RATIONAL IMAGING

Imaging transient ischaemic attack with diffusion weighted magnetic resonance imaging

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This series provides an update on the best use of different imaging methods for common or important clinical presentations. The series advisers are Fergus Gleeson, consultant radiologist, Churchill Hospital, Oxford, and Kamini Patel, consultant radiologist, Homerton University Hospital, London.

Transient ischaemic attack can be difficult to diagnose clinically. This article guides you through the radiological options available and highlights the role of diffusion weighted magnetic resonance imaging in detecting acute ischaemia

The patient

A 72 year old man with a history of diabetes and hypertension presented to his general practitioner with a transient history of slurred speech and left sided numbness earlier the same day. Symptoms had resolved over four hours, and on examination he had no focal neurological signs. His blood pressure measured 156/84 mm Hg and heart sounds and electrocardiography were normal. The patient was started on 300 mg aspirin daily and referred to the transient ischaemic attack (TIA) clinic.

What are the next investigations?

TIA is defined as any focal neurological ischaemic event with symptoms lasting less than 24 hours, but in practice most last less than one hour. Abrupt focal symptoms that are maximal at onset and are compatible with ischaemia in a single vascular territory are good diagnostic indicators of a TIA or minor stroke rather than a mimic. The estimated risk of completed stroke after a TIA is 8-12% at one week and 11-15% at one month.[1] It is now recognised that a TIA needs to be treated as a medical emergency in the same manner as an acute coronary syndrome. Secondary prevention is needed to prevent the occurrence of disabling stroke.

Box 1 | The ABCD^2 score [3]

A (age): 1 point for age ≥60 years
B (blood pressure ≥140/90 mm Hg): 1 point for hypertension at the acute evaluation
C (clinical features): 2 points for unilateral weakness, 1 for speech disturbance without weakness
D (duration of symptoms): 1 point for 10-59 minutes, 2 points for ≥60 minutes
D (diabetes): 1 point
Total scores range from 0 to 7
- Scores 0-3: low risk
- Scores 4-5: moderate risk
- Scores 6-7: high risk

Patients with TIA can now be triaged using the ABCD^2 score (box 1), which can identify patients with TIA at highest and lowest risk of recurrent stroke.[2] The ABCD^2 score is not a substitute for taking a good history when establishing the diagnosis of a vascular event, and it may be less useful in posterior circulation stroke.

Computed tomography

Modern neuroimaging in TIA aims to provide evidence for a vascular origin and mechanism of symptoms, and to allow the investigation of alternative non-ischaemic diagnoses.[4] In patients presenting with a possible stroke, 30% have symptoms caused by a stroke mimic.[5] These include partial seizure, migraine, vestibular lesion, space occupying lesion, and haemorrhage.

Unenhanced computed tomography can be performed rapidly and allows exclusion of haemorrhage and space occupying lesion. It is widely available, can be performed quickly, and does not involve administration of intravenous contrast media. The technique has a relatively low sensitivity (<60%) in the detection of acute ischaemia[6] but a higher specificity (88%).[7] In TIA, however, magnetic resonance imaging with diffusion weighted imaging is the imaging modality of choice.

Diffusion weighted magnetic resonance imaging

Diffusion weighted magnetic resonance imaging is an established technique in the detection of acute infarction. It is better than conventional magnetic resonance imaging and computed tomography, and it can differentiate acute from chronic ischaemia, which is useful for patients with pre-existing cerebrovascular disease and new transient symptoms. The sensitivity and specificity of this technique in the detection of acute ischaemia is 88-100% and 86-100%, respectively.[8]

Diffusion weighted imaging measures the Brownian motion of water molecules within a tissue. Two sets of images are acquired—diffusion weighted images and the apparent diffusion coefficient map. Diffusion weighted images are susceptible to artefact and old lesions may appear bright (called "T2 shine through"), but only true restricted diffusion shows up dark on the quantitative apparent diffusion coefficient map.

In acute infarction, excess accumulation of intracellular water (cytotoxic oedema) reduces free water diffusion and results in a drop in the apparent diffusion coefficient in the

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Recent rational imaging articles
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- Definitive characterisation of adrenal lesions (*BMJ* 2009;338:a3092)
- Investigating the hoarse voice (*BMJ* 2008;337:a1726)

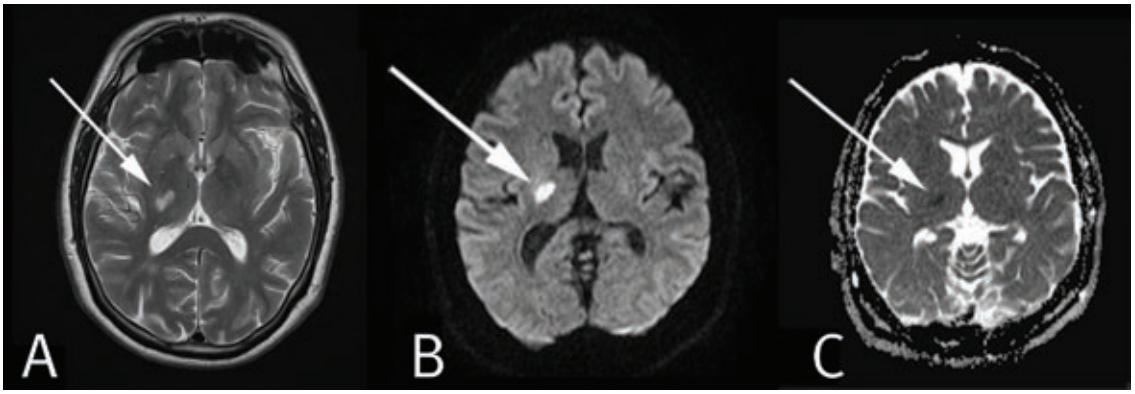

Fig 1 | Axial magnetic resonance imaging (A: T2 weighted image; B: diffusion weighted image; C: apparent diffusion coefficient map) showing an acute infarct (arrow) in the right thalamus and posterior limb of the internal capsule. The infarct has high signal on T2 weighted imaging, high signal on diffusion weighted imaging, and low value on the apparent diffusion coefficient map

region of infarct. These areas with a low apparent diffusion coefficient value appear bright on diffusion weighted images (fig 1).

The value of the apparent diffusion coefficient decreases from within 30 minutes of acute infarction and reaches a nadir at about three days. As the infarct evolves, free water diffusion increases as cells lyse and release fluid into the extracellular compartment and the permeability of vessels increases. Hence the value of the apparent diffusion coefficient increases and equals that of normal brain (pseudonormalisation) before becoming abnormally high.

In chronic ischaemia the value of the apparent diffusion coefficient remains abnormally high owing to the largely extracellular water content, and diffusion weighted images are dark. Diffusion weighted imaging can accurately differentiate a region of acute infarct from surrounding regions of chronic ischaemic change (fig 2).

These sequences do not require the use of intravenous contrast media, although the usual contraindications to the use of magnetic resonance imaging apply (for example, pacemakers, metallic orbital foreign bodies, and aneurysm clips). Claustrophobia is a common problem, but diffusion weighted imaging sequences take less than one minute to complete.

Patients with TIA whose symptoms lasted longer than one hour or who have motor weakness or aphasia are most likely to have a positive lesion on diffusion weighted imaging.[9] Within an hour of the attack, analysis of signal intensity on diffusion weighted imaging allows patients with TIA to be differentiated from those with stroke. Diffusion weighted imaging is positive in 40% of patients with possible transient ischaemic attack, and patients with positive diffusion weighted imaging are 10 times more likely to have early stroke after TIA than patients who are negative on diffusion weighted imaging.[10] In contrast, patients with clinical TIA who are negative on diffusion weighted imaging are 4.3 times less likely to have a stroke at one year but 4.6 times more likely to have a subsequent TIA than patients with positive diffusion weighted imaging.[11]

The American Heart Association suggested that because of the high number of patients with clinical TIA and positive diffusion weighted imaging, the definition of TIA be changed to: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.[4] Although patients with positive diffusion weighted imaging are clearly at increased risk of early stroke, clinical risk scores are not necessarily associated with positive imaging.[12] The extent to which findings on magnetic resonance imaging influence validated prognostic scales such as the ABCD^2 score remains the subject of future large studies. A recent study has shown that the combination of a low ABCD^2 score and a negative result on early diffusion weighted imaging has excellent sensitivity in predicting low risk of early stroke.[13]

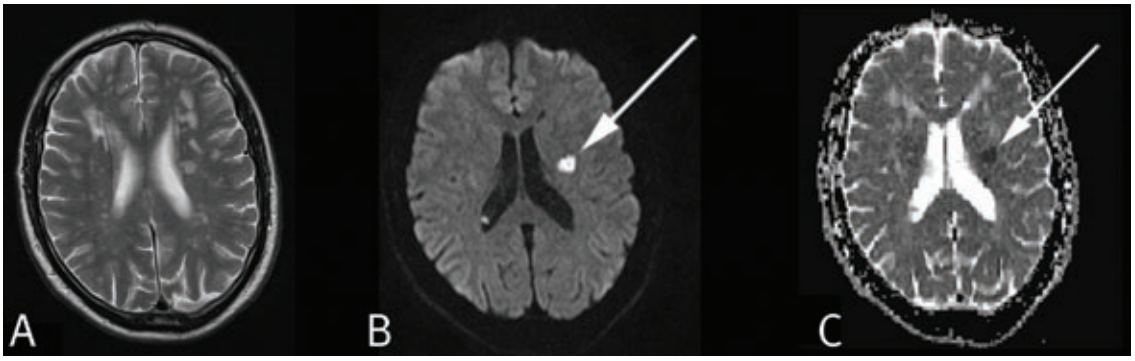

Fig 2 | Axial T2 weighted magnetic resonance image showing multiple high signal foci bilaterally in keeping with small vessel ischaemic change (A). However, a focal area of restricted diffusion (arrow) in the left corona radiate is seen as high signal on diffusion weighted imaging (B) and low value on apparent diffusion coefficient mapping (C). This corresponds to a small acute infarct, and it shows the ability of diffusion weighted imaging to differentiate acute from chronic ischaemic change. The foci of high signal seen on T2 weighted imaging and not on diffusion weighted imaging represent chronic ischaemia

Box 2 | **Treatment recommendations (adapted from National Institute for Health and Clinical Excellence guidelines)**

Patient with suspected transient ischaemic attack (TIA) at high risk of stroke ($ABCD^2$ score of ≥4):

- Aspirin (300 mg daily) started immediately
- Specialist assessment and investigation within 24 hours of onset of symptoms
- Measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors

Patient with suspected TIA at lower risk of stroke ($ABCD^2$ score of ≤3) or any patient with suspected TIA presenting more than one week after symptoms resolved:

- Same as above but specialist assessment and investigation should be as soon as possible, definitely within one week of onset of symptoms

Additional imaging

Gradient echo imaging is an additional magnetic resonance imaging sequence recommended in patients with suspected TIA that may identify small acute or chronic bleeds (microbleeds) and may therefore influence antithrombotic treatment.[14] Additional computed tomography or magnetic resonance imaging angiographic sequences may be used to define symptomatic stenoses or intracranial thrombosis and to evaluate the carotid and vertebral arteries of the neck. All patients with suspected TIA or non-disabling stroke who are candidates for carotid intervention should have carotid imaging within one week of onset of symptoms.[15]

National Institute for Health and Clinical Excellence recommendations[15]

Patients with suspected TIA should be assessed by a specialist before a decision is made about brain imaging. The recommended brain imaging modality if required is diffusion weighted magnetic resonance imaging except where contraindicated. Using the $ABCD^2$ score the imaging can be timed appropriately. Patients with a score of 4 or more, or with crescendo TIA, should have brain imaging within 24 hours of onset of symptoms if required. Patients with a lower score should have imaging within one week.

Imaging in TIA, particularly magnetic resonance imaging, is also helpful in patients being considered for carotid endarterectomy in whom it is uncertain whether the anterior or posterior circulation is involved, and in patients where an alternative diagnosis such as migraine, epilepsy, or tumour is being considered. The $ABCD^2$ score also has implications for patient management (box 2).

LEARNING POINTS

The $ABCD^2$ score is a useful tool for triaging patients with suspected transient ischaemic attack (TIA) for time
ly imaging, and for predicting future outcome

Diffusion weighted magnetic resonance imaging is the most sensitive and specific imaging modality in the detection of acute ischaemia

TIA and minor stroke can be difficult to diagnose clinically, and magnetic resonance imaging with diffusion weighted imaging can help exclude mimics or confirm the diagnosis

Patients with clinical TIA and positive diffusion weighted imaging are most at risk of subsequent completed stroke

Patients with clinical TIA and negative diffusion weighted imaging are at risk of subsequent TIA

Outcome

Our patient underwent magnetic resonance imaging, which showed a background of small vessel ischaemic changes and a new small lacunar infarct (fig 2). He was at high risk of stroke ($ABCD^2$ score 4) and the TIA clinic arranged urgent echocardiography with bubble studies, carotid Doppler ultrasound, and three day electrocardiography. No cardiac or carotid cause was identified, and the lacunar infarct probably arose from occlusion of a small deep perforating artery. Secondary prevention was optimised with additional antihypertensive drugs to control his blood pressure and the addition of a statin because his serum cholesterol was 4.99 mmol/l. His diabetes was well controlled and lifestyle advice was given. He was told that he was not legally allowed to drive for 28 days, and he has had no further events.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

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10-MINUTE CONSULTATION

Stridor in children

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs

A 6 month old presents to the general practitioner's surgery with his mother. She is concerned because he has a runny nose and makes a "funny" loud noise when breathing in, which you diagnose as stridor.

What issues you should cover

Stridor is caused by partial upper airway obstruction and is typically heard in inspiration, although it can also be heard on expiration if the obstruction is below the larynx. It sounds different from wheeze, which is a high-pitched whistling expiratory sound, and from stertor, a snoring sound.

How long has the stridor been present?

- Acute onset stridor is typically associated with infection or an inhaled foreign body.
- Chronic stridor (weeks to months) is most commonly due to laryngomalacia, "floppy larynx." It may also be secondary to congenital anomalies (such as haemangioma), birth trauma (such as vocal cord paralysis), or gastro-oesophageal reflux.

Associated features

- Cough—a "barking" cough, often worse at night, in young children (infants and toddlers) suggests viral croup, the most likely diagnosis in the scenario and the commonest acute cause.
- Fever—low grade pyrexia is typically seen in croup. A high fever (>38.5°C) indicates bacterial tracheitis or epiglottitis.
- Shortness of breath—breathing difficulties or "blue episodes" suggests severe illness requiring referral.
- Unexpected drooling—may indicate a foreign body or epiglottitis.
- Feeding difficulties and reduced wet nappies—dehydrated children may need referral.
- Exacerbating factors—can provide useful information, especially if stridor is absent when you see the child. In laryngomalacia, for instance, stridor is usually intermittent and worsens with effort (for example, during feeding, crying, or intercurrent illness).

History

- Neonatal history—preterm infants are at increased risk because of their smaller airways. Previous intubation is associated with subglottic stenosis and vocal cord paralysis, both causes of stridor.
- Allergies—consider anaphylaxis.
- Immunisation history—check Hib vaccination status, although epiglottitis can occur in immunised children.
- History of choking—suspect foreign body.
- Recent travel—consider diphtheria.

Normal heart and respiratory rates at rest by age

Age (years)	Heart rate (beats per minute)	Respiratory rate(breaths per minute)
<1	110-160	30-40
1-2	100-150	25-35
2-5	95-140	25-30
5-12	80-120	20-25
≥12	60-100	15-20

From: Advanced Life Support Group. *Advanced Paediatric Life Support: The Practical Approach*. 4th ed. Wiley Blackwell, 2004.

What you should do

Physical examination

Is the child well (talking, smiling) or unwell (cyanosed, lethargic)? Is stridor present at rest or only when agitated? Determine respiratory rate, pulse (table), temperature, capillary refill time, and oxygen saturations. Look for signs of respiratory distress such as recessions and tracheal tug. Auscultate the chest to check for equal air entry and to detect or exclude other pathology (for example, consolidation).

If the child is distressed or unusually drooling, or if you suspect foreign body inhalation, do not upset or inspect the child's mouth; this can precipitate complete airway obstruction.

Management

- Urgently refer any child who is unwell, has respiratory distress, or may have inhaled a foreign body, by ambulance. Clinically dehydrated children may need referral.
- Croup is usually self limiting, lasting a few days. Mild croup can be managed at home with careful observation and good hydration. Inhalation of steam from a hot bath, shower, or humidifier in a supervised closed room may help, although there is no scientific evidence of efficacy. Advise parents to seek urgent medical attention if symptoms worsen.
- Pharmacological treatments include dexamethasone (150 µg/kg, oral/injection), prednisolone (1-2 mg/kg, oral), or budesonide nebuliser (2 mg as single dose or in two divided doses separated by 30 minutes) for moderate or severe croup. Adrenaline nebulisers are usually reserved for severe croup. Rarely, intubation is necessary.
- Refer children with chronic stridor to paediatric or ear, nose, and throat clinics, urgently for those with associated failure to thrive. Most cases will be due to laryngomalacia, which typically resolves by age 18-24 months, but it is important to exclude other causes.

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Provenance and peer review: Not commissioned; externally peer reviewed.
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USEFUL READING

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Recent 10-minute consultation articles

- "My baby keeps bringing up his feeds!" (*BMJ* 2010;340:c2189)
- Hoarse voice (*BMJ* 2010;340:c522)
- Sexual health consultation for men who have sex with men (*BMJ* 2010;340:c958)
- Acute cough in adults (*BMJ* 2010;340:c574)
- Pollen food syndrome in a teenage student (*BMJ* 2010;340:b3405)

LESSON OF THE WEEK

Sexual precocity in a 4 year old boy

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Caution men treated with testosterone gel to wear clothing when in close contact with children

A boy aged 4.8 years was referred by his general practitioner with a year's history of progressive pubic hair development and increase in length and width of the penis (figure). Parents had also noticed a growth spurt in the previous year; the boy was now wearing age 6-7 clothes and his shoe size had increased during the past six months. There was no axillary hair, acne, or body odour.

The mother was aged 43 years and in good health. The father, aged 50, had undergone pituitary surgery and radiotherapy followed by bilateral adrenalectomy for Cushing's disease at the age of 19 and was receiving hormone replacement therapy for adrenal insufficiency and central hypogonadism.

On examination the boy measured 115.1 cm and weighed 23.8 kg. Both these measurements are above the 97th centile, according to current UK growth standards, with height well above the range expected for the parents' heights (mother 3rd-10th centile, father 10th centile). The penis was 5.5 cm long and 6.5 cm in circumference, equivalent to Tanner stage G4[1] (see box); pubic hair Tanner stage 3-4; axillary hair Tanner stage 1. Testes were prepubertal, measuring 2 cm long and 1.2 cm wide (volume 1.5 ml).

Tanner stages of puberty in boys[1]

Genital staging

G1 Prepubertal penis, scrotum, and testes (volume ≤3 ml)

G2 Testes ≥4 ml with scrotal laxity, but no penile enlargement

G3 Penile lengthening with further development of testes and scrotum

G4 Penile lengthening and broadening, further development of the testes (volume usually 10-12 ml)

G5 Adult genitalia, testes 15-25 ml

Pubic hair staging

P1 No pubic hair

P2 Fine hair over mons or scrotum

P3 Adult type hair (coarse, curly) but distribution confined to pubis

P4 Extension to near adult distribution

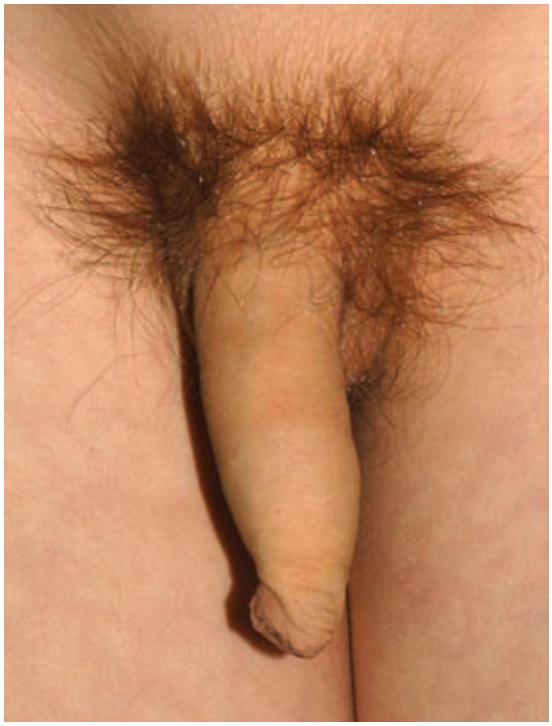
P5 Adult

Axillary hair staging

A1 No axillary hair

A2 Hair present but not adult amount

A3 Adult



Genitalia of 4 year old boy exposed to testosterone gel showing penile enlargement (Tanner stage G4) and pubic hair development (Tanner stage P4)

We made a clinical diagnosis of simple virilising congenital adrenal hyperplasia and gave a small dose of hydrocortisone, pending the results of blood and urine tests. Bone age, assessed by the TW2 system of Tanner and Whitehouse,[2] showed a relatively modest advance at 7.3 years (chronological age 4.8 years). Serum 17-hydroxyprogesterone and cortisol concentrations before and after stimulation with synthetic adrenocorticotrophic hormone were 6/13 and 131/717 nmol/l respectively, excluding classic 21-hydroxylase deficient congenital adrenal hyperplasia. Serum androgens showed androstenedione <1.4 nmol/l (normal range <2 nmol/l), dehydroepiandrosterone sulphate (DHAS) <0.8 µmol/l (<2 µmol/l), testosterone 6.4 nmol/l (<0.7 nmol/l). The luteinising hormone and follicle stimulating hormone response to luteinising hormone releasing hormone (LHRH) stimulation was prepubertal, with all values below 1.4 U/l. Urine steroid profile was unremarkable.

These findings did not support the initial diagnosis of simple virilising congenital adrenal hyperplasia, and hydrocortisone treatment was stopped. At follow-up the child's mother volunteered the information that the father had been receiving testosterone gel 50 mg daily and that the child had been sleeping in the parents' bed for the past six months while major structural repair to the house, involving the child's bedroom, was being carried out. Contact with the

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Recent lesson of the week articles

- Copper deficiency as a treatable cause of poor balance (*BMJ* 2010;340:c508)
- Treatment for lymph node tuberculosis (*BMJ* 2010;340:c63)
- Tachycardia due to atrial flutter with rapid 1:1 conduction following treatment of atrial fibrillation with flecainide (*BMJ* 2010;340:b4684)
- Protein and creatine supplements and misdiagnosis of kidney disease (*BMJ* 2010;340:b5027)
- Reduced level of consciousness from baclofen in people with low kidney function (*BMJ* 2009;339:b4559)

testosterone gel was discontinued. When the boy was reassessed at 5.1 years, the penis was 7 cm long and 7.5 cm in circumference, testes were unchanged in volume, and height velocity was 10 cm/year. Basal testosterone had fallen to 0.7 nmol/l; other serum androgens were low or unrecordable. At 5.5 years the boy's pubic hair had regressed to Tanner stage 2, penile length was 6 cm and circumference was 7 cm, and height velocity was 5.3 cm/year. Testes were 2 ml in volume.

Discussion

Testosterone gels are approved for use in men with congenital or acquired primary and secondary hypogonadism who need substitution therapy and have the advantage of avoiding the need for painful intramuscular injections. Passive hormone transfer from skin to skin contact is a recognised adverse event in children[3-5] and female partners,[6] but the risk is greatly reduced by washing the skin within 10 minutes after application[7] and by wearing clothing (sleeping in pyjamas, for example). Current label instructions advise patients to apply testosterone gel topically to the shoulders, upper arms, or abdomen and then to wash their hands and cover the treated area with clothing.

Despite the new label precautions imposed by the US Food and Drug Administration (FDA) in May 2008, eight new reports of children being exposed to testosterone were received in the following six months.[8] Most cases were attributable to patients failing to follow the label instructions, and being unaware of the risk.[4] Although symptoms regressed when testosterone exposure was stopped in most of the eight cases reported to the FDA, residual genital enlargement and advanced bone age were recorded in a few.[3] In their publication of five cases, Kunz et al reported two children as having an advanced bone age at the time of initial presentation.[4] Among the three children in whom clinical examination after discontinuation of exposure to androgens was documented, one girl showed regression of virilisation, and one boy and the other girl showed no change two and four months after contact with androgen had been discontinued. Moreover, many children had undergone invasive procedures to determine the cause of their symptoms before the correct diagnosis was made.

Our case highlights the serious clinical consequences of contamination by transdermal testosterone in a child. The clinical presentation resembled simple virilising congenital adrenal hyperplasia. However, the normal serum 17-hydroxyprogesterone and absence of extreme bone age advance were not consistent with the diagnosis, and the absence of raised serum adrenal steroids or urinary steroid metabolites also pointed to a non-adrenal cause. In the context of normal prepubertal testes, the raised concentration of testosterone was initially hard to explain, although testotoxicosis or a very small Leydig cell tumour were possible diagnoses. Until the mother volunteered the information about the father's medication we were considering more invasive investigation, including selective venous sampling from the testicular veins.

In the light of increased use of transdermal testosterone products to influence libido, muscle strength, and behaviour,[9] we advise extra vigilance in counselling patients as to unwanted side effects. This case underlines the importance of taking a careful drug history from the family members of children presenting with sexual precocity.

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Parental consent obtained.

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Guinea pigs for the "developed" countries

I was listening to a guest lecture by an acclaimed professor on groundbreaking research—work that is probably going to save a whole generation of currently unsalvageable patients. The research seemed well founded and is going to be implemented soon. It has got huge funding and seems to have ticked all the necessary boxes. The only slight hitch is that it is still undergoing a randomised control trial in a remote village in India. Everyone in the audience sat mesmerised, while my thoughts went miles away.

As a graduate from a state run medical college in India, I have seen the hardships that the peasants endure. With sparse medical knowledge and sparser money but abundant respect for life for their loved ones, they treat doctors as gods and hang on to any ray of hope offered. They are unassuming and do not doubt or question the treatment being offered. In such situations "ethical approval" may not be stringent and in some cases may not be needed at all.

As I sat viewing the slides of this village in India and the recruits (nurses and patients), I was struck by their naivety and innocence. They will have unquestioning faith in a professor from a top university in England.

If the research is good enough to be implemented in our hospitals, I am sure it is more sensible to do a clinical trial here, under pretty much similar conditions and cohort of patients. This is a common short cut employed by many. Do you think it's right?

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