Lesson of the week

Depot corticosteroid treatment for hay fever causing avascular necrosis of both hips

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Consider immunotherapy rather than depot corticosteroid treatment for hay fever

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The prevalence of hay fever (seasonal allergic rhinitis) has increased dramatically over the past four decades in the United Kingdom, with a doubling from 10 per 1000 people in the 1970s to 20 per 1000 in the 1980s.[1] The British Society for Allergy and Clinical Immunology has published guidelines on the management of rhinitis that recommend that, when measures for avoiding pollen are insufficient, treatment should be either oral or topical antihistamine, to be taken as required, or topical sodium cromoglycate, to be taken regularly.[2] If these treatments are ineffective, intranasal corticosteroids should be taken regularly, with oral or topical antihistamines added if required. If this stepped programme is adhered to the vast majority of patients will respond, but if patients fail to respond systemic corticosteroids may be used.

Over the last few decades the practice of treating severe symptoms with depot corticosteroids has become common, mainly because the duration of treatment of 4-6 weeks is often sufficient to cover the whole season. If the season is exceptionally severe or the patient experiences prolonged symptoms as a result of multiple allergies (for example, a combination of tree and grass pollen allergy), more than one depot corticosteroid injection may be required. Oral corticosteroids are less commonly used, perhaps because of the inconvenience of taking daily medication for 6-8 weeks every year.

The United Kingdom is unusual in the developed world in that it has minimal provision of allergy services, hence only small numbers of patients with severe seasonal allergic rhinitis have access to immunotherapy despite the growing evidence for the efficacy of this treatment.[3 4] We report a case of a man who developed avascular necrosis of both hip joints after depot corticosteroids were used to treat his severe hay fever.

Case report

A 42 year old man of Sri Lankan origin developed hay fever at 21 years of age, but his symptoms became severe and disabling only at the age of 27. Every year in mid-April he developed uvular swelling, palatal irritation, profuse rhinorrhoea, incessant sneezing, nasal obstruction, and conjunctivitis. Symptoms continued until the end of July, peaking in June, consistent with tree and grass pollen allergy. His symptoms were so severe that he was unable to work, and he had to sleep with a towel over his pillow. For the past eight years he had also developed seasonal asthma that started in early July and lasted for 2-3 weeks. He had used antihistamines and a number of topical nasal corticosteroids, including beclometasone, fluticasone, and budesonide, but without relief of symptoms; therefore his general practitioner resorted to depot corticosteroids. From 1987 to 1997 he was given 16 injections of depot corticosteroid: nine of Kenalog (triamcinolone; Bristol-Myers Squibb, Hounslow) 40 mg and seven of Depo-Medrone (methylprednisolone; Pharmacia & Upjohn, Milton Keynes) 80 mg. After each injection his symptoms were substantially relieved for up to six weeks. He had no history of atopy or asthma outside the grass pollen season. He was a non-smoker, did not drink alcohol, and had no history of substance abuse or previous musculoskeletal problems.

In August 1997 he developed a limp, with pain in his right hip, and a few months later developed similar symptoms in his left hip. Plain radiographs showed abnormalities in both hip joints (figure 1). A magnetic resonance scan arranged by an orthopaedic surgeon showed avascular necrosis of the superior segment of the right femoral head, with early avascular necrosis of the left femoral head (figure 2). It was thought that he would require bilateral total hip replacement at some stage in the future.

Comment

A man with severe hay fever was given at least one depot corticosteroid injection each year for 11 years, leading to avascular necrosis of both femoral heads. Depot corticosteroids are widely used in general practice for severe cases and at the patient's request. Avascular necrosis, an uncommon though serious complication of corticosteroid treatment, has not previously been described in hay fever or with the use of depot corticosteroids.

Avascular necrosis of the hip is associated with corticosteroid therapy, but there is no direct relation

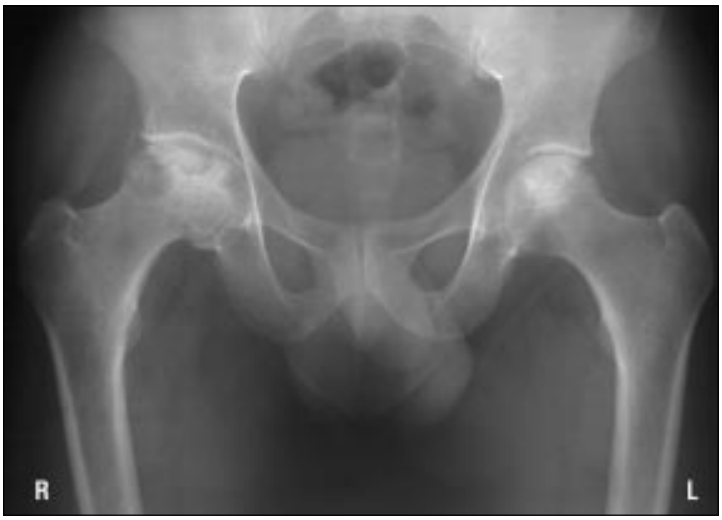

Fig 1 Plain radiograph of the hip joints, showing severe avascular necrosis on the right, with collapse of the femoral head associated with underlying lysis and sclerosis. The acetabular joint surface is normal, confirming that this is not a degenerative (osteoarthritic) process. Mild avascular necrosis is seen on the left, with an area of lysis surrounded by a diffuse area of sclerosis

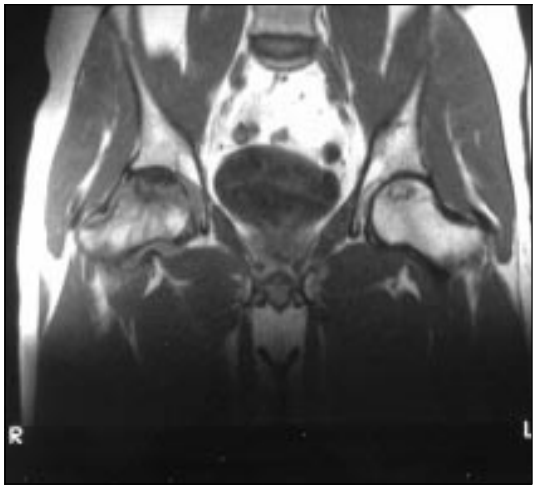

Fig 2 Magnetic resonance image (T1 weighted) of the hips. The entire femoral head is reduced in signal on the right, indicating diffuse oedema around the necrotic segment. On the left, a line of low signal surrounds an area of normal signal, indicating a previous avascular insult. The normal signal within the lesion corresponds to normal fat and indicates that the marrow at this site is still viable

with the total corticosteroid dosage.[5] Avascular necrosis has been reported to develop after as little as two weeks of corticosteroid treatment,[6 7] but susceptibility factors remain elusive. In our case it is difficult to know whether the pharmocokinetics of a depot preparation contributed to avascular necrosis of the femoral head. Avascular necrosis affects patients in their 30s or early 40s, corticosteroids being the leading cause, although alcohol and substance misuse have also been implicated. Patients who develop advanced stages of avascular necrosis of the femoral head at a young age must undergo total hip replacement, which carries a poor long term prognosis.

Specialist advice for hay fever

Hay fever is common and can be debilitating, as in this case, and we suggest that patients whose hay fever is poorly controlled despite treatment with topical corticosteroids and antihistamines should be referred at an early stage to an allergy centre for specialist advice. This patient was eventually referred at age 41 years, when allergy to grass and tree pollens was confirmed by skin tests, and an extremely high grass pollen specific IgE concentration (325 kU/l (normal: <0.35 kU/l)) was found. He is currently undergoing grass pollen immunotherapy, which is showing clear benefit.

A recent article advised against the use of depot corticosteroids in hay fever and advised that corticosteroids could be given orally but only in special circumstances and only for short periods at the lowest effective dose.[8] However, if conventional drug therapy fails, patients with hay fever should be referred to an allergist and considered for pollen immunotherapy. In seasonal allergic rhinitis (grass and birch pollen) the efficacy of immunotherapy has been confirmed in a number of carefully controlled studies.[3 4 9–15] Immunotherapy consists of a series of injections with incremental doses of allergen extract and is a specific treatment for allergic disease that can alter the course of the allergy. A recent study showed that three years of grass pollen immunotherapy in carefully selected patients had benefit for at least three years after discontinuation.[4]

Allergy services need improving

In 1986 the Committee on the Safety of Medicines expressed concerns about 25 deaths over 30 years from severe bronchospasm and anaphylaxis in patients receiving immunotherapy (desensitisation). These deaths were almost exclusively in patients with asthma. Furthermore, the injections were given in general practice by people without experience of immunotherapy or an understanding of the potential side effects and without monitoring of the patient. It is now recommended that allergen immunotherapy should be given only by experienced doctors and where facilities are available for resuscitation and monitoring of patients for at least one hour after the injection. In view of the safety issues, patients with multiple allergies, chronic asthma, or other serious medical diseases are excluded from this treatment.[2 16] Seasonal asthma is not a contraindication, provided that the patient is asymptomatic outside the pollen season.

It was a failure in management that this patient was not referred to an allergist sooner. The lack of consultant allergists and good quality allergy services has led to the poor availability of immunotherapy in the United Kingdom (about 1000 patients are currently being treated). This is in sharp contrast to the rest of Europe, especially Scandinavia, and the United States, where immunotherapy is used widely. The newer vaccines, which are more potent (a higher content of the major allergen(s)) and biologically standardised, are particularly effective. Immunotherapy is never without risk, but the risks are low if treatment is undertaken in specialised allergy clinics by staff experienced in treating large numbers of patients. More allergists are urgently needed in the United Kingdom. Better provision of allergy services will be cost effective and save NHS funds, as exemplified by this patient.

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Lesson of the week

Reye's syndrome and aspirin: lest we forget

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Reye's syndrome represents an abrupt, profound failure of mitochondria, the cause of which is uncertain. It is a biphasic illness, occurring mainly in childhood, which consists of an acute viral prodrome followed several days later by an acute encephalopathy associated with selective hepatic abnormality and metabolic decompensation. A consistent association has been shown between Reye's syndrome and the use of aspirin during the prodromal illness.[1] Of the 56 children with Reye's syndrome treated at this centre between January 1979 and December 1986, 46 (82%) had been given aspirin. During the past 13 years just five cases have been seen—two occurred in February 1999, and in both cases the child had been given aspirin.

Case 1

A boy aged 12.5 years had flu-like symptoms of mild fever, headache, and generalised aches for five days. He was given aspirin (300 mg every four hours for 24 hours) after which his symptoms seemed to resolve. However, 12 hours later he began vomiting, and this continued almost hourly for 24 hours, at which time his parents sought medical help.

There was no relevant medical history. The boy was admitted to hospital and managed with intravenous fluids. Twelve hours later he became agitated and uncontrollable; no lateralising neurological features were present and fundoscopy findings were normal. No abnormalities were noted in cerebrospinal fluid or on urine toxicology screening or on a computed tomogram of the brain. The boy's liver transaminase activities and blood ammonia concentration were noticeably high (table). He was admitted to the paediatric intensive care unit for neurological observation and was given intravenous glucose and electrolytes. The confusion resolved within 48 hours, and over the next few days his liver test results became normal. However, the boy remained tired and lethargic and it was three months before he had recovered sufficiently to return to school full time.

Case 2

A 9 month old boy was seen four weeks after case 1. He had had a low grade fever for about 24 hours, and his mother had given him 150 mg aspirin on one occasion. Twelve hours later he began to vomit and this persisted for 24 hours. When the general practitioner examined him the boy was limp and lifeless, and hypoglycaemia was confirmed (table). The boy improved rapidly after intravenous infusion of a 10% glucose and electrolyte solution, but as he was still drowsy he was transferred to a paediatric intensive care unit. No other neurological features developed. His liver transaminase activities and blood ammonia concentration were raised and the prothrombin time was prolonged (table). Twelve hours after admission to hospital he had a brief generalised seizure; it was not associated with hypoglycaemia, and his cerebrospinal fluid was normal. The seizure responded to intravenous diazepam, and treatment with phenobarbitone was continued for several days. After 24 hours the boy was fully conscious and he subsequently made a full recovery.

Discussion

The diagnostic criteria of Reye's syndrome were fulfilled in each of these cases. In addition, we excluded inherited metabolic disorders, the group most likely to mimic Reye's syndrome (β oxidation defects, urea cycle disorders, and other organic acidurias[2]), and other plausible diagnoses.

Reye's syndrome occurred fairly frequently in the late 1970s and early 1980s. In the 24 months between January 1983 and December 1984, there were 26 cases in Northern Ireland. Throughout the 1980s, there was increasing awareness of Reye's syndrome in published

Aspirin is an avoidable risk factor for Reye's syndrome: heightened vigilance can prevent an increasing incidence

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Results of investigations in two patients with Reye's syndrome

Investigation	Case 1	Case 2
Serum aspartate transaminase or alanine transaminase (U/l; maximum)	1113/946	725/1034
Blood ammonia (μmol/l; maximum)	181	108
Plasma glucose (mmol/l; minimum)	4.0	0.6
Prothrombin time (s; normal 11-15 s)	15.1 (18 h after admission]	41 (on admission)
Urinary organic acids/amino acids	Both normal	Both normal
Tandem mass spectrometry	Normal	Normal
Influenza titres in serum	320 (influenza A virus)	Not known
Reye score (maximum 25 points)	21	20
Serum salicylate	Not detected 18 h after admission	Not detected on admission