

**Table 1** Numbers of outpatients and inpatients with active tuberculosis and unknown HIV status offered and accepting an HIV antibody test, and numbers found to be positive

	Outpatients (N = 178)	Inpatients (N = 58)	p value
Offered HIV test	88 (49%)	43 (74%)	0.001*
Accepted HIV test	61/88 (69%)	42/43 (98%)	<0.0001†
HIV positive	1/61 (2%)	17/42 (40%)	<0.0001†

\* $\chi^2$  test; †Fisher's exact test.

known to be HIV positive and were excluded from further analysis. Of the remaining 236, 131 (56%) were offered an HIV test. 109 (83% of those offered) took this up and 18 (17% of sample tested, 8% of all TB patients) were found to be HIV positive.

When subjects were divided on the basis of where the diagnosis of TB was made, striking differences in HIV rates were noted (table 1). Inpatients were much more likely to be offered, to accept, and to test positive on HIV testing. There was no difference in the demographic parameters between inpatients and outpatients, although inpatients tended to have more symptoms and to be smear positive (data not shown). Where no HIV test was offered, we found common themes in patient care. The most important of these was a lack of TB nurses to offer testing, and patients being diagnosed outside the focused TB service. A problem specific to the outpatient setting was the lack of appropriate clinic space in which to discuss HIV testing.

The most common reason given by patients who declined to undergo testing was a perceived inability to cope with the dual diagnosis (46% of cases), especially if the initial diagnosis of TB itself had been difficult to deal with. Such individuals would rarely agree to further discussion on HIV testing at a later date. Other reasons—such as patients regarding themselves to be at low risk of HIV infection—were much less frequently reported (10%).

The overall high rate of HIV co-infection is in line with other metropolitan studies.<sup>2</sup> Our data, as well as that of others,<sup>3</sup> may appear to suggest that we should predominately target inpatients (in whom the rates of HIV were 20 times greater than in outpatients). However, given the increasing HIV/TB rates in the UK, we feel that this is a short sighted approach as we would expect that more individuals will present with TB as their first HIV related illness in an outpatient setting.<sup>4</sup>

HIV testing was unacceptable to some patients. There is need for in-depth qualitative analysis to explore issues such as the timing of the discussion on HIV testing and the belief systems and coping mechanisms of individuals.<sup>5</sup>

Despite attempts to provide a focused HIV testing service within our TB clinics, we find low rates of uptake. Much of this stems from an apparent failure to offer testing to almost half our patients. This may be an overestimate as it is conceivable that other healthcare workers might have discussed testing but not documented it in the patient's notes. Data systems need to be implemented which can accurately capture this information.

Achieving HIV testing targets will require dedicated resources as well as improvements in both staff and patient education. This would argue for a greater interaction between local TB and HIV services.

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doi: 10.1136/thx.2005.048066

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## Suppression of HPA axis in adults taking inhaled corticosteroids

Fluticasone propionate, a frequently prescribed potent inhaled corticosteroid, is an effective and generally safe treatment for chronic asthma. However, rare cases of dose related systemic absorption of inhaled corticosteroids leading to suppression of the hypothalamic-pituitary-adrenal (HPA) axis have been reported, particularly in children.<sup>1,2</sup> Using the insulin tolerance test (ITT), we report two cases of symptomatic adrenocortical suppression in asthmatic adults taking inhaled fluticasone. The two patients reported here were selected from a review of 59 patients undergoing ITTs for investigation of suspected HPA dysfunction.<sup>3</sup>

Patient 1, a 38 year old woman (weight 49.9 kg) with a history of chronic asthma and allergic rhinitis, was referred for investigation of a 2 year history of fatigue, presyncope, and reduced libido. She denied symptoms of neuroglycopenia, thyroid dysfunction, headaches, arthralgia, myalgia, weight change, constipation, and diarrhoea. Past history

included depression (in remission, on no current treatment) and bulimia nervosa. Menses were regular. There was no history of postpartum haemorrhage. Medications included fluticasone propionate/salmeterol xinafoate (Seretide) 250/25 µg one inhalation twice daily and mometasone furoate monohydrate (Nasonex) nasal spray 50 µg each nostril twice daily. However, adherence and dosing were variable. Of note, the patient reported that her presenting symptoms improved significantly whenever she had received oral steroids for asthma exacerbations in the past. Initial blood results are shown in table 1. Given low early morning cortisol levels in the absence of increased levels of adrenocorticotropin hormone (ACTH), an ITT was performed which revealed HPA axis suppression (table 1). Magnetic resonance imaging (MRI) demonstrated loss of upper concavity of the pituitary gland. Prednisone 2.5 mg/day was commenced and the dose of fluticasone propionate/salmeterol xinafoate was reduced to 125/25 µg one inhalation twice daily, with good symptomatic response. The patient was concurrently diagnosed with celiac disease following small bowel biopsy.

Patient 2, a 61 year old woman (weight 55 kg) with chronic asthma, treatment resistant osteoporosis, Hashimoto's hypothyroidism and celiac disease, reported fatigue, presyncope, neuroglycopenia, adrenergic symptoms of hypoglycaemia, anorexia and weight loss. Menopause was premature at age 45 years. There was no history of significant haemorrhage. Medications included inhaled fluticasone propionate (Flixotide) 250 µg and salmeterol xinafoate (Serevent) 50 µg one inhalation of each twice daily (for 12 months prior to presentation). As morning cortisol levels were low and the ACTH level was normal, an ITT was undertaken which demonstrated suppression of the HPA and growth hormone axes (table 1). Pituitary MRI scan was unremarkable. Prednisone 2 mg/day was commenced with symptomatic improvement. The dose of prednisone was reduced to 1 mg after 4 months without recurrence of presenting symptoms.

Using the ITT, we detected HPA suppression in two adult asthmatic patients taking inhaled/intranasal corticosteroids. The variable and unpredictable absorption of inhaled corticosteroids, low body weight, and intermittent adherence and dosing in patient 1 may have contributed to the patients' symptoms of adrenal insufficiency. The high lipophilicity of fluticasone, which results in an increased volume of distribution and prolonged elimination half life, is thought to account for the greater frequency of adrenal insufficiency in patients taking fluticasone compared with other inhaled corticosteroids.<sup>2</sup>

Adrenal suppression in asthmatic adults taking inhaled fluticasone is thought to occur less frequently than in children, particularly in patients taking <800 µg/day,<sup>4</sup> due to a lower effective steroid dose per unit body surface area.<sup>2</sup> However, previous studies have used relatively insensitive discriminators of HPA dysfunction such as early morning serum and salivary cortisol levels, 24 hour urinary free cortisol, and the 250 µg cosyntropin stimulation test to examine the integrity of the HPA axis in adult asthma patients taking inhaled corticosteroids.<sup>4,5</sup> We are aware of no previous study that has used the ITT, the current "gold standard" test of HPA function,<sup>1</sup> in this patient group. Although potentially dangerous in patients with seizure

**Table 1** Baseline biochemistry and peak cortisol levels following insulin induced hypoglycaemia in two female adult patients taking inhaled/intranasal corticosteroids

	Patient 1	Patient 2
08.00 cortisol (200–600 nmol/l)	169/198	113/198
08.00 ACTH (<12 pmol/l)	4.5	2.8/2.9
Insulin-like growth factor-1 (0.4–1.6 U/ml)	0.54	0.89/0.79
Free thyroxine (10–21 pmol/l)	11	15.9/15.6*
Thyroid stimulating hormone (0.3–4 mIU/l)	0.77	1.77/1.95*
Prolactin (50–370 mIU/l)	224	111/87
Luteinising hormone (IU/l)†	11.3	26.4/18.4
Follicular stimulating hormone (IU/l)‡	6.5	50.1/42.7
$\alpha$ -subunit (IU/l)§	0.41	Not done
Anti-microsomal antibodies	Negative	Positive
Dehydroepiandrosterone ( $\mu$ mol/l)¶	<1.0	<1.0
Results of insulin tolerance test		
Baseline cortisol (200–600 nmol/l)	160	159
Minimum blood glucose (<2.2 mmol/l)	1.9	1.6
30 minute cortisol (nmol/l)	327	343
60 minute cortisol (nmol/l)	450	492
90 minute cortisol (nmol/l)	313	388
120 minute cortisol (nmol/l)	227	282
Peak growth hormone (>13 mIU/l)	40.3	4.9

Normal ranges and units are in brackets. "Normal" peak cortisol level following hypoglycaemia >550 nmol/l. When more than one value is quoted, the tests were performed on different days.

\*On thyroxine.

†Reference range (RR): females – premenopausal 2.5–130 IU/l, postmenopausal >15 IU/l, males 1.5–14 IU/l.

‡RR: females – premenopausal 1.6–33 IU/l, postmenopausal >16 IU/l, males 0.9–8.1 IU/l.

§RR: males and females – premenopausal 0.05–0.4 IU/l, postmenopausal 0.37–1.15 IU/l.

¶RR: females – premenopausal 2.2–9.1  $\mu$ mol/l, postmenopausal 0.3–1.7  $\mu$ mol/l, males 5.3–9  $\mu$ mol/l.

disorders and ischaemic heart disease, the ITT is a safe test when performed in experienced centres.<sup>3</sup> Indeed, a review of >6500 ITTs reported that only seven patients (0.1%) experienced an adverse event, all of which reversed following intravenous glucose.<sup>6</sup> To our knowledge, only two studies have used the ITT to investigate the HPA axis in asthmatic children treated with inhaled fluticasone. The first reported an inadequate response to insulin-induced hypoglycaemia in three children taking 1000–2250  $\mu$ g/day.<sup>7</sup> In the second study, nine of 18 subjects treated with 250–750  $\mu$ g/day for up to 16 weeks exhibited evidence of adrenal suppression which recovered following cessation of treatment.<sup>1</sup>

Finally, as hypopituitarism of probable autoimmune aetiology has been reported in patients with celiac disease,<sup>8</sup> the possibility that autoimmune hypophysitis contributed to the patients' symptoms and pituitary deficiency cannot be definitively excluded.

In summary, this report suggests that inhaled (together with intranasal) fluticasone may suppress the HPA axis in adults and that symptomatic adrenal insufficiency may develop, particularly if dosing is variable and intermittent. These cases illustrate that clinical symptoms may alert the physician to the possibility of adrenal suppression which can then be confirmed using basal and/or stimulated tests of HPA function in selected patients. Further investigation to determine the prevalence of these effects in adult patients is warranted.

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doi: 10.1136/thx.2005.049643

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## BTNL2 gene variant and sarcoidosis

Sarcoidosis is an inflammatory granulomatous disorder that primarily affects the lungs and lymph nodes. Other organs such as the brain, eyes, heart, and skin can also be affected. The disease is characterised by non-caseating granulomas and an exaggerated cellular immune response caused by increased inflammatory activity.<sup>1</sup> The course of the disease is acute and mild in approximately 20% of all patients. In most patients a

chronic stage develops which can lead to lung fibrosis. Although the exact pathogenesis of sarcoidosis remains unclear, familial clustering of the disease and the increased risk of relatives to develop sarcoidosis suggest that there might be a genetic predisposition to develop the disease.<sup>2</sup>

A significant association was recently reported in Germany between sarcoidosis and a frequent single nucleotide polymorphism (SNP) in the *BTNL2* gene, rs2076530.<sup>3</sup> *BTNL2* is a member of the immunoglobulin gene family and is related to *CD80* and *CD86* co-stimulatory receptors, although its exact function is unknown.<sup>4</sup> *BTNL2* is located on chromosome 6p21.3 in close proximity to the *HLA* gene cluster. rs2076530 is located at position 1 of the donor splice site in intron 5 and the associated A allele causes the usage of an alternative donor site leading to a 4 bp deletion at the mRNA level, frameshift, and premature truncation at the protein level.<sup>3</sup> The rs2076530 SNP alone was also associated with sarcoidosis in a case-control study of white American subjects.<sup>4</sup> No replication of the *BTNL2* rs2076530 susceptibility to sarcoidosis has yet been studied in an independent German case-control study. We therefore performed a case-control association study in 210 patients with sarcoidosis and 202 controls. Written informed consent was given by each participant and the study was approved by the ethics committee of Bonn University School of Medicine.

The diagnosis of sarcoidosis was based on evidence of non-caseating epithelioid cell granuloma in biopsy specimens and chest radiographic abnormalities. Different stages were defined as previously described.<sup>5</sup> A chronic course was defined as disease over at least 2 years or at least two episodes in a lifetime. Acute sarcoidosis was defined as one episode of acute sarcoidosis which had totally resolved at the date of the examination. None of the individuals in the control group (healthy white German subjects of mean age 38.32 (15.53) years) had a history of lung disease or showed any symptoms of lung or other disease by chest radiography or laboratory blood tests. Genotyping of rs207653 was performed using the Taqman technique with a commercially available assay (Applied Biosystems, Germany). SPSS Version 12 was used for statistical analysis. The genotype distributions in the cohort were in accordance with the Hardy-Weinberg equilibrium.

The A allele frequency of rs2076530 was significantly increased in sarcoidosis patients compared with controls ( $A = 0.6929$ ,  $G = 0.3071$  in cases;  $A = 0.6188$ ,  $G = 0.3812$  in controls). It was significantly associated with an increased risk of sarcoidosis in co-dominant and dominant models (OR 2.31 (95% CI 1.27 to 4.23);  $p < 0.006$ , table 1), but not in a recessive model ( $p = 0.276$ ). The calculated population attributable risk (PAR) for AA homozygotes and AG heterozygotes was 34.6%. Our results were in accordance with the reported association between *BTNL2* and sarcoidosis and replicated the finding that A allele carriers of rs2076530 have a more than twofold increased risk of developing sarcoidosis compared with GG homozygotes in the German population.

We also examined whether this increased risk is present in both chronic and acute forms of sarcoidosis. Interestingly, we found that the chronic form—but not the acute form—was significantly associated with the A allele in co-dominant and dominant models (OR 2.87