education

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Bedside test for raised intracranial pressure


SPL

Just lie back and close your eyes. Here's some gel on your closed eyelid so I can measure your optic nerve sheath diameter by ultrasound. Is this any good as a diagnostic test for raised intracranial pressure? From a practical perspective it's more appealing than a CT, MRI, or lumbar puncture.

Koziarz and colleagues meta-analysed 71 studies involving over 4000 patients to determine the accuracy of this non-invasive technique in traumatic and non-traumatic brain injury settings. They found that optic nerve ultrasonography was a useful test for ruling out raised intracranial pressure when normal (nerve sheath <5 mm), whereas an increased diameter (>5 mm) may indicate raised intracranial pressure and a need for a confirmatory test.

Ann Intern Med doi:10.7326/M19-0812

Ubrogepant for migraine

The ACHIEVE II trial is a double blinded randomised controlled trial of two doses of a calcitonin gene related peptide antagonist called ubrogepant as an acute treatment for migraine. The participants were adults experiencing between two and eight episodes of migraine (with or without aura) each month. The primary endpoint was a combination of freedom from pain two hours after the treatment and absence of the patient's self selected other most bothersome symptoms—a novel but laudable addition to the endpoint.

While ubrogepant was more effective than placebo, only 20% of people were pain free, which isn't many given that 14% were pain free in the placebo group. And for the absence of the most bothersome symptom, it was only really the higher ubrogepant dose that was effective.

JAMA doi:10.1001/jama.2019.16711

Umbilical cord care for the premature brain

Randomised evidence in perinatal care is limited, so Katheria and colleagues should be congratulated on their study comparing umbilical cord milking with delayed umbilical cord clamping. They set out to assess rates of death or severe intraventricular haemorrhage in preterm infants. The trial was stopped early because at the first interim analysis, umbilical cord milking was associated with much higher rates of severe intraventricular haemorrhage. Unfortunately, as noted by the authors, definitive conclusions from this study are therefore limited.

Umbilical cord milking is pushing placental blood down the cord to the newborn before clamping the umbilical cord. Perhaps this is too much for the underdeveloped newborn. The authors note that that premature infants lack adequate cerebral autoregulation and explain that improved blood flow in a fragile brain may do more harm than good.

JAMA doi:10.1001/jama.2019.16004

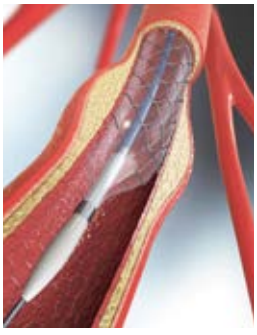
Anti-CD38 for multiple myeloma

As we all know, CD38 has an important role in white blood cell function. Isatuximab is a monoclonal antibody that binds to CD38, thus targeting tumour cells for programmed cell death in myeloma. The ICARIA-MM study tested its impact on top of pomalidomide and low dose dexamethasone in an open label randomised controlled trial of 307 people with refractory multiple myeloma.

In the control group median progression-free survival was 6.5 months, but, with the addition of isatuximab, progression-free survival was 11.5 months. In this study progression-free survival was adjudicated by an independent committee, but there was a high risk of bias. The trial would have provided more useful evidence had it been designed and powered for overall survival. Alternatively, it could have been fully blinded. As it stands, it is really unclear whether isatuximab truly benefits patients.

Lancet doi:10.1016/S0140-6736(19)32556-5

Ticagrelor after stenting



For a cardiologist, the most feared complication of a stent is stent thrombosis. Aside from the technical aspects of performing the procedure, dual antiplatelet therapy for one year has been the main approach to preventing this. In recent years, there has been a lot of work into whether dual antiplatelets can be switched to a single antiplatelet agent sooner. This isn't just a pill numbers game. This is about reducing bleeding risk.

Mehran and colleagues randomised 7119 people who had had a stent three months earlier to either ticagrelor and aspirin or ticagrelor only in a double blinded fashion. The primary endpoint (bleeding) was much less common in the ticagrelor only group with no difference in rates of death, myocardial infarction, or stroke.

N Engl J Med doi:10.1056/NEJMoa1908419

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CLINICAL UPDATE

Diagnosis and treatment of sciatica

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Sciatica is commonly used to describe radiating leg pain. It is caused by inflammation or compression of the lumbosacral nerve roots (L4-S1) forming the sciatic nerve.[1] Sciatica can cause severe discomfort and functional limitation.

Recently updated clinical guidelines in Denmark, the US, and the UK highlight the role of conservative treatment for sciatica.[2-4] In this Clinical Update, we provide an overview for non-specialists on diagnosing sciatica and key principles in its management.

The term "sciatica" is not clearly defined and it is often used inconsistently by clinicians and patients.[5] Radicular pain and lumbosacral radicular syndrome have been suggested as alternatives.[6] In this article, we use sciatica and radicular pain synonymously. Radiculopathy describes involvement of the nerve root, which causes neurological deficit including weakness or numbness.

How do patients present?

People with sciatica usually describe aching and a sharp leg pain radiating below the knee and into the foot and toes.[7] The pain can have a sudden or slow onset and varies in severity. Most people report coexisting low back pain. Disc herniations affecting the L5 or S1 nerve root are more common and cause pain at the back or side of the leg and into the foot and toes.[8] If L4 root is affected, pain is localised to the front and lateral side of the thigh.[7] Tingling or numbness and loss of muscle strength in the same leg are other symptoms that suggest nerve root involvement (see box overleaf).

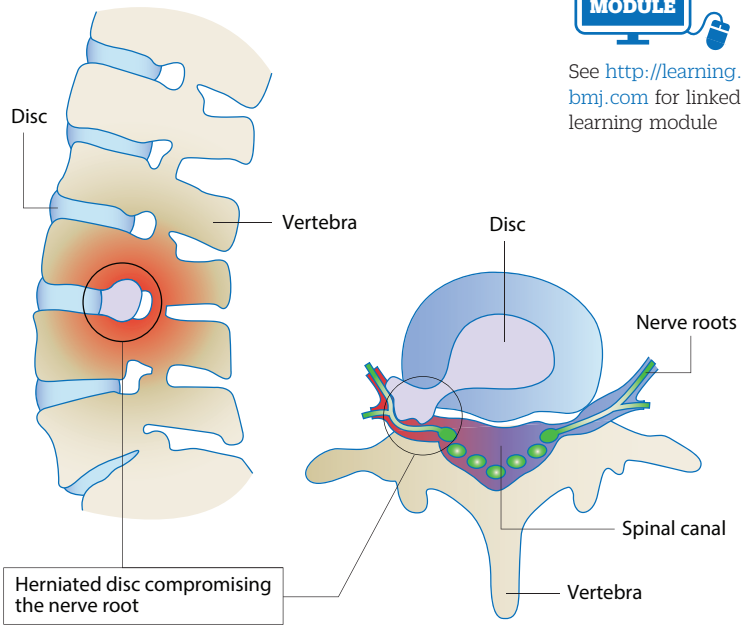

Fig 1 | Herniated disc with nerve root compromise. Figure reproduced with permission from the Danish Chiropractors' Association

How common is sciatica?

The prevalence of sciatica varies between studies. In a primary care study in the UK (609 patients) about 60% of patients with back and leg pain were clinically diagnosed with sciatica.[9] In a Danish primary care study in patients with low back pain, 2% of patients in chiropractic clinics (947 patients) and 11% in general practices (324 patients) had associated neurological findings confirming sciatica.[10]

What are the causes?

Compression of the nerve root and resultant inflammation play a role in pathogenesis of sciatica.[1] Disc herniation resulting from age related degenerative changes, and rarely trauma, is the commonest cause[1 9] (fig 1). The inflammatory response induces resorption of the herniated disc material, and is thought to be the reason why most people improve without surgery.

Foraminal stenosis and, less commonly, soft tissue stenosis caused by cysts, tumours, or extraspinal pathology are other causes.[11] Rarely, extraspinal pathology in the lumbosacral nervous plexus such as neoplasm, trauma, infection, or gynaecological conditions, or muscle entrapment such as piriformis syndrome can mimic symptoms of disc herniation.[11]

Smoking, obesity, and manual labour are modifiable risk factors for the first episode of sciatica as per a recent systematic review (eight studies), and suggest the potential for prevention.[12]

WHAT YOU NEED TO KNOW

- Sciatica is a clinical diagnosis based on symptoms of radiating pain in one leg with or without associated neurological deficits on examination
- Most patients improve over time with conservative treatment including exercise, manual therapy, and pain management
- Imaging is not required to confirm the diagnosis and is only requested if pain persists for more than 12 weeks or the patient develops progressive neurological deficits
- Urgently refer patients with signs of urinary retention or decreased anal sphincter tone, which suggest cauda equina syndrome
- Surgery is an option if symptoms do not improve after 6-8 weeks of conservative treatment. It may speed up recovery but the effect is similar to conservative care at one year

How is sciatica diagnosed?

Sciatica is largely a clinical diagnosis based on the person's symptoms and findings on examination. A history of leg pain worse than back pain or pain below the knee should raise suspicion of sciatica. Inquire about the onset and distribution of pain, and associated symptoms such as tingling sensation, numbness, or muscle weakness in the legs.

There is no specific test for sciatica but a combination of positive findings on examination increases the likelihood.[13] Figure 2 (see bmj.com) shows examination for radiculopathy in those patients where sciatica is suspected. A recent cohort study proposed clinical criteria of unilateral leg pain, monoradicular distribution of pain, positive straight leg raise test at <60° (or femoral stretch test), unilateral motor weakness, and asymmetric ankle reflex to predict sciatica caused by lumbar disc herniation.[14]

Exclude serious pathology such as cancer, trauma, and infection. Urinary retention and decreased tone of anal sphincter indicate cauda equina syndrome, which should prompt immediate referral.

Symptoms and signs suggesting sciatica

- Unilateral leg pain more severe than low back pain
- Pain most commonly radiating posteriorly at the leg and below the knee
- Numbness and/or paraesthesia in the involved lower leg
- Positive neural tension test with provocation of pain in the affected leg (straight leg raise test/femoral nerve test/slump test)
- Neurological deficit associated with the involved nerve root (muscle weakness/absence of tendon reflexes/sensory deficit)

What is the role of imaging?

Routine imaging is not advised in people with non-specific low back pain with or without sciatica, as per most clinical practice guidelines.[15] It can lead to unnecessary tests, referrals, and intervention, and increased costs.[16 17] Disc herniation is a common age related finding. A recent meta-analysis (14 magnetic resonance imaging (MRI) studies, 3097 individuals) reported disc protrusion in 57% of symptomatic and 34% of asymptomatic individuals and disc extrusion in 7% and 2% of individuals, respectively.[18]

Consider imaging if symptoms progress for more than 12 weeks, or if the person has progressive neurological deficits or worsening pain.[4-20] The box right lists red flags for referral. Based on your practice settings, you may request imaging or refer the patient to a specialist. MRI is preferred over computed tomography as it is safer. Radiography is not useful.[21]

People with persistent or recurrent symptoms after treatment sometimes request a repeat MRI. This is not usually helpful as MRI interpretation is difficult after the initial episode and does not appear to change outcomes.[22]

A PATIENT'S PERSPECTIVE

It started after an episode of flu. One night, I suddenly had a lot of pain in my leg. The next day, I went to the doctor who told me it was my sciatic nerve that was squeezed. I would have liked more information on what that meant and how long it would take to get better.

During the first three weeks I saw four different clinicians because I had a lot of pain. Only the fourth clinician explained to me what it was and told me that it could take at least a few months to recover. This was useful because then I had a timeframe. I know that the course differs from person to person, but it helps to think, "now I only have four weeks left."

I have been on sick leave and still am. But now I have started to work a little again. I think it's getting better. I still have pain in my leg, but it is not quite so fierce, and it is not constant pain any more.

What is the prognosis?

Most people experience an improvement in symptoms over time with either conservative treatment or surgery.[23] In a five year follow-up of a Dutch randomised controlled trial (231 patients), 8% of patients showed no recovery and 23% reported ongoing symptoms that fluctuated over time.[24] Low back pain with pain radiating to the leg appears to be associated with increased pain, disability, poor quality of life, and increased use of health resources compared with low back pain alone.[10] Severity and duration of symptoms, radiological findings, or patient characteristics do not consistently predict recovery of pain and function with conservative management, as per a systematic review (seven studies).[20]

About 55% of patients with sciatica reported improvement in pain and disability at one year in a recent UK primary care cohort study (452 patients). Treatment was based on clinical guidelines and included physiotherapy sessions. Eleven per cent of patients were referred to secondary care. Fourteen patients had surgery and 21 received spinal injections. Longer pain duration and patient beliefs that the problem would continue were associated with a poor prognosis.[19]

RED FLAGS FOR REFERRAL

- Severe or progressive neurological deficits
- Suspicion of cauda equina syndrome with signs of urinary retention and/or decreased anal sphincter tone
- Suspicion of cancer or infection
- History of trauma
- Acute, severe sciatica for epidural injections where patients would otherwise go on to have surgery
- Persistent sciatica for 12 weeks from onset of symptoms despite conservative care

QUESTIONS FOR FUTURE RESEARCH

- What is the prevalence of sciatica in different populations such as primary and secondary care, as well as in different age groups and in different professions?
- What is the natural course and prognosis of sciatica?
- What is the optimal conservative treatment plan, including different treatment modalities and duration?
- What are the criteria for surgery and optimal timing to consider surgery?

How is it managed?

Symptoms can be distressing and affect daily life and productivity. Acknowledge the person's concerns and fears. Share information about the natural course of sciatica and reassure them that symptoms usually diminish over time. Discuss treatment options, taking into consideration their preferences, to develop a plan.

Conservative treatment

Initial treatment is aimed at managing pain and maintaining function while the compression and/or inflammation subsides.[2 3] Encourage patients to remain active and avoid bed rest[2 3] so that the condition interferes as little as possible with daily life. Ask the person to watch for and report any change in symptoms, such as increasing leg pain or neurological deficits.

Exercise and manual therapy

Exercise reduces intensity of leg pain in the short term, as per a systematic review (five randomised controlled trials)[25] but the effects are small. Clinical guidelines from the UK, US, and Denmark recommend exercise therapy and mention a range of exercises, but do not indicate whether one type of exercise is better than another.[2-4] Based on your practice settings, general practitioners, chiropractors, or physiotherapists can guide patients on appropriate exercises. Consider the severity of the person's pain and their ability when recommending exercises. Discuss the options for supervised or group exercise based on what is feasible for your patient.

Manual therapy, such as spinal mobilisation, can be offered alongside exercise, and may be provided by manual therapists, physiotherapists, and chiropractors based on local practice.[2 3] Acupuncture is not recommended in patients with sciatica.[2 3] Guidelines from the National Institute for Health and Care Excellence (NICE) advise against traction and electrotherapies for patients with back pain with or without sciatica.[3]

Medication

Pain medications have uncertain benefit for sciatica and can have adverse effects. Discuss their role and use these only very sparsely for a short period of time (weeks rather than months) and in the lowest possible dose for pain relief.[26] A systematic review (three trials) found that non-steroidal anti-inflammatory drugs are no more effective than placebo in improving pain and disability, though there is low quality evidence of overall improvement in patients. Corticosteroids may improve symptoms in the short term (six weeks) compared with placebo, as per a systematic review (two trials).[27] The results were less favourable in two subsequent trials. An increased risk of adverse events is reported with either treatment.[28] Evidence for the use of paracetamol, benzodiazepines, opioids, and antidepressants for patients with sciatica is limited, and their use is not recommended.[28] The available evidence does not suggest any benefit with anticonvulsants or biological agents[28] compared with placebo.

Spinal injections

Guidelines on spinal injections differ in their recommendations. NICE guidelines[3] recommend offering epidural injection of local anaesthetic and steroid in the lumbar nerve root area in people with acute, severe sciatica where they would otherwise be considered for surgery. The Danish national clinical guidelines do not recommend their use as the beneficial effect was estimated to be very low and only short term based on limited evidence.[2]

EDUCATION INTO PRACTICE

- How would you discuss with a person newly diagnosed with sciatica why referral for MRI is not necessary?
- At your practice, what is the conservative treatment that patients with sciatica have received in the past 12 months? How have they improved?

Surgery

People with persistent pain for more than 12 weeks from the onset of symptoms despite conservative treatment may be considered for surgery.[2] Imaging should confirm lumbar disc herniation at the nerve root level corresponding with findings on clinical examination. Open micro discectomy for removal of disc herniation is the commonest procedure, and minimally invasive surgical techniques such as endoscopic surgery are commonly used.

A systematic review[30] (five randomised controlled trials) reports low quality evidence (based on a single trial) that early surgery within 6-12 weeks of radicular pain provided faster relief compared with prolonged conservative care.[31] At one and two year follow-ups, there were no differences in any clinical outcomes between surgery and conservative care.[23-31]

Surgery is also indicated in serious or progressive neurologic deficits such as motor weakness or bladder dysfunction.[32]

Competing interests: None declared.

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HOW WERE PATIENTS INVOLVED IN THE CREATION OF THIS ARTICLE?

One of our patients with sciatica shared their perspective and highlighted how more information would have made a difference to her. We have emphasised how clinicians can share information about the condition and prognosis with patients. A patient also kindly reviewed this paper for *The BMJ* and suggested we discuss the severity of disability and the impact on daily living. We have done so now. We thank these patients for their input.

INFORMATION RESOURCES FOR PATIENTS

National Institute for Health and Care Excellence (NICE) National clinical guidelines providing recommendations to the public on low back pain and sciatica https://www.nice.org.uk/guidance/ng59/ifp/chapter/Low-back-pain-and-sciatica-the-care-you-should-expect

International Association for the Study of Pain (IASP) provides a list of webpages with resources relevant to patients in pain http://www.iasp-pain.org/PatientResources.

International Society for Advancement of Spine Surgery (ISASS) patient information material on sciatica https://www.isass.org/for-patients/spine-conditions/sciatica/

Investigating cortisol excess or deficiency: a practical approach

0.5 HOURS

See http://learning.bmj.com for linked learning module

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School.

A 67 year old woman with no significant medical history required urgent orthopaedic surgery after a fall. In preparation, her bloods were collected and a random cortisol was requested, which came back at 763 nmol/L. She did not have diabetes or hypertension. The anaesthetist reviewed and commented: "High cortisol, not safe for surgery until further evaluation."

Cortisol, secreted by the adrenal cortex, regulates blood pressure, glucose metabolism, and physiological responses to stress. Both cortisol over-secretion (hypercortisolism, Cushing's syndrome) and under-secretion (hypocortisolism such as in Addison's disease) are uncommon.[1 2] However, given the potential for life threatening consequences (such as in acute adrenal crisis) and the range of associated non-specific symptoms, it is critical for clinicians to understand how to interpret and manage cortisol status.

Interpreting cortisol results can be confusing because cortisol secretion is pulsatile, shows diurnal variation, is regulated via a feedback system, and is influenced by a range of stressors. Furthermore, the tests involve measuring cortisol on its own (static testing) or as part of a stimulation or suppression test (dynamic function testing), and in a range of sample types (such as from serum, saliva, or urine).

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patient involvement. The cases provided are fictitious but based on commonly encountered clinical scenarios.

WHAT YOU NEED TO KNOW

- Random, untimed cortisol levels are of limited clinical value
- Cortisol measured at around 8-9 am (when the level is expected to be highest) is the preferred initial screening test for cortisol deficiency
- If high clinical suspicion for hypercortisolaemia, patients should be referred to specialist care for testing and interpretation of results
- Dynamic testing is often required to confirm cortisol deficiency or excess given the pulsatile nature of cortisol secretion and the influence of diurnal variation, feedback control, and stress.
- Salivary cortisol has better specificity for diagnosis of Cushing's syndrome than urinary cortisol and is easier to collect; if this test is available, it is increasingly preferred to urinary free cortisol

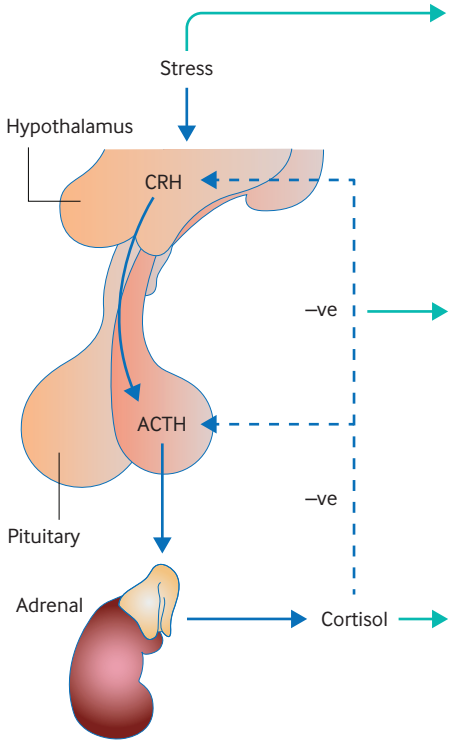
Factors affecting cortisol production and measurement

Cortisol is secreted from the adrenal cortex and is influenced by (fig 1):

Circadian rhythm—Cortisol is secreted in response to pulses of corticotrophin releasing hormone (CRH) and ACTH.[3] These pulses contribute to a circadian rhythm with peak cortisol levels just before waking and the nadir around bedtime. Hence, if cortisol deficiency is suspected, cortisol should be measured at around 8-9 am (when it is expected to be highest). If this is low, it would suggest deficiency. If excess cortisol is suspected, cortisol levels should be checked when they are expected to be lowest (around midnight). A random, untimed cortisol measurement is of minimal clinical value and should be avoided in assessing cortisol status.

Feedback control—Exploiting the physiologic feedback mechanisms is the underlying principle behind dynamic function tests (both stimulation and suppression tests).[4 5] CRH produced in the hypothalamus stimulates the pituitary to produce ACTH, which stimulates the adrenal gland to produce and release cortisol.[3 6] Rising cortisol levels suppress further CRH and ACTH production, thereby creating a negative feedback loop. In cases of cortisol insufficiency due to adrenal causes, CRH and ACTH levels are expected to be high. However, in cases of cortisol insufficiency due to a hypothalamic or pituitary cause (such as a tumour), the ACTH level would be low. The same principles apply to cortisol excess.

Stress—Cortisol is often referred to as the stress hormone. Its secretion is promptly induced in response to a range of stressors including severe trauma, sepsis, pain, anxiety, exercise, and hypoglycaemia. The extent of impact on cortisol levels will depend on the severity of the stress. If there is suspicion of cortisol deficiency (for example, unexplained hyponatraemia, hypoglycaemia, or hypotension in a severely septic patient), interpretation of cortisol levels should take into account the underlying stress.[7]



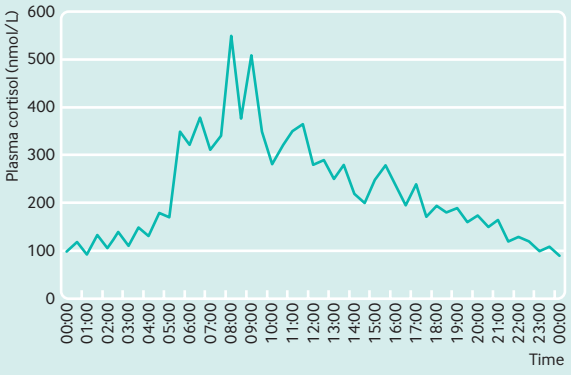
Stress

- Interpret static cortisol levels in context of underlying stressors
- For example, severe trauma can result in high cortisol levels irrespective of time of day
- Stress response underpins the insulin stress test, with the insulin induced hypoglycaemia being perceived as a stressor

Feedback

- For suspected cortisol deficiency:
  - Short synacthen test reproduces the stimulatory effect of ACTH on cortisol secretion
  - If cortisol levels fail to rise, suggests deficiency
- For suspected cortisol excess:
  - Dexamethasone suppression test uses exogenous steroid to suppress production of ACTH and hence cortisol, exploiting the negative feedback loop
  - Failure to suppress cortisol secretion suggests excess endogenous cortisol production

Circadian rhythm



- For suspected cortisol deficiency:
  - Check 8-9 am levels (at expected peak)
  - If low, cortisol deficiency likely
- For suspected cortisol excess:
  - Check midnight levels (at expected trough)
  - If high, cortisol excess likely
- Random cortisol measurement unlikely to be helpful

Fig 1 | **How cortisol testing is affected by its underlying physiology**

Cortisol binding globulin—Cortisol is bound strongly to cortisol binding globulin (CBG) in serum. Serum cortisol measurement reflects the total rather than free concentration. Factors affecting CBG, such as acute illness or medicines such as hormonal contraception, could alter reported serum cortisol without having a bearing on free cortisol concentrations. By contrast, saliva and urine samples reflect the free component of cortisol and may thus be clinically more useful. For example, in a recent study, women taking the contraceptive pill were found to have total plasma cortisol and CBG levels 2.9 and 2.6 times higher, respectively, when compared with controls, whereas 24 hour urinary free cortisol and plasma free cortisol were not significantly different.[8] Given the wide availability of total serum cortisol assays (which includes the CBG-bound component), the effect of CBG may need to be taken into consideration.

Exogenous glucocorticoids used for the treatment of other diseases may also suppress the hypothalamo-pituitary-adrenal axis. This includes the use of inhaled, nasal, transdermal, and intra-articular preparations.

When to consider testing cortisol function

Cortisol deficiency[9 10]

- Unexplained electrolyte imbalance (hyponatraemia, hyperkalaemia)
- Hypotension (especially if resistant or associated with other factors such as weight loss, electrolyte imbalance, increased pigmentation)
- Unexplained or accelerated weight loss
- Tiredness (unexplained, overwhelming, or associated with other above symptoms)
- Unexplained reduced appetite, salt cravings, increased thirst or urination, nausea and vomiting
- Combinations of autoimmune disease (such as type 1 diabetes, hypothyroidism or hyperthyroidism, vitiligo, pernicious anaemia, chronic active hepatitis, alopecia, coeliac disease, rheumatoid arthritis)
- Family history of autoimmune disease (as above)
- Hypothyroidism with expected or confirmed autoimmune disease
- Type 1 diabetes with recurrent unexplained hypoglycaemia
- Cancer with bilateral adrenal lesions
- Use of exogenous corticosteroids
- Pregnancy with unexplained persistent nausea, hypotension, and/or fatigue[11]

Cortisol excess[11]

- Unexplained electrolyte imbalance (hypokalaemia)
- Hypertension (especially in young patients, resistant to treatment, or associated with diabetes, central obesity, increased bruising)
- Unexplained or accelerated weight gain
- Deteriorating diabetes control
- Unexplained bruising
- Adrenal incidentaloma

When to consider measuring cortisol in routine clinical practice?

Cortisol measurement is not routinely required unless there are specific features to suspect adrenal disease. For example, rapid onset of diabetes with weight gain, easy bruising, and muscle weakness could point to possible Cushing's syndrome. The box lists some of the clinical features that should prompt a clinician to consider measuring cortisol.

Cortisol excess could be due to a cortisol-secreting tumour or to a functional pituitary tumour (Cushing's disease) secreting ACTH that is not responsive to the normal negative feedback loop. Less often, malignant tumours can secrete ACTH ectopically. Cortisol deficiency could be due to primary adrenal malfunction (such as autoimmune-mediated atrophy "Addison's disease," malignant infiltration, or haemorrhage) or secondary to either pituitary or hypothalamic disease resulting in reduced secretion of ACTH.

What tests are available and how to interpret them

In general, initial testing consists of static tests that are timed to correspond with physiologic diurnal cortisol variation:

- If cortisol excess is suspected, midnight cortisol should be measured
- If cortisol deficiency is suspected, cortisol levels should be checked at 8-9 am.

If initial static tests are abnormal, dynamic tests are then used to confirm abnormal results. The approach to testing is depicted in fig 2.

Investigating suspected cortisol excess

There are three tests that can be considered initial screening tests when investigating suspected hypercortisolism. These are midnight serum or salivary cortisol, 24 hour urinary free cortisol, and the overnight dexamethasone suppression test. Serum testing was extensively used in the past, but it requires hospitalisation and venepuncture at midnight, causing stress that could falsify the results. If available, salivary cortisol is increasingly being used for outpatient testing instead (mostly by specialists). Although an overnight dexamethasone suppression test is a dynamic test, it can be performed as an outpatient, and GPs could consider this test with select patients, particularly when clinical suspicion is low and testing can be done quickly to rule out cortisol excess.

While many of these tests can, in theory, be performed by general practitioners, if they have a high clinical suspicion of hypercortisolism, we recommend referral to specialist care for testing because of the complexity of interpreting the results and potential confounders.

Urinary cortisol—Urinary cortisol testing relies on urine collection over 24 hours to measure the cumulative cortisol produced in that time. An elevated 24 hour urinary cortisol level has been found to be 84-93% sensitive and 56-79% specific for diagnosis of Cushing's syndrome.[12 13]

Salivary cortisol—Salivary cortisol has better specificity than urinary cortisol and is useful for ruling out cortisol excess. A value above the reference interval has an average sensitivity of 95% and specificity of 91.6%[14] for the diagnosis of Cushing's syndrome. Because it is easier to collect and has the advantage of measuring free rather than bound cortisol, salivary cortisol has been advocated as a first line test.[13] However, salivary cortisol assays have limited availability.

Dexamethasone suppression test—The overnight 1 mg dexamethasone suppression test can be performed on an outpatient basis and consists of a patient taking 1 mg of dexamethasone orally between 11 and 12 pm and then a serum cortisol sample being taken at 9 am the following morning.[16] A cortisol level of <50 nmol/L has high sensitivity (95%) and moderate specificity (80%) for excluding Cushing's syndrome. Some drugs can interfere with the test results by accelerating dexamethasone metabolism (such as antiepileptics and rifampicin) or impairing it (such as diltiazem and fluoxetine). Other drugs, such as oestrogens and carbamazepine, increase the concentration of cortisol binding globulin, resulting in falsely elevated cortisol levels. Other forms of the dexamethasone suppression test (such as the two day, low dose test) are available and could be considered by endocrinologists.

Further testing—Once cortisol excess is confirmed, the source of excess production along the hypothalamo-pituitary-adrenal axis (or ectopic ACTH secretion) needs to be identified, typically by an endocrinologist.

Investigating suspected cortisol deficiency

For initial screening of suspected cortisol deficiency, an 8-9 am cortisol sample is taken to measure cortisol at its expected peak. Unless the results are reassuring, further discussion or referral to endocrinology is required. See figure 2 for details.

Non-dynamic serum cortisol testing

Deficiency is highly unlikely if the 8-9 am cortisol level is above 400-475 nmol/L (the exact cut-off will vary depending on the assay used in the local laboratory). Recent work proposed that values between 336 and 506 nmol/L had a 100% specificity of predicting passing a short synacthen test.[17] Cortisol levels <150 nmol/L at 8-9 am warrant immediate discussion with, or referral to, endocrinology, and hydrocortisone replacement should be started urgently. Cortisol levels between 150 and 400 nmol/L (or agreed limit from the local laboratory) require further evaluation to rule out cortisol deficiency. If the sample was not collected at 8-9 am, then a repeat cortisol measurement can be performed.

Neither urinary nor salivary cortisol has a role in the assessment of cortisol deficiency.[18]

Dynamic tests: short synacthen test

Synacthen mimics the effect of ACTH in stimulating cortisol production: administration of synacthen should therefore result in a predictable rise in serum cortisol.[5] The short synacthen test has equivalent performance to that of the gold standard insulin stress test.[4-20] As it can be performed in an outpatient setting, it has become the most common dynamic test of cortisol deficiency. The cut-off values for a satisfactory response depend on the cortisol assay used[9]: 450 nmol/L is the threshold used in many centres, though this again will need to align with the local assay.[21]

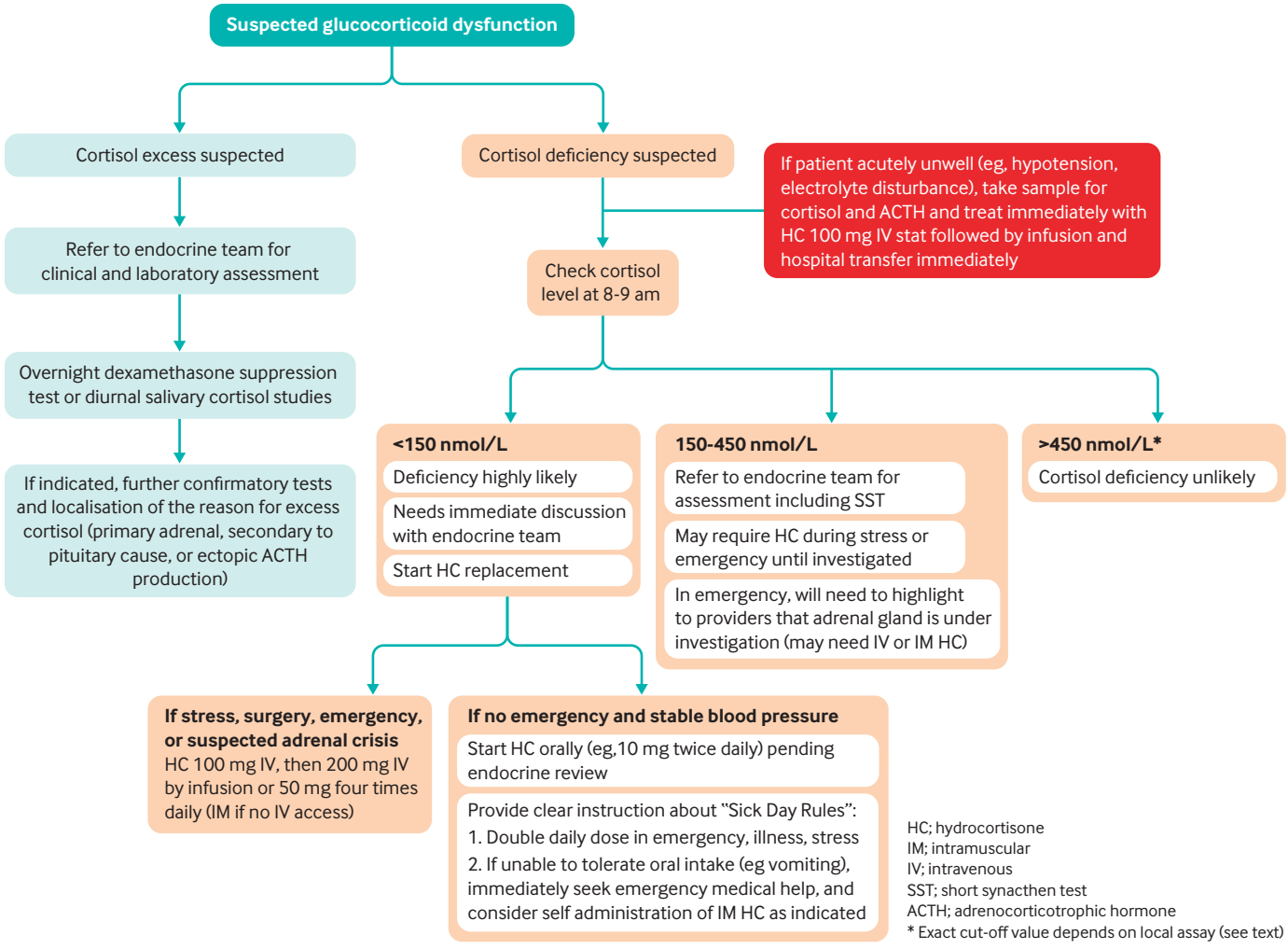


Fig 2 | **Action plan for suspected glucocorticoid dysfunction**

Falsely reassuring test results could be obtained in a case of (*a*) early pituitary failure before adrenal atrophy develops or (*b*) postoperative testing in patients who had recently undergone surgical removal of the pituitary gland for Cushing's syndrome (as persistent adrenal hypertrophy may lead to adequate response).

The role of ACTH measurement

ACTH is almost always measured by specialists to determine the source of cortisol excess or deficiency along the hypothalamic-pituitary-adrenal axis. For example, in a case of cortisol excess, low ACTH levels point to an adrenal source. In practice, for the assessment of cortisol deficiency, baseline ACTH is measured only if the short synacthen test result is abnormal.

Exogenous steroids and impact on cortisol measurement: a pragmatic approach

Patients taking oral glucocorticoids at a dose higher than the physiological cortisol level (prednisolone 5 mg or dexamethasone 1-2 mg daily) will have a suppressed pituitary-adrenal axis. They may need tapered withdrawal of their glucocorticoids, but do not need to have their cortisol concentrations measured routinely.

EDUCATION INTO PRACTICE

- How do you ensure accurate timing for collection of a 9 am serum cortisol sample?
- Audit the cortisol requests made in the past six months in your practice and review the timings and results in relation to the recommendations in this article.
- Reflect on the last time you considered an adrenal disorder in your practice. Would the recommendations in this article alter your management plan?

Case resolution

Given the absence of clinical features of Cushing's syndrome in this 67 year old woman with physiological stress due to injury, an elevated random cortisol level requires no further action and should not delay orthopaedic management. However, for further reassurance, we would recommend that the woman is reassessed when she is well.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l6039

CASE REVIEW

A pain in the neck

A 39 year old woman presented with a one week history of progressive swelling and pain on the right side of her neck that was aggravated by eating. She had no relevant dental history. She was apyrexial and physical examination revealed a swelling of the right submandibular region extending to the angle of the mandible posteriorly. The swelling was firm in consistency and tender on palpation. The woman's blood test results are shown in the table.

Abdominal ultrasonography showed a normal liver and gall bladder and no evidence of cholelithiasis.

Computed tomography imaging of the head and neck (fig 1) was performed to eliminate the possibility of an underlying abscess, cellulitis, or tumour.

Results of relevant blood investigations

Investigation	Result	Normal range
Gamma-glutamyl transferase (GGT)	>1200	<40 U/L
Alkaline phosphatase (ALP)	91	42-98 U/L
Alanine transaminase (ALT)	35	7-35 U/L
Aspartate transaminase (AST)	33	13-35 U/L
Hepatitis studies (A, B, C)	Negative	
Viral studies	Negative	
Autoimmune panel	Negative	
C-reactive protein	<10	<10 mg/L
Erythrocyte sedimentation rate	1	0-10 mm/h

1 **What are the possible causes of elevated GGT?**

2 **What is the most likely cause of elevated GGT in this patient?**

3 **How would you manage this condition?**

Submitted by Farzahna Mohamed and Frederick Raal

Patient consent obtained.

Cite this as: *BMJ* 2019;367:l6008

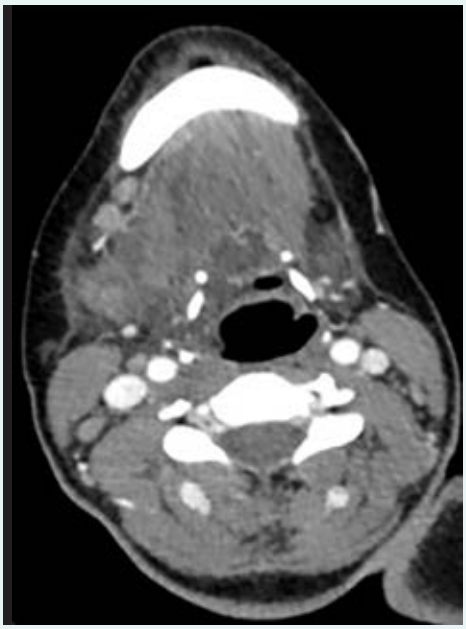


Fig 1 | Computed tomography of the head and neck

answers

CASE REVIEW

A pain in the neck

1 What are the possible causes of elevated GGT?

GGT is not specific for hepatobiliary disease. Hepatobiliary causes of elevated GGT include

- biliary duct obstruction
- primary biliary cirrhosis
- primary sclerosing cholangitis
- infiltrative liver disease
- hepatitis (viral, toxic, alcoholic)
- cirrhosis
- primary and secondary liver tumours.

Non-hepatic causes include

- obesity
- alcoholism
- pancreatitis
- chronic kidney disease
- congestive heart failure
- intestinal injury
- sialolithiasis
- anticonvulsants, barbiturates, tricyclic antidepressants, anticoagulants, oral contraceptives.

2 What is the most likely cause of elevated GGT in this patient?

Sialolithiasis of the submandibular glands (fig 2), causing GGT release from salivary ductal cells.

Sialolithiasis is the commonest benign disorder of the salivary glands. It most frequently involves the submandibular salivary glands. Stones are usually <1.5 mm. GGT is present in the submandibular and sublingual salivary glands but not in the parotid salivary glands.

3 How would you manage this condition?

Management aims to preserve salivary gland function. Conservative therapy includes hydration, salivary gland massage, sialogogues, antispasmodics, analgesics, and antibiotics if secondary infection is present. Failure of conservative therapy requires invasive management with extracorporeal lithotripsy, sialoendoscopy, sialolithectomy, or sialoadenectomy.

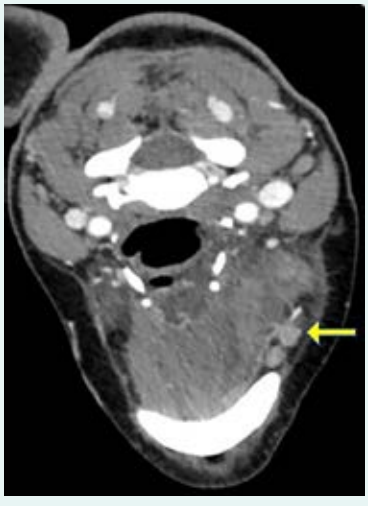


Fig 2 | Computed tomography of the head and neck showing right submandibular giant sialolith measuring 20 mm × 13 mm, complicated by acute sialadenitis

LEARNING POINTS

- Exclude hepatic pathology when GGT is elevated, but also consider non-hepatic causes.
- Use computed tomography to assess sialolith location, size, and number.

CPD READING 0.5 HOURS

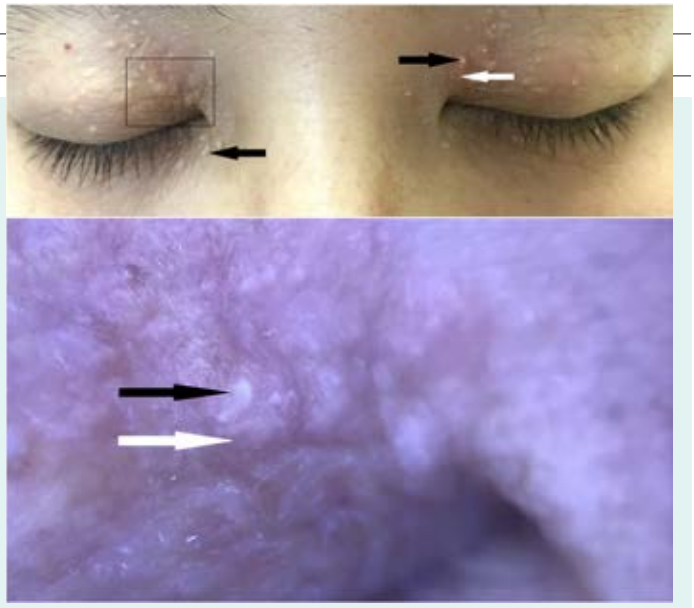
You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

MINERVA

Syringoma and milia on the eyelids



The picture shows secondary milia that have developed predominantly on top of existing syringoma.

The patient was a 37 year old woman with typical syringoma (painless, non-pruritic, flesh coloured eyelid papules) (white arrow) since puberty. Frequent rubbing and scratching is thought to have caused trauma to underlying sweat ducts and hair follicles, and encouraged the formation of more than 20 secondary milia (small hard white papules) (black arrow) over the past three years. She could dig these milia out with her fingernails.

Her mother also had syringoma. Both conditions are benign.

The periorbital location makes molluscum contagiosum unlikely. Lesions of molluscum contagiosum typically have central umbilication from which cheese-like matter can be expressed.

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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Nutrient supplements for small babies

Infants who are preterm and small for gestational age are often given nutrient supplements in the first weeks after birth to improve growth and neural development, despite observational evidence that any benefits come at the cost of a greater risk of obesity and metabolic disease later. A systematic review of relevant randomised trials produced unexpected results (*PLoS Med* doi:10.1371/journal.pmed.1002952). In contrast to the observational data, it found no indications that metabolic risk factors worsened. Indeed, children who had received supplements tended to have lower fasting blood glucose concentrations than children who had not. On the other hand, there was little support for the idea that supplementation improved later cognitive function.

Physical activity

A longitudinal study in Korea recruited nearly half a million people, of whom nearly a third had been diagnosed with cardiovascular disease. It found an inverse relation between level of physical activity at baseline and mortality over six years of follow-up (*Eur Heart J* doi:10.1093/eurheartj/ehz564). This relation was stronger in people with existing disease than in those without a history of cardiovascular events. Neither of these findings is at all surprising. The benefits of physical activity are well established and preventive interventions are bound to be most effective in high risk groups.

A stranger on a bridge

What should a passer-by do if they encounter someone who they think is about to take their own life by jumping from a high place? A qualitative investigation reports the findings of interviews with 33 people who had been in this situation either as a survivor or as someone who had tried to help. The conclusion is that no specialist skills are needed and that people who intervene don't need to worry about saying the wrong thing. There are three things to do: make contact, try to move to a safer place, and summon help (*BMJ Open* doi:10.1136/bmjopen-2019-032319).

Bariatric surgery and congenital anomalies

A retrospective analysis of health insurance and hospital discharge data from Quebec identified two million pregnant women who had delivered between 1989 and 2016. Offspring of women who had become pregnant after bariatric surgery had roughly twice the risk of birth defects—mainly heart and musculoskeletal defects—when compared with offspring of women who were not obese or who were obese but hadn't had surgery (*Am J Clin Nutr* doi:10.1093/ajcn/nqz195).

Mobile phones

Mobile phones expose users to radio frequency electromagnetic fields but, even after two decades of research, there's no convincing evidence that this has any adverse effect on health. A large prospective study from Sweden and Finland adds hearing loss and tinnitus to the list of things not caused by using a mobile phone (*Int J Epidemiol* doi:10.1093/ije/dyz127). The data contained a suggestion that heavy users of these devices were more likely to complain of headaches, but the finding didn't survive adjustment for likely confounders. By far the biggest threat to health posed by mobile phones comes from using them while driving.

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