in those already taking fludrocortisone is generally not required for minor stress or intercurrent illness.

7. Intercurrent illness: [1]

Frequently there will be an intercurrent precipitating illness, and attention should also, of course be directed to this when managing the patient with acute adrenal crisis.

- During significant intercurrent illness, glucocorticoid dosage should be doubled, and it may be necessary for this to be given parenterally in patients who are significantly unwell.

  The dose can usually be doubled for 2 to 3 days without adverse effect.

  An increased dose is also appropriate after physical trauma, and may be required after emotional stress.

- Any features of impending adrenocortical crisis (eg nausea, vomiting, abdominal pain) suggest the need for **parenteral** hydrocortisone therapy.

Secondary adrenal insufficiency:

Secondary adrenal insufficiency is treated with glucocorticoid alone, at the same dose as for primary adrenal insufficiency.

Mineralocorticoid replacement is not needed in secondary adrenal insufficiency, because the renin–angiotensin–aldosterone axis remains intact. [1]

Patient supply of corticosteroid:

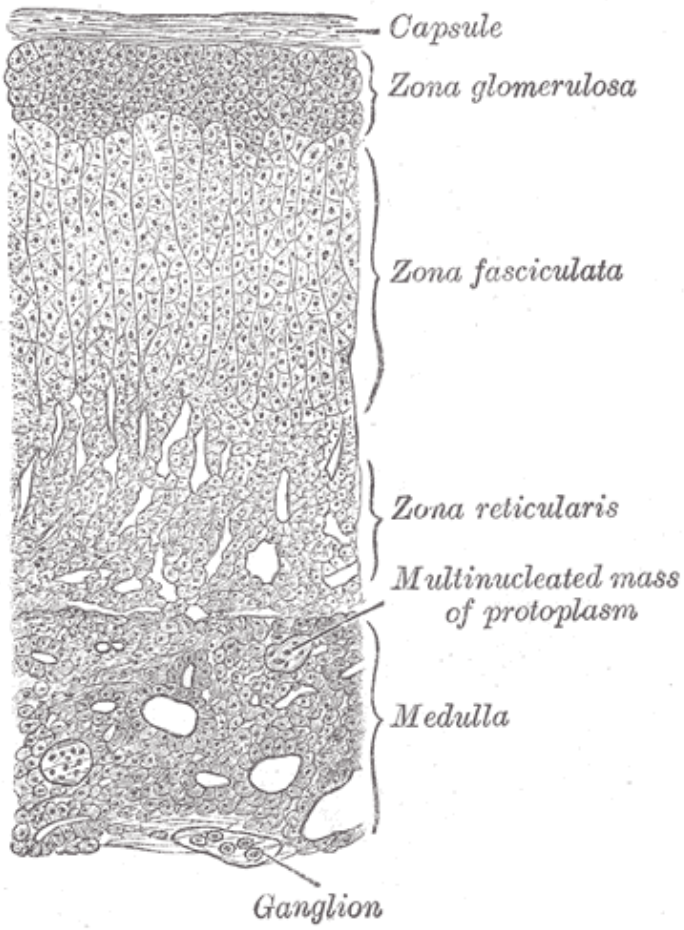
If patients are more than 12 hours away from emergency medical care, they should ideally carry a supply of injectable hydrocortisone 100 mg or dexamethasone 4 mg vials for intramuscular injection with appropriate syringes and instructions for administration.

Disposition:

Any patient suspected of having acute adrenal insufficiency must be urgently referred to a specialist Endocrinologist.

Appendix 1

Physiology of the Adrenal Gland:



Cross sectional anatomy of the adrenal gland, (Gray's Anatomy 1918).

The Adrenal Cortex:

This consists of **3 zones**:

- Zona glomerulosa:
  - ♥ This layer is the main site for production of the **mineralocorticoid** hormone, **aldosterone.**
- Zona fasciculata:
  - ♥ This layer is the main site for production of the **glucocorticoids** (mainly **cortisol**).
- Zona reticularis:

- ♥ This layer is the main site for production of **androgens**; mainly dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione (the precursor to testosterone) in humans.

The Adrenal Medulla:

- The chromaffin cells of the medulla are the body's main source of the circulating catecholamines; **adrenaline** (80 %) and **noradrenaline** (20 %).

References

1. eTG - March 2015.
   - Endocrinology Therapeutic Guidelines, 5th ed 2014.
2. A. Maclean, Hypoadrenal States in Cameron et al. "Textbook of Adult Emergency Medicine" Churchill Livingston - Elsevier, 2015.

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