Leukoaraiosis in Normotensive Patients to Assay Factors Other than Hypertension

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To evaluate factors other than hypertension that may be related to leukoaraiosis (LA), a neuroimaging finding and risk factor for stroke thought to be related to high blood pressure.

From September 2000 to June 2004, we enrolled 45 normotensive patients (systolic BP less than 100 mm Hg and/or diastolic BP less than 60 mm Hg) with LA changes on MR imaging. We retrospectively reviewed their age, sex, and laboratory data (platelet count, erythrocyte sedimentation rate, and creatinine, uric acid, lactate dehydrogenase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, and fasting glucose levels). Not all variable laboratory data were available for all patients. Among the 45 patients, six patients (13%) were men and 39 were women (87%). Their age ranged from 22 to 72 years, with mean ±SD of 52 years ± 11. Thirty-four patients (77%) were younger than 60 years. Twenty-two patients had normal creatinine and nineteen patients had normal uric acid levels. Seven (35%) of twenty patients had elevated (>130 mg/dL) triglyceride levels. Six (30%) of twenty patients had elevated total cholesterol concentrations, and only one patient had hyperglycemia. Nine (82%) of 11 patients had an elevated (>10 mm/h) erythrocyte sedimentation rate.

Arterial hypertension and hyperlipidemia were expected to be the main factor associated with LA. However, in normotensive patients, LA predominated in women and in younger (<60 years) patients, and was associated with an elevated erythrocyte sedimentation rate.

Key words: Hypertension; Leukoaraiosis; Magnetic Resonance Imaging (MRI)

In 1987, Hachinski et al defined the term leukoaraiosis (LA) as an abnormal CT appearance of the subcortical brain white matter [1]. Bilateral, patchy or diffuse areas of hypoattenuation with ill-defined margins are present in the periventricular regions or extend to the centrum semiovale. On T2-weighted or fluid-attenuated inversion recovery MR images, LA appears as a hyperintense change. LA also occurs inBinswanger disease and in a pathologic presentation called subcortical arteriosclerotic encephalopathy [2], in which it involves changes of demyelination, gliosis, cavitated and noncavitated small and deep infarctions.

LA is associated with previous stroke and also predictive of future ischemic or hemorrhagic strokes [3]. LA is thought to be ischemic, caused by hypoperfusion in small vascular territories [4]. Arterial hypertension is considered the main factor associated with LA, though there are other factors including atherosclerosis, cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy and ischemic leukoencephalopathy [5].

The purpose of this study was to evaluate factors other than hypertension that may be related to LA.

MATERIALS AND METHODS

Patients

We performed a computerized search of the medical records at the Buddhist Tzu Chi Medical Center in Hualien, Taiwan to identify patients who

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underwent physical examination and brain MR imaging between September 2000 and June 2004. All patients had normal blood pressure, which was defined as systolic BP less than 100 mm Hg and/or diastolic BP less than 60 mm Hg and which was checked twice. None had medication history, and none had a history of stroke. Only one patient had diabetes mellitus, but this was not controlled with medication. General physical examination and neurological examination showed no specific finding in those patients.

We reviewed their laboratory data, which included the following: platelet count, erythrocyte sedimentation rate (ESR), and creatinine, uric acid, lactate dehydrogenase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, fasting glucose, hemoglobin, and serum electrolyte (sodium and potassium) levels.

**MR Imaging**

MR imaging had been performed in all 45 patients. LA was defined as a small, patchy, hyperintense lesion in the periventricular white matter depicted on T2-weighted images (3.0 T; Signa, GE Medical Systems) obtained with a fluid-attenuated inversion recovery sequence (FLAIR 9000/80 TR/TE).

**Image Interpretation**

An experienced neuroradiologist interpreted the MR images. LA was staged as follows: stage 0 was no definite periventricular hyperintensity lesions; stage I, fewer than 10 lesions (Fig. 1); stage II, 10–20 lesions (Fig. 2); stage III, 20–30 lesions (Fig. 3); and stage IV, more than 30 lesions (Fig. 4).

**RESULTS**

Not all variable laboratory data were available for all patients. Our study population consisted of 45 patients, six (13%) men and 39 women (87%), aged 22 to 72 years (mean ± SD, 50 years ± 11). Thirty-four patients (77%) were younger than 60 years.

Twenty-two (100%) of 22 patients had normal (<2 mg/dL) creatinine levels, and 19 (100%) of 19 had normal (<7 mg/dL) uric acid levels. Seven (100%) of seven patients had normal (<400 IU/L) lactate dehydrogenase values, and five (63%) of eight patients had a decreased (<60 mg/dL) HDL-C concentration. Seven (35%) of 20 patients had elevated (>130 mg/dL) triglyceride levels, and six (30%) of 20 had an elevated (>200 mg/dL) total cholesterol value. One (5%) of 19 patients had hyperglycemia (fasting glucose concentration, >126 mg/dL). Nine (82%) of eleven patients had an elevated (>10 mm/h) ESR. Nine (100%) of nine had a normal (130–148 mg/dL) serum sodium value, and one (11%) of nine had a decreased (3.2–4.4 mg/dL) serum potassium value. Eight (44%) of 18 patients have mild anemia (hemoglobin value, male <13 mg/dL, female < 12 mg/dL). Fifteen (33%) of 15 patients had a normal (>130 × 103 per cubic millimeter platelet count). (The normal range of data was based on Laboratory department of Buddhist Tzu Chi Medical Center, Hualien, Taiwan).
In terms of staging, none of the patients had stage 0 LA, twelve had stage I, 15 had stage II, 15 had stage III, and 3 had stage IV.

**DISCUSSION**

Hypertension has been thought to be the main risk factor of LA, and a history of stroke is the single most important predictor of LA [6, 7]. In our study, however, we excluded the association of these two factors to LA and found some other trends related to the observed periventricular hyperintensity. For instance, in normotensive patients with LA, women were affected more frequently than men (87% vs 13%) and 77% were younger than 60 years. However, in previous studies, male sex was thought to be related to transient ischemic attack and LA [8]. Hyperlipidemia has also been discussed [9, 10, 11], though the conclusions are equivocal. We noted elevated triglyceride and total cholesterol in about only one-third of the patients in the study. The most obvious positive laboratory result in our study was the ESR, as 82% patients had an ESR greater than 10 mm/h. Izumi et al reported that a decreased ESR may be an index of a reduction in plasma viscosity, since ESR is an index of RBC aggregation due to defibrination and decreased ESR might indicate the improved cerebral circulation [11]. On the contrary, an elevated ESR might mean increased plasma viscosity and decreased cerebral blood flow, which might lead to LA.

In the study of Monje et al, bacterial lipopolysaccharide was injected into female rats to induce systemic inflammation and cause sequential signal transmission [12]. Their results showed that inflammatory blockade restores hippocampal neurogenesis. In their opinion, serum interleukin-6 levels in humans are correlated with poor cognitive performance and predictive of the risk of dementia. Clinical treatment with indomethacin and other NSAIDs improves the risk and/or progression of memory loss. ESR is an indicator for inflammatory process. An increased ESR may be another presentation of blocked neurogenesis and may be imply the relationship between LA and inflammatory processes. In our series, many patients started receiving NSAIDs after first time of MR image. Those patients will be followed up in one year and the following data and images will discussed in the future.

The intent of this article is to provide a pioneer study of risk factors of leukoaraiosis other than hypertension, and the following limitations are acknowledged: (1) The sample sizes are relatively small. (2) Because of the retrospective nature of our study, the various laboratory data were not available for all patients. Though the percentage of patients with elevated ESR is 82%, the case number is only nine out of eleven, which might not be of statistical significance.

**CONCLUSION**

Arterial hypertension was expected to be the main factor associated with LA. However, our study
demonstrated LA in normotensive patients with LA. Our results showed that the condition was predominant in women, more common in relatively younger (<60 y) patients and associated with an elevated ESR.

REFERENCE

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正常血壓病人之大腦小血管缺血性疾病危險因子之評估

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腦白質小病灶（Leukoaraisis）在神經影像學上被認為是一種危險因子，並且與高血壓有相關性。本研究的目的在評估除了高血壓外，有哪些因子與腦白質小病灶相關。在2000年九月至2004年六月間，共45位正常血壓之病人（收縮壓低於100毫米汞柱以及/或舒張壓低於60毫米汞柱）。回溯性收集這些病人之年齡、性別以及實驗室資料包括血小板數目、紅血球沉降速率、肌酸酐、尿酸、乳酸脫氫、高密度膽固醇、低密度膽固醇、三酸甘油酯、總膽固醇、以及空腹血糖。並非每位病人都能收集到完整的資料。有6位男性病人以及39位女性被納入這個實驗：年齡分布從22歲至72歲，平均為52 ± 11歲。34位（77%）小於60歲。22位病人有正常血清濃度的肌酸酐以及19位病人有正常血清濃度的尿酸。20位病人中有7位（33%）的三酸甘油酯上升超過正常值。20位病人中的6位（30%）有升高的總膽固醇濃度。只有一位病人有高血醣。11位病人中有9位（82%）有紅血球沉降率升高的現象。

過去的研究中認為高血壓以及高血脂是與腦白質小病灶相關的主要因子。但是在我們的實驗中發現在正常血壓的病人中，腦白質小病灶是與女性以及比較年輕（小於60歲）以及紅血球沉降率升高有關聯。

關鍵詞：高血壓、腦白質小病變、核磁共振造影