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POST-COVID AVASCULAR NECROSIS OF THE FEMORAL HEAD

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Abstract

The severe acute respiratory syndrome (SARS) was a highly infectious pneumoni that emerged in Uzbekistan due to Covid-19 pandemic. A large number of SARS patients experienced large joint arthralgia, although this was, for the most part, not associate with any abnormality on magnetic resonance imaging. The main musculoskeletal complication of SARS were osteonecrosis and reduced bone mass, and these arose not from the disease per se but as a sequel to treatment of SARS with high-dose steroids. SARS patient were almost universally steroid naive with no other known predisposition to osteonecrosis. Prevalence of osteonecrosis in SARS patients treated with steroids ranged from 5% to 58%. Osteonecrosis most commonly affected the proximal femur and femoral condyles and was most strongly related to cumulative steroid dose and duration of steroid therapy. Most osteonecrotic lesions tended to improve with a reduction in lesion volume over a follow-up period of 5 years. The relative reduction in osteonecrotic lesion volume was greatest for smaller lesions.

Keywords: Covid-19, Osteonecrosis, SARS, Steroids.

Introduction

As a pathological process, aseptic necrosis of femoral head is characterized by avascularity of the femoral head, cellular necrosis, microfracture, and collapse of the articular surface. The coronavirus 2 (SARS-CoV-2) (COVID-19) pandemic has stimulated an unprecedented response by the global scientific community to better understand the disease. However, many questions about SARS-CoV-2 remain unanswered. Various hypotheses have been formulated in regard to its pathogenetic mechanisms. One of them single nucleotide polymorphisms in various genes encode for proinflammatory proteins, such as IL-1b, IL-6 and IL-8, which may affect biological activity and contribute to hypercoagulability in COVID-19 patients, thereby increasing the risk of thrombosis of femoral head vessels and its aseptic necrosis or avascular necrosis(AVN).

Risk Factors of AVN

Osteonecrosis of the femoral head (ONFH) is a complex, polygenic, or multifactorial disease which is caused by a number of genetic factors of relatively smaller effects and environmental factors. Diverse conditions have been implicated in the development of ONFH. There are several well accepted common associations: corticosteroids use (1), alcohol abuse (2), systemic lupus erythematosus (3), Legg-Calvé-Perthes disease (4), sickle cell disease (5), radiation (6), cytotoxic agents (7), Gaucher disease [8], dysbarism (9), HIV (10), hyperlipidemia (11), pancreatitis (12), and gout (13). Idiopathic ONFH defines only when there are no identifyable factors identified. Metabolic conditions such as diabetes, dysfunctional lipid metabolism and even pregnancy are also associated with osteonecrosis, as are coagulopathies, rheumatologic diseases and malignancies.

The Role of Anatomy

The femoral head is particularly susceptible to osteonecrosis due to the anatomy of the vascular supply to this area, which is discussed in more detail in the section on pathogenesis. However, other sites can be affected including the humeral head, femoral condyles, tibial plateau, distal tibia, talus, bones of the feet, bones of the wrist and hand, jaw, and vertebrae. (14)

Genetic Predisposition

Why is it that some people with certain illness can be given large doses of corticosteroids on a chronic basis and not develop osteonecrosis, whereas some development osteonecrosis with much smaller doses. There clearly seems to be a role of genetics in the development of osteonecrosis. Genes that may play a role in osteonecrosis include eNOS, PAI-1, VEGF and ApoA. (14)

The cause of ONFH is multifactorial. Both genetic predisposition and exposure to certain environmental factors are associated. The incidence or prevalence of idiopathic ONFH reflects ethnic differences (15). Some patients who have taken high dose of corticosteroids or excessive alcohol intake for long period develop ONFH, but rare cases of ONFH occur after short corticosteroid treatment indicating the presence of differences in susceptibility to risk factors as well as genetic predisposition to ONFH between individuals (16). Particularly, idiopathic ONFH in identical twins or a clustering of cases in families implicates involvement of genetic factors (17).

Steroids

Many SARS patients were treated with high-dose steroids over a variable time period, depending on their clinical status. A well-recognized serious side effect of steroid therapy is osteonecrosis. Unlike many of the other side effects of steroids, such as immunosuppression, myopathy, or bone loss, established osteonecrosis is not known to fully recover on discontinuation of steroid therapy. High-dose steroids administered over a short period to patients not otherwise at risk of osteonecrosis, such as those following spinal cord injury, seem to confer little or no risk of osteonecrosis. [18] However, high-dose steroids administered over a longer period to patients who are also otherwise predisposed such as those with an inflammatory arthropathy, malignancy, or following an organ transplant, have a significant dose-related risk of developing osteonecrosis that varies from 4% to 52%.[19] SARS patients fell between these two groups in that they were otherwise healthy patients who were administered high-dose steroids over a medium time period.

The first large series of patients with glucocorticoid-induced osteonecrosis was reported in 1971. From 482 patients with osteonecrosis seen at the Mayo Clinic from 1961 to 1968, 77 had received glucocorticoids. The report caused some confusion because “hematologic conditions,” pancreatitis, pregnancy, rheumatoid arthritis, glomerulonephritis, colitis, and gout were all listed as causes of “avascular necrosis,” but these patients had been treated with glucocorticoids and there was no evidence that the conditions listed were independent causes of osteonecrosis, although that was assumed for more than 40 years (20)

The pathophysiology of Steroid Induced Femoral Head Osteonecrosi (SI-FHON) is multifactorial, complex, and poorly understood. Although host factors and underlying diseases have been shown to play a significant role in the development of SI-FHON, investigators have failed to explain why only a fraction of patients are at greater risk than others. Additionally, the multisystemic effects of glucocorticoids and their interactions make the pathological mechanisms more complicated. In this context, the multi-hit theory proposed by several investigators is a plausible explanation for the development of SI-FHON (21). In susceptible patients who have a genetic predisposition or an underlying disease that threatens bone and vascular tissues, the accumulative glucocorticoid effects may result in the occurrence of GI-FHON. Genetic factors will be discussed in another chapter.

Osteonecrosis from steroid therapy is believed to result from impairment of bone circulation. The femoral head is the most commonly affected bone area. Less commonly affected areas are the femoral condyles, the humeral head, and the talus. The femoral head is particularly susceptible because it is a bone area that has

inherently poor vascular perfusion. Perfusion of the femoral head is normally only about a third that of the femoral neck and a fifth that of the acetabulum. (22)

The effects of corticosteroids on coagulation in the pathogenesis of osteonecrosis may be intricately related to the vascular endothelium. Endothelial cell damage can lead to a coagulopathy which results in the formation of thrombi. (14)

GCs can induce endothelial cell apoptosis by a different signalling pathway.52–55 Endothelial cell apoptosis consequently promotes thrombus formation and ON by two major mechanisms. First, apoptotic bodies can indirectly lead to coagulopathic changes by endothelial dysfunction. Second, apoptotic endothelial cells can stimulate adhesion of platelets to endothelial cells and activate platelets, eventually leading to thrombus formation. However, GCs can induce endothelial cell apoptosis and lead to a hypercoagulable state. Cessation or a reduction in blood flow along capillaries could also play an aetiological role in endothelial cell apoptosis (23).

The osteonecrosis that occurred in SARS patients is more likely the result of steroid therapy. There was no clear recognizable factor associated with SARS infection per se that would induce osteonecrosis de novo and no clear cases of osteonecrosis occurring de novo in SARS patients not treated with steroids. (22)

Also, MR imaging screening of a cohort of 50 patients with community acquired pneumonia that did not receive steroids revealed evidence of osteonecrosis in only one patient, and this patient had undergone prior treatment for disseminated prostate metastases. Of the many potential contributory factors considered (smoking, alcohol consumption, severity of SARS infection, steroid dose),multivariate analysis revealed that cumulative steroid dose was the most important risk factor in predicting osteonecrosis. The risk of osteonecrosis was found to be 0.6% in patients receiving <3 g and 13% for patients receiving >3 g cumulative prednisolone-equivalentdose.20 Chan et al also concluded that a cumulative dose of >2 g methylprednisolone and a duration of therapy >18 days were significant risk factors for the development of osteonecrosis.

In conclusion, it is premature to make conclusions regarding the genesis of osteonecrosis after suffering COVID-19. Probably, the development of the disease is synergistically affected by many factors, including steroid and ischemic. The accumulation of information about such patients will allow in the future to form an informed opinion on this issue.

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