IMMUNOLOGY NEWS

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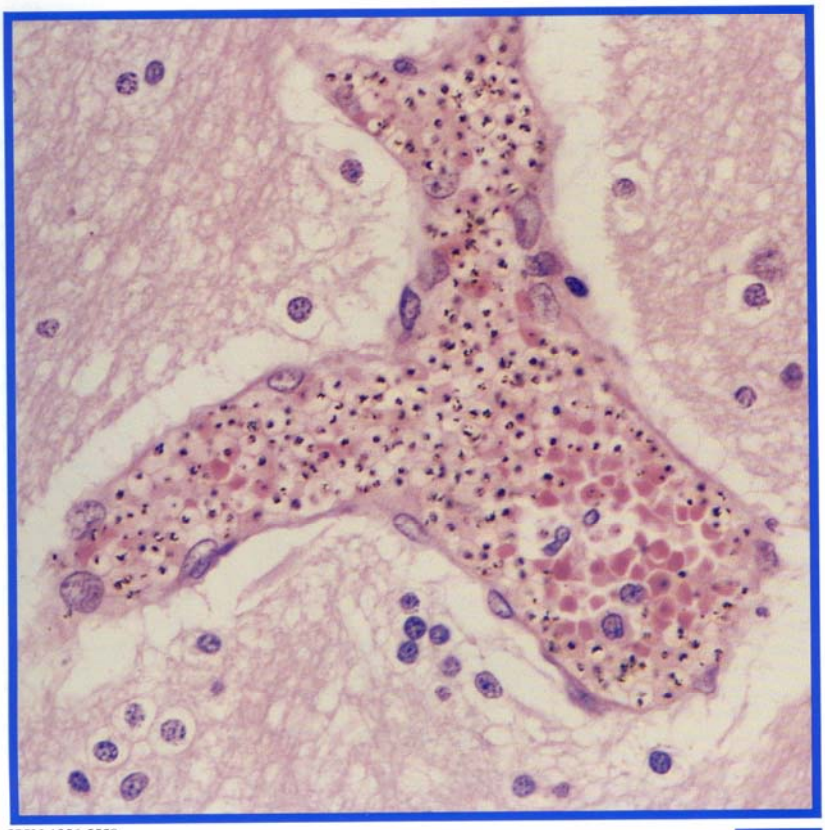

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Organ transplant-related osteoporosis

Introduction

Organ transplants may be the last hope for many patients suffering chronic and life-threatening heart, liver, lung, kidney and bone marrow diseases. The trauma of surgery soon gives way to relief as the new organ improves, beyond recognition, the patient's quality of life. However, when the complexities of life after transplant take over, the daily struggle against rejection, infection and now, increasingly, bone disease begins. In recent years, as the number of transplants has escalated and patient survival and longevity has increased, transplant-associated bone disease has been identified as an increasingly worrying side effect of organ transplantation.

Hidden ill

Margaret (not her real name) is a 55 year old mother of 2 and grandmother of 4. Last year, she seized her chance to escape the imprisonment of chronic emphysema by undergoing a double lung transplant. Margaret is realistic in her attitude to life and acknowledges "My quality of life is better than I expected since the operation, but I still have good and bad days. Simple things like walking my dog and playing with the grandchildren, bring me a lot of pleasure now. Before, I was so restricted in my movements and activities." One problem she did not expect to experience after her transplant, however, was bone thinning or osteoporosis (OP). Margaret, unfortunately, is now one of many transplant-related OP sufferers.

What is osteoporosis?

Bone is made up of a strong protein framework, impregnated with mineral salts. Even in adulthood, bone is constantly renewed and repaired. As old bone is reabsorbed, new bone is laid down. A balance between these two processes is crucial as a small increase of bone reabsorption over formation can translate, over time, into bone thinning. Bone density measurements, performed on patients using a special x-ray machine or DXA, are a way of assessing the extent of bone thinning. Osteoporosis is a bone-wasting disease which disrupts the reabsorption-formation balance and involves both the protein framework and the deposition of the mineral salts. OP sufferers have low bone density measurements. The result is painful fractures from the slightest of incidents. For example, it is not uncommon to break ribs whilst coughing. Amongst well-recognized causes of OP are lack of weight-bearing exercise, a low intake of dietary calcium (calcium is required for healthy bone formation), cigarette smoking, excessive consumption of alcohol and, in women, the menopause (which leads to a reduction in sex hormones which keep the bones healthy). In recent years, organ transplantation has been added to this list.

Pre-transplant osteoporosis - contributory factors

Before transplant, patients are exposed to numerous factors which may directly result in bone disease or may increase the chances of developing bone disease later on. Direct pre-transplant causes of bone thinning may include the prolonged bed rest which inevitably accompanies chronic disease and poor eating habits.

Drugs, such as steroids and anticoagulants are necessary to the treatment regimes of many patients, but can also increase the risk of osteoporosis. The chronic conditions suffered before transplants take place may also directly result in bone thinning. For example, studies have shown that cardiac patients, chronic renal failure patients and liver disease patients are all likely to suffer bone diseases, including OP, before they reach the stage of transplant. Inevitably, each individual patient will have reached a different stage of bone disease before undergoing transplantation. A simple bone scan or DXA for potential transplant patients before surgery would give an indication of the stage of development of any existing OP.

Better diagnosis required

During the earlier years of transplant surgery, OP was not recognized as an associated problem so pre-transplant scans were not routinely performed. This meant that the extent of bone loss before surgery was unknown so it was impossible to assess whether the OP had started before transplant or had occurred as a result of transplant. Now that the extent of risk is better understood, the fact that the UK medical community does not routinely investigate more recently transplanted patients for the disease is difficult to comprehend.

Diagnosis of the disease still seems to be left to chance. Margaret's bone condition was diagnosed, unexpectedly, in January 1996, just 6 months after her transplant. She thought that the terrible low back pain she was experiencing was due to a kidney infection, but was shocked to learn from her doctor that it was due to OP of the spine. Despite the diagnosis, she has not been offered a

bone scan to back it up. The fact that she was not scanned before her operation makes it impossible to tell if she already had the disease, or if she developed it afterwards. Either way, she was not alerted to her condition early on in its development so her option to reduce her risk factors was effectively withheld.

Drugs effect osteoporosis post-transplant

After transplant, it could follow that because the defective organ and hence the chronic disease and the associated lifestyle have all been removed, then the bone thinning should slow down or stop. Unfortunately, the situation is more complex. In bone marrow, renal, liver and cardiac patients, bone density actually reduces after transplantation, more so in older patients than younger ones. The causes are difficult to define, but it may be that the immunosuppressive drugs prescribed to stop the body's immune system rejecting the transplanted organ are, in part, responsible for continued bone thinning.

Cyclosporin A (CsA) is an immunosuppressive drug widely used by transplant patients and thought to play some role in bone thinning. CsA's relatively recent discovery was heralded as a major breakthrough in transplant medicine and, since then, it has dramatically increased the survival rates of transplant patients. However as CsA's long term effects continue to emerge, the possible side effect of OP cannot be ignored. This is also the case for the steroid, prednisalone, prescribed extensively to transplant patients due to its effectiveness in holding rejection at bay. Specific ways in which these drugs influence bone thinning are both complex and still not fully understood.

However, some simplified proposed theories for how prednisalone may contribute to bone thinning exist. Prednisalone is thought to alter the body's level of sex hormones (required for healthy bone formation), it may vary the extent to which calcium is absorbed from the diet and is made available for bone formation, and it may also cause loss (via the urine) of the minerals required to build healthy bones. The immune system is known to play a part in mineralization of bones so CsA's effect of depressing the immune system to stop organ rejection may have the added unwanted effect of also reducing bone mineralization, leading to fracture. CsA may also cause bone breakdown to occur at a faster rate than build up, accelerating bone disease. Prednisalone and CsA are given in high doses immediately after transplant and are tapered gradually, as the new organ is accepted.

Although experts have yet to discover exactly how these drugs relate to the OP disease process, the implication of their involvement is reinforced by studies which have shown the extent of bone loss is greatest in the first six months after transplant and it then tapers off. Despite this pattern of OP slowing down, the damage has already been done.

The sad part about Margaret's story is that before her transplant, her risk factors for developing osteoporosis were so low. She had hardly been treated with steroids at all, mainly because they proved largely ineffective in her case. Her age meant that for 4 years before her transplant, she was taking hormone replacement therapy (HRT), which is known to protect against osteoporosis. Her doctors have told her that her bone disease is a likely result of the high doses of prednisalone prescribed to her after transplant, but lack of evidence cannot prove this. She is currently taking HRT and a calcium supplement but still receives no bone scans which could help chart the progress and, therefore, facilitate more effective management of the disease.

Improving the management of osteoporosis

Consultant rheumatologist Annie Cooper, working at Airedale General Hospital in Keighley, West Yorkshire, has developed a recent research interest in transplant-related OP. Margaret's experience did not surprise her. Dr Cooper admits the current shortcomings of the British medical fraternity in this disease area, "Now the problem of post-transplant osteoporosis has been identified, new developments and treatments in this field are becoming more widely available. It is important to measure bone density post-operatively, and where possible, pre-operatively, to assess which patients are at risk from developing osteoporosis or are already osteoporotic. These "at risk" patients should be targeted with treatment and can be educated to modify their lifestyle to help reduce their risk of developing or worsening the disease."

A brighter future?

For some patients, the risk is raised by their pre-transplant illness, but for those whose lifestyle and habits also contribute, raising their awareness of their condition could help to significantly reduce their risk factors. Dr Cooper explained that in America, recognition of the prevalence of transplant-related bone disease has prompted the routine treatment of patients awaiting heart transplants with calcium and vitamin D (which increases absorption of dietary calcium and therefore helps maintain healthy bones) pre-operatively. Even so, this treatment is strictly controlled as it can prove hazardous under certain circumstances and should not be taken without medical supervision. If Dr Cooper's own research in the area of vitamin D-related prevention of OP proves successful, similar treatment could be carried out on suitable candidates and the debilitating effects of osteoporosis for some British patients, could be reduced in years to come.

Sam Hamilton, 29, studied at Newcastle University, following her first degree with a PhD in gastrointestinal physiology. She developed an interest in science writing whilst working in lung transplant research. Sam now works in the pharmaceutical industry but continues to pursue her main interest as a freelance science writer.