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Case Report

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Polymorphisms of the glucocorticoid receptor and avascular necrosis of the femoral heads after treatment with corticosteroids

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Abstract

A female patient developed avascular necrosis of the femoral heads after receiving low doses of glucocorticosteroids (GC) for 3 months. Genotyping of the GC receptor (GR) showed that she was heterozygous for the Bcl-1 allele and heterozygous for the N363S allele. Interestingly, these GR variants are both associated with higher sensitivity to glucocorticoids. It is not known whether the GR gene polymorphisms are causally related to osteonecrosis. However, the presence of these GR variants, as a combination present in only 1% of the normal Caucasian population, seems suggestive. Studies are warranted to investigate the importance of polymorphisms related to GC sensitivity.

Keywords: avascular necrosis; glucocorticoid receptor; glucocorticosteroids; polymorphism

Introduction

Glucocorticosteroids are frequently used as immunosuppressive drugs to prevent acute rejection after organ transplantation. The well-known adverse effects of long-term therapy with corticosteroids have motivated increasing interest in steroid-free immunosuppression for kidney transplant recipients [1]. Despite this change in the use of GCs, the side effects of GC treatment are still a relevant problem in clinical practice.

Because the sensitivity of individuals to GC is different, the risk of developing side effects from the GC differs as well. Genetic variation is one of the reasons why the effects of GC show interindividual variability. Avascular necrosis of the femoral heads is thought to be a side effect that is less frequent and mainly related to plasma concentrations of glucocorticoids and duration of therapy [2,3]. We report a patient who developed avascular osteonecrosis despite relatively low GC doses.

Case report

A 51-year-old woman received a kidney from a living unrelated donor. There was no history of dialysis prior to transplantation. The cause of renal failure was chronic pyelonephritis, and other than the progressive renal insufficiency she had been healthy. There was no history of autoimmune disease or other diseases for which corticosteroid therapy had been given. No drugs having a drug interaction with glucocorticosteroids had been used. Before transplantation, 0.25 mcg of 1-25-diOH-D3 (cholecalciferol) was given and discontinued after transplantation. No bisphosphonates were used. There was immediate graft function after transplantation. Immunosuppression consisted of a combination of tacrolimus, mycophenolate mofetil and prednisone. During the first 3 days, prednisolone was given i.v. (dose 100 mg/day). Thereafter, the prednisone dose was tapered from 20 mg p.o. in the first week to 5 mg in the third month, and completely discontinued at 3 months post-transplantation. One week after transplantation, she experienced a presumed (not biopsy confirmed) acute rejection that responded to a 3-day course of pulse methylprednisolone (1000 mg i.v.). After 6 months, she developed rest pain and motion-induced pain in both groins and thighs. Initially, a bursitis was suspected to be the cause of her pain, and she was treated with NSAIDs for 4 weeks. However, later she was found to have bilateral avascular necrosis of the femoral heads. She underwent total hip arthroplasty on both sides. There were no other prednisone-related side effects observed, such as steroid-induced diabetes, weight gain or a Cushingoid phenotype.

As cumulative GC exposure had been relatively low in this patient, we suspected her of having increased sensitivity to GC, which may be attributable to genetic vulnerability. To elucidate the genetic factors involved in this pathogenesis, we examined whether the development of avascular necrosis was associated with glucocorticoid receptor polymorphisms using genetic analysis. We investigated five different GR polymorphisms: *TthIII-I*

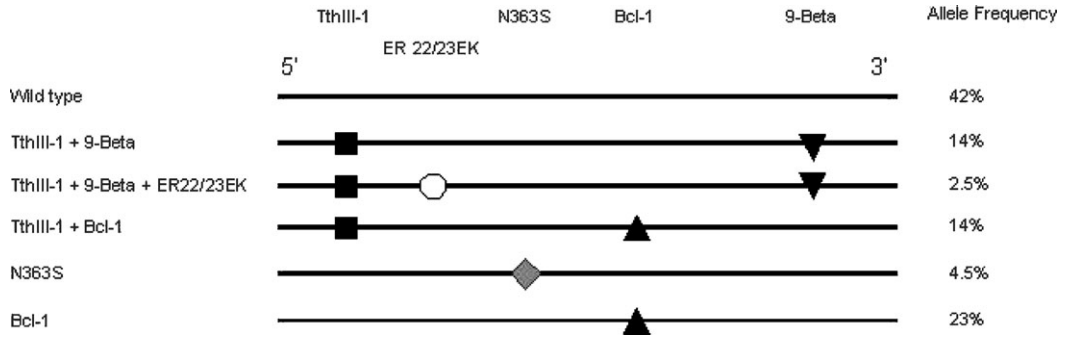

Fig. 1. The alleles of the glucocorticoid receptor gene and their frequencies.

(rs10052957); N363S (rs6195); *Bcl*-1 (rs41423247); 9-Beta (rs6198) and ER 22/23EK (rs6189+rs6190) using methods as previously prescribed [4].

Figure 1 shows how the different combinations of these polymorphisms result in six alleles of the GR gene and their frequencies in the general population. We used two independent DNA samples from the patient. The results showed that the patient is heterozygous for the allele *TthIII-1* + *Bcl*-1 and heterozygous for the *N363S* allele. The combined presence of both these alleles in one patient is observed in <1% of the general population.

Discussion

Osteonecrosis is thought to be a side effect that is less frequent and related to plasma concentrations of glucocorticoids and duration of therapy [2,3]. Huizenga *et al*. [3] reported that a polymorphism at nucleotide position 1220 (rs195) in the GR was associated with a higher sensitivity to exogenously administered glucocorticoids [3]. Felson *et al*. [6] reported that a steroid dose is the major predictor for avascular necrosis of the bones, taking into account that the steroid dose that was used had been much higher than nowadays. They reported that the low-dose GC regimes have resulted in very low rates of avascular necrosis of the femoral heads (0–2%) [6]. However, several case reports [5–7] have shown that some patients still develop osteonecrosis despite only low-dose glucocorticoids. The exact mechanism of this complication caused by the corticosteroids remained obscure [6].

The *Bcl*I polymorphism as well as the N363S polymorphism were both found to be associated with a higher sensitivity to glucocorticoids [2,7]. We found two polymorphisms in this patient, which are both associated with increased sensitivity to GC *in vivo*. Interestingly, two polymorphisms, previously reported to be associated with decreased sensitivity to GC, were not present in this patient [2,8]. In addition, it is remarkable that this patient did not suffer from other side effects of GC treatment.

It is known that the effects of GC can be tissue specific, due to differences in the distribution of GR per tissue. The known functional GR polymorphisms have also been reported to be tissue specific, which accounts in particular for the *Bcl*I variant [2]. The pathogenesis of avascular necrosis is not clarified, but an increase in osteoblast apoptosis and osteoclast apoptosis has been demonstrated in mice and humans receiving corticosteroids [9]. Glucocorticosteroid receptors have been characterized on osteoblast-like bone cells and also on osteoclasts. Histological studies of bone in patients treated with GC have indicated increased osteoclastic bone resorption and decreased osteoclastic bone formation. The effect of glucocorticosteroids on bone, therefore, can be explained by effects of GC on these receptor interactions [10]. For this case, there is no evidence that such tissue-specific differences in GR expression were present, but this may explain why she only suffered from avascular necrosis and not from other steroid-related side effects.

It is not known whether in this patient the GR gene polymorphisms are causally related to osteonecrosis. However, the presence of these GR variants, as a combination present in only 1% of the normal Caucasian population, seems suggestive. We could at least expect a contribution of this GR genotype to increased sensitivity to GC. We, however, cannot rule out that other factors, such as decreased breakdown of GC, alterations in the activity of the intracellular factors e.g. GR chaperone proteins, transcription factors or enzymes (e.g. 11 beta hydroxysteroid dehydrogenase type 1 and 2), also contribute to these enhanced GC effects.

It remains an open question how to balance genotype analysis and the administration of steroids. Further GC use seems (relatively) contra-indicated for this patient. Future studies focusing on a complete genotypic profile, which is related to the sensitivity to GC, can be very helpful to prevent severe side effects due to GC treatment in the future.

Conflict of interest statement. None declared.

References

1. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: changing paradigms, improving outcomes, and remaining questions. *Clin J Am Soc Nephrol* 2006; 1: 1080–1089
2. van Rossum EF, Lamberts SW. Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Prog Horm Res* 2004; 59: 333–357
3. Huizenga NA, Koper JW, De Lange P *et al*. A polymorphism in the glucocorticoid receptor gene may be associated with and increased

sensitivity to glucocorticoids *in vivo*. *J Clin Endocrinol Metab* 1998; 83: 144–151
4. Di Blasio AM, van Rossum EF, Maestrini S *et al*. The relation between two polymorphisms in the glucocorticoid receptor gene and body mass index, blood pressure and cholesterol in obese patients. *Clin Endocrinol (Oxf)* 2003; 59: 68–74
5. van Rossum EF, Koper JW, Van Den Beld AW *et al*. Identification of the BclI polymorphism in the glucocorticoid receptor gene: association with sensitivity to glucocorticoids *in vivo* and body mass index. *Clin Endocrinol* 2003; 59: 585–592
6. Felson DT, Anderson JJ. Across-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. *Lancet* 1987; 1: 902–906
7. Derijk RH, de Kloet ER. Corticosteroid receptor polymorphisms: determinants of vulnerability and resilience. *Eur J Pharmacol* 2008; 583: 303–311
8. Van Den Akker EL, Russcher H, van Rossum EF *et al*. Glucocorticoid receptor polymorphism affects transrepression but not transactivation. *J Clin Endocrinol Metab* 2006; 91: 2800–2803
9. Weinstein RS, Jilka RL, Parfitt AM *et al*. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998; 102: 274–282
10. Canalis E, Mazziotti G, Giustina A *et al*. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* 2007; 18: 1319–1328

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