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ORIGINAL ARTICLE

White Matter Lesions in Femoral Head Osteonecrosis patients: Manifestation of vascular disease or not?

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ABSTRACT

Background: Osteonecrosis has been associated with the presence of white matter lesions. The objective of this study was to investigate the association between macro- and micro- vascular disease and white matter lesions.

Methods: Sixty-four patients with femoral head osteonecrosis were assessed during a cross sectional study in our university-based hospital. A vascular 'profile' was obtained for each patient and included measurement of plasma lipids, fundoscopic examination and common carotid artery triplex ultrasonography. All patients had brain MRI to assess for presence of white matter lesions. The two groups formed, with and without white matter lesions, were compared in order to define the association between white matter lesions and vascular disease.

Results: Patients without white matter lesions had more frequently corticosteroid induced osteonecrosis. There was no difference in the two groups with respect to intima media thickness and ApoB/ApoA1 ratio. Only one of our patients demonstrated retinopathy.

Conclusions: There is no evidence of concurrent macro- and micro- vascular pathology in young patients with white matter lesions and femoral head osteonecrosis. Cortisone appears to have a 'protective' effect against occurrence of white matter lesions. Hippokratia 2011; 15 (3): 265-268

Key words:white matter lesions; femoral head osteonecrosis; avascular necrosis; corticosteroids; vascular disease

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Femoral head is the most vulnerable site in the skeleton for the development of necrotic lesions. The etiology is multifactorial and many theories have been postulated regarding the pathogenesis of the disease, the majority of which agree that the common final pathway is the occlusion of terminal vessels (arterioles, capillaries and venules) distributed at the area of the affected bone [1].

Recently a high incidence (56.9%) of white matter lesions has been reported in young patients with non traumatic osteonecrosis of the femoral head (white matter lesions in osteonecrosis, WMLeON).[2,3,4] Etiology of WMLeON in this young patient population remains obscure. Is it a sequela of vascular disease? As a first step towards understanding the pathogenesis of WMLeON, we tested the hypothesis that these lesions are not coexistent with micro- or macro- vascular disease.

Materials and Methods

In this cross sectional study 75 consecutive patients (57 male and 18 female) with nontraumatic femoral head osteonecrosis were recruited from our outpatient clinics, from January 2004 to June 2007. The study was approved by the bioethical committee of our institution and all participants gave their informed consent.

Diagnosis and evaluation of the severity of the necrotic lesions was carried out using radiographs and MR scans of the hips. Patient characteristics (age, gender, duration of symptoms and risk factors for ON e.g. exposure to high dose glucocorticoids, smoking, alcohol abuse) were recorded. A thorough assessment of presence of vascular disease was undertaken utilizing plasma lipid levels, carotid artery ultrasonography, retinal photography and brain MRI.

Plasma lipids: A thorough evaluation was done to establish the vascular 'profile' of each patient. After a 12-hour fast and with the patient seated for 10 minutes, blood was collected between 8:30 AM and 9:30 AM to minimize circadian influence. Serum was examined for

apolipoprotein A1 and apolipoprotein B. The ratio ApoB/ApoA1 was calculated. ApoB transports all potentially atherogenic very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and LDL particles and apoA1 transports and acts as the major antiatherogenic protein in the HDL particles. The cholesterol balance determined as the apoB/apoA-1 ratio has been repeatedly shown to be an accurate index of the lipoprotein-related risk of vascular disease and is a better marker than lipids, lipoproteins and lipid ratios.[5] The lower the ratio, the lower is the risk for cardiovascular disease.

Carotid artery ultrasonography: Triplex ultrasonography (7.5 MHz linear array, ATL 3000) of both common carotid arteries was done and intima media thickness (IMT) was recorded as a measure of systemic macrovascular disease .[6] The parameter was calculated by the average of 6 measurements (3 highest of each carotid artery). The radiologist was also blinded regarding information of patients' health status.

Retinal photography: Retinal photographs were taken from both eyes after appropriate mydriasis. The procedure is described elsewhere.[7] The images were interpreted by two ophthalmologists expert in retinal pathology, using a standardized protocol, blinded about patients' information. Retinopathy was defined as present if any of the following lesions were detected: soft exudates microaneurysms, retinal haemorrhages, arteriovenous nicking, hard exudates and optic disk swelling.

Brain MRI: All MRI scans were performed with a 1.5 Tesla MR imager (Intera NT; Philips Medical Systems, Best, The Netherlands). Fast Spin Echo (FSE) FLAIR (Fluid Attenuated Inversion Recovery) sequences were used for detecting WML as it has been shown to be superior to conventional Spin Echo and FSE T2 weighted sequences (Figure 1).[4,8] A thorough clinical neurologic examination was performed as part of the screening process.

To minimize the effect of confounding factors we used the following exclusion criteria: History of diabetes mellitus, hypertension, peripheral vascular disease, coronary artery disease, transient ischemic attack, stroke, migraine, multiple sclerosis, systemic lupus erythematosus, sickle cell disease and ophthalmic disease. Nine patients were excluded due to these comorbidities and two patients denied to participate to the screening process leaving a total of 64 patients (48 male, 16 female). Mean patient age was 36.6 (SD 8.4) years.

Statistical analysis

In initial univariate models, we compared the groups with and without WML with regards to the patient specific characteristics as well as with the results of fundoscopic examination, intima media thickness and lipid profile.

T-test was used for characteristics with continuous distribution and Pearson's chi square test was used for dichotomous or categorical characteristics.

In order to investigate which parameters were independently associated with presence of WML (i.e. to adjust for possible confounding) we calculated an overall multivariate logistic regression model with WML as the dichotomous outcome. For predictor selection, in addition to standard demographics (age and gender), we were guided by the previous univariate models (i.e. we simultaneously included in the model the variables that were significantly associated with WML) (Table 1).

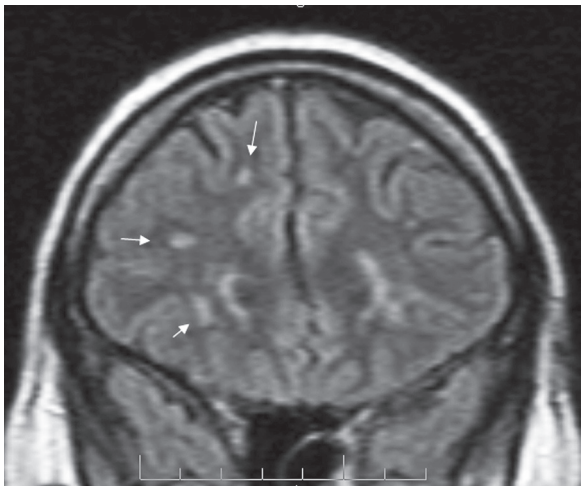

Figure 1: Coronal image in a 38-year-old man with idiopathic femoral head osteonecrosis shows multiple lesions in the frontal white matter (arrows)

Results

In fifty-four out of 64 patients the diagnosis of secondary osteonecrosis was established. WMLeON were found in 38 out of 64 patients. Neurologic examination was normal in all patients. Inter-reader agreement for retinal photographs was investigated with Kappa statistics and was excellent (1.0). Results are summarized in Table 1.

Etiology and symptom duration of ON were not associated with presence of WMLeON (p=0.15 and p=0.18). There was no difference between the two groups of patients (with and without WML) with regards to intima media thickness (p=0.19) and retinopathy (p=0.41).

In the multivariate logistic regression models simultaneously considering age, gender, use of corticosteroids and smoking (i.e. all the factors with significant associations in the univariate models), the parameters of age (OR, 0.949; 95% CI 0.801-1.126; p = 0.551) and gender (OR, 0.039; 95% CI 0.001-53.302; p = 0.378) did not present any significant association to WML. In contrast, absence of corticosteroid intake (OR, 0.001; 95% CI 0.001-0.811; p = 0.043) and history of smoking (OR, 0.001, 95% CI 0.001-0.173; p = 0.026) were found to be significantly associated with presence of WML.

Discussion

As osteonecrosis is multifactorial in etiology it is rather difficult to isolate the contribution of a single factor in the pathogenesis of bone infarct as well as in the pathogenesis of WML. For example a common clinical scenario is that of a renal transplant patient who has been

Table 1: Demographics, clinical and laboratory findings of the two patient groups with and without WML (white matter lesions).

Variables	Without WML (n=26)	With WML (n=38)	P-value
Age at onset of ON (yrs, mean±SD)	33.5±10.1	38.8±7.3	**0.03**
Male/ Female	18/8	30/8	0.38
Duration of symptoms (months)	20.3±12.6	16.6±9.3	0.18
Secondary ON etiology	24	30	0.15
Smoking	19	18	**0.04**
Pack-years	14.6±16.1	13.0±16.8	0.7
Alcohol	16	28	0.3
History of cortisone use	20	16	0.006
ApoB/ApoA1	0.74±0.38	0.82±0.24	0.28
Increased Carotid intima-media thickness	5	13	0.19
Pathologic changes to retinal vessels	0	1	0.41

in chronic renal failure and dialysis for years, suffers from osteodystrophy, is on daily steroids for immunosuppression and has lipid abnormalities. In that patient, osteocytes are under a chronic stress and each upcoming event makes them more vulnerable to death.[9] Corticosteroids may be the triggering event but not the sole cause of ON. Similarly WML can be the result of premature microvascular disease which accompanies renal failure or may be due to a direct toxic effect on the white matter.

Anatomy, physiology and embryology of the retinal arterioles shares similarities with the cerebral arterioles.[10] Microvascular changes in the retina, as the ones observed by retinal photography can reliably provide an assessment of the potential presence of cerebral microangiopathy.[11,12] In our series only one patient with WML was found to have abnormal retinal photography and therefore this should be interpreted conservatively. Studies with larger sample size may elucidate the relevance of retinal microvascular pathology and WMLeON. Retinopathy may follow a temporal different course than cerebral microangiopathy, but this needs support by further investigation. Literature supports the association between presence of WML and retinal microvascular abnormalities in middle-aged adults.[11] Nevertheless, there is no clinical data available for young adults.

ApoB/ApoA1 ratio which represents a more reliable atherogenic index (compared to lipids and lipoproteins) was not associated with the presence of WMLeON.[5] In previous reports, IMT has been associated with presence of WML in healthy individuals older than sixty.[13,14] In our cohort of mainly young patients with osteonecrosis, there was no significant difference between the groups with and without WML with respect to IMT. It appears from the above that atherosclerosis and large vessel disease are not implicated in the pathogenesis of WML in patients with osteonecrosis, unless those two processes develop in different chronological patterns.

We found that patients with history of corticosteroid therapy had a decreased incidence of WMLeON. A number of studies have shown that WML in elderly are associated with hypoperfusion and ischemia with resultant oxygen radical formation and peroxidation of lipids.[15,16] It is well known that corticosteroids offer protection against the harmful effects of oxygen radicals and lipid peroxidation.[17] In younger adults, a mechanism of neuroinflammation has been postulated to explain the presence of WML. Corticosteroids have a potent effect on diminishing neuroinflammation and this may explain our findings.[18,19]

Our analysis showed an association between smoking and absence of WML. This is somewhat paradoxical. However our group of ON patients were young and the pack-year smoking history was relatively short. Similarly, other authors did not find correlation between smoking and vascular pathology in renal biopsies of patients younger than the age of fifty or smoking and atherosclerosis of the small arteries of brain.[20,21] This should not be taken as evidence against the damaging effect of smoking and should be interpreted cautiously since the effect of smoking on cerebral vasculature may become evident later in life. Repeated examination with brain MRI scan later in time could help clarify this.

One of the limitations is that due to small number of patients we could not perform subgroup analysis of patients with diverse etiology of secondary ON. For the same reason no attempt was made to grade severity of WML.

In summary we could not demonstrate any concurrent micro- or macro- vascular pathology in patients with femoral head ON and WML at the time of ON diagnosis. This lack of association possibly reflects a different pathogenetic mechanism of WML in patients with osteonecrosis of femoral head compared to that of WML seen in elderly people. Patients who had a history of corticosteroid therapy were protected against formation of WMLeON. A longitudinal study is required to demonstrate possible progress of WML and development of any pathologic changes to the vascular beds screened. Other factors (genetic, environmental) may precipitate the for-

mation of WML in these patients and studies investigating the effect of toxic and demyelinating insults could be useful.[22,23] Further research is needed to investigate the common linkage between those two entities.

Conflict of Interest Statement

The corresponding author declares on behalf of all authors that there is no conflict of interest.

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References

1. Lafforgue P. Pathophysiology and natural history of avascular necrosis of bone. Joint Bone Spine 2006;73: 500-507.
2. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32: 94-124.
3. Zalavras CG, Dailiana Z, Elisaf M, Bairaktari E, Vlachogiannopoulos P, Katsaraki A, et al. Potential aetiological factors concerning the development of osteonecrosis of femoral head. Eur J Clin Invest 2000; 30: 215-221.
4. Hadjigeorgiou GM, Karantanas AH, Zibis A, Dardiotis E, Aggelakis K, Papadimitriou A, et al. Increased frequency of white matter lesions in patients with osteonecrosis (WMLeOn) of the femoral head. Eur J Radiol. 2004; 50: 278-284.
5. Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy-a review of the evidence. J Intern Med 2006; 259: 493-519.
6. Hurst RT, Ng DW, Kendall C, Khandheria B. Clinical use of carotid intima-media thickness: review of the literature. J Stroke Cerebrovasc Dis. 2007; 16: 14-20.
7. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology 1999; 106: 2269-2280.
8. Gawne-Cain ML, O'Riordan JI, Thompson AJ, Moseley IF, Miller DH. Multiple sclerosis lesion detection in the brain: A comparison of fast fluid-attenuated inversion recovery and conventional T2-weighted dual spin-echo. Neurology 1997; 49: 364-370.
9. Kenzora JE. Ischemic necrosis of femoral head. Part I. Accumulative cell stress: a hypothesis for the etiology of idiopathic osteonecrosis. Instr Course Lect. 1983; 32: 242-252.
10. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. Surv Ophthalmol. 2001; 46: 59-80.
11. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002; 288: 67-74.
12. Wong TY. Is retinal photography useful in the measurement of stroke risk? Lancet Neurol. 2004; 3: 179-183.
13. Pico F, Dufouil C, Lévy C, Besançon V, de Kersaint-Gilly A, Bonithon-Kopp C, et al. Longitudinal study of carotid atherosclerosis and white matter hyperintensities: the EVA-MRI cohort. Cerebrovasc Dis. 2002; 14: 109-115.
14. De Leeuw FE, de Groot JC, Bots ML, Witteman JC, Oudkerk M, Hofman A et al. Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. J Neurol. 2000; 247: 291-296.
15. Hall ED, Braughler JM. Central nervous system trauma and stroke, II: physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation. Free Radic Biol Med. 1989; 6: 303-313.
16. Meguro K, Hatazawa J, Yamaguchi T, Itoh M, Matsuzawa T, Ono S, et al. Cerebral circulation and oxygen metabolism associated with subclinical periventricular hyperintensity as shown by magnetic resonance imaging. Ann Neurol. 1990; 28: 378-383.
17. Hall ED. Neuroprotective actions of glucocorticoid and nonglucocorticoid steroids in acute neuronal injury. Cell Mol Neurobiol. 1993; 13: 415-432.
18. Pomper MG, Miller TJ, Stone JH, Tidmore WC, Hellman DB. CNS vasculitis in autoimmune disease. Am J Neuroradiol. 1999; 20: 75-85.
19. Tischner D, Reichardt HM. Glucocorticoids in the control of neuroinflammation. Mol Cell Endocrinol. 2007; 275: 62-70.
20. Lhotta K, Rumpelt HJ, König P, Mayer G, Kronenberg F. Cigarette smoking and vascular pathology in renal biopsies. Kidney Int. 2002; 61: 648-654.
21. Reed DM, Resch JA, Hayashi T, MacLean C, Yano K. A prospective study of cerebral artery atherosclerosis. Stroke 1988; 19: 820-825.
22. Hadjigeorgiou GM, Malizos K, Dardiotis E, Aggelakis K, Dardioti M, Zibis A, et al. Paraoxonase 1 gene polymorphisms in patients with osteonecrosis of the femoral head with and without cerebral white matter lesions. J Orthop Res. 2007; 25: 1087-1093.
23. Sachdev P, Wen W, Chen X, Brodaty H. Progression of white matter hyperintensities in elderly individuals over 3 years. Neurology 2007; 68: 214-222.