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Leuko-Araiosis, Vascular Risk Factors, and Cognitive Function in the Elderly

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=국문초록=

노년에서 Leuko-Araiosis와 혈관 위험인자 및 인지 기능

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목 적 : 뇌 영상 촬영기법의 발달로 흔히 "leuko-araiosis"(LA)라 일컫는 대뇌 백질의 미만성 또는 다발성 변화는 노인에서 흔히 관찰되는 소견이지만, 병태생리는 아직 명확히 알려져 있지 않다. LA와 혈관 위험 인자와의 연관성 및 LA가 인지 기능장애에 미치는 영향을 알아보기 위하여 본 연구를 시행하였다.

실험재료 및 방법 : 치매 평가를 위해 의뢰된 55세 이상의 환자들을 대상으로 자기공명영상에서 관찰된 LA 척도와 통상적인 혈관 질환의 위험인자(혈압, 당뇨, 흡연 및 혈관질환의 병력) 및 인지 기능의 변화(최소신경검사 척도 및 P300 잠복기)와의 상호관계를 알아보았다.

결 과 : 40명의 환자들이 연구에 포함되었다. LA 척도와 혈관 질환의 병력은 유의한 상관 관계를 보였다. LA 척도가 높은 군에서 P300 잠복기의 지연과 최소 신경검사 척도의 감소를 보이고 있었다.

결 론 : 본 연구에서 LA의 진행에 혈관 질환의 과거력이 유의한 상관관계를 가지며, LA의 진행이 인지능력의 저하와 관련됨을 확인 할 수 있었다.

중심 단어 : Leuko-araiosis · MRI · Risk factor · MMSE · P300.

Introduction

The emergence of sensitive techniques for brain imaging has drawn attention to the occurrence of diffuse or multifocal changes affecting the cerebral white matter. The white matter changes are usually termed periventricular leukoencephalopathy, or leukoaraiosis (LA) [1)2)]. The etiology of LA may be heterogeneous but is most likely ischemic in nature[3)4)]. Not surprisingly, diffuse periventricular LA affects cognitive function[5)6)]. However, the clinical significance of LA remains controversial.

The P300 component of evoked potential has demonstrated considerable utility in the study of aging because it is thought to result from neural activity associated with attention and memory process[7)]. It has been reported that P300 latency increases as cognitive capability decreases because of dementing illness[8)9)]. The aim of our study was to identify poten-

tial risk factors for and cognitive correlates of LA. The relationships among LA grade, conventional vascular risk factors, Mini-Mental State Examination(MMSE) score and p300 were studied.

Material and Methods

All patients were registered at the EWHA Womans University Mokdong hospital, between August 1998 and July 1999, referred for the investigation of dementia. A history and neurologic examination, questions about conventional vascular risk factors including hypertension, diabetes mellitus, smoking and history of vascular events such as cerebrovascular events or myocardial infarction, and the MMSE were performed. The MMSE is a simple composite cognitive test that consists of 5 fields(orientation, registration, attention and calculation, recall, language). The MMSE has been shown to be valid and reliable[10][11].

P300 component was elicited with a simple discrimination task, oddball paradigm. An odd-ball paradigm with 128 stimuli(80% frequent tones at 1,500Hz and 20% rare tones at 6,000Hz), interstimulus interval of 0.4 s, bandpass 20Hz and 0.1Hz, analysis time of 1 sec. and sensitivity of 50 microV was used. The stimulus intensity was adjusted for each subject in order to obtain the same subjective intensity in both ears. Subjects were instructed to ignore the frequent tones, count mentally the rare tones and give the total number at the end of recording. At least two artifact-free recordings(auto reject level 100%) were obtained for each subject during "on" stage. On the basis of other studies, the P300 component of latency was taken in this study. Latency(ms) was defined as the time from stimulus onset to the point of maximum positive amplitude within the latency window. The P300 latency was registered by surface electrodes placed in Cz according to 10-20 International System with reference to both linked mastoids process.

All patients underwent brain magnetic resonance imaging, with a 1.5-T magnet. LA was defined by means of Inzitari's criteria[2] and scored by means of the 0-2 points Breteler's rating scale(Fig. 1)[12]. Grade 0 showed no or slight periventricular hyperintensity (small caps or pencil-thin lining), fewer than five lesions, and no confluent lesions. Grade 1 showed moderate periventricular hyperintensity(caps on both anterior and posterior horns of the lateral ventricles, corpus only partly involved, not irregularly extending into the deep white matter) or five or more focal lesions, or both, but no confluent lesions. Images with severe periventricular hyperintensity(irregularly extending into the deep white matter or marked areas of hyperintensity completely surrounding the lateral ventricles) or confluent lesions were classified as grade 2

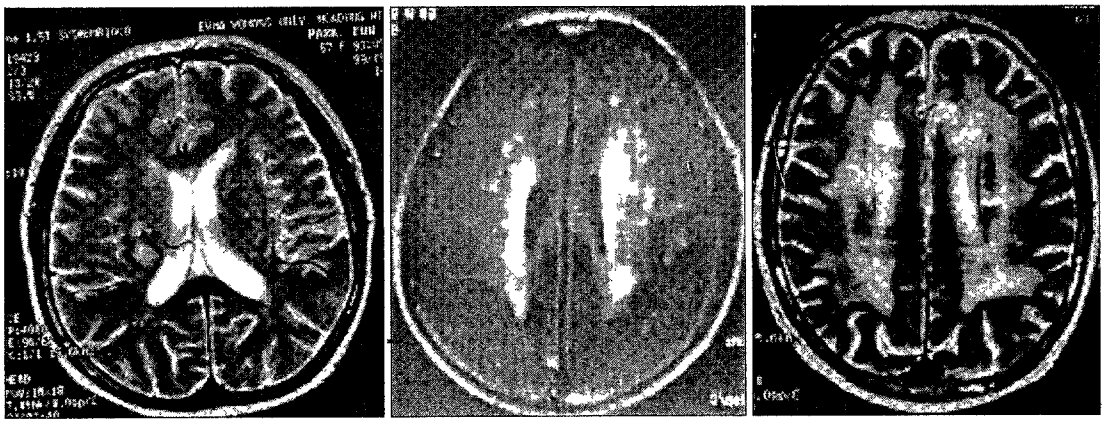

Fig. 1. 3 consecutive axial images of illustrative cases are presented. The severity of LA is graded as 0,1 or 2. Focal lesions without confluent lesions(grade 0, left), moderate periventricular hyperintensity(grade 1, middle), and confluent lesions(grade 2, right).

Table 1. Comparison of demographic data and vascular risk factors in patients for LA grade

LA grade	0	1	2
Number of patients	15(38%)	14(35%)	11(28%)
Age, y(mean)	64.6	67.2	67.0
Female sex	8(53%)	8(57%)	6(55%)
Vascular risk factors			
History of hypertension	10(67%)	9(64%)	8(73%)†
Diabetes mellitus	3(20%)	2(14%)	2(18%)
Smoking	2(13%)	6(43%)	2(18%)
History of vascular events	8(53%)	9(64.%)	9(82%)†

Values are number and percentages of subjects in each categories, unless otherwise indicated
†$p<.05$ by bivariate analysis using the Chi-square test

Table 2. Comparison of cognitive functions in patients for LA grade

LA grade	0	1	2
P300 latency	353.8±21.0	356.6±30.7	411.0±24.8†
MMSE	26.4± 3.2	22.3± 3.7†	17.6± 3.1†

Values are meansSD
†$p<.05$ vs. LA 0 by ANOVA and Student t test

regardless of the presence of the focal lesions.

Statistics were performed by means of SPSS statistical software. We related changes in LA grades to p300, MMSE, and vascular risk factors by means of bivariate statistical analysis with crude odds ratios with 95% confidence intervals. To examine the association of LA grade with vascular risk factors and cognitive functions, we constructed for these variables whose partial correlation coefficients for LA grade adjusted for age and sex. were significant at $p<.01$.

Results

We examined 46 patients ; because a reliable P300 was recorded in all but six subjects, we finally evaluated 40 patients(18 men and 22 women). The average age was 65.8 years(range, 57 to 81 years). Some characteristics of the subgroups according to LA grade are shown in Table 1. Those who with higher LA scores were more likely have a history of hypertension and cerebrovascular events or myocardial infarction and smoked. After adjusted for age and sex, LA grade was significantly related to the history

Table 3. Association between vascular risk factors and LA grade

Risk factors	Partial correlation coefficient*
Demographics	
Age, y	.176
Sex(man=0 ; woman=1)	.156
Vascular risk factors	
History of hypertension(no=0 ;	.1695
Diabetes mellitus(no=0 ; yes=1)	-.1839
Smoking(no=0 ; yes=1)	.2276
History of vascular events(no=0 ; yes=1)	.4755†

*Each row represents partial correlation of risk factor with LA grade adjusted for age and sex. Partial correlation coefficients for age and sex are from a model containing only these two variables.
†$p<.05$.

Table 4. Association between cognitive factors and LA grade

Cognitive functions	Partial correlation coefficient*
P300 latency	.5045†
MMSE	-.7070§

†$p<.01$, §<0.001.

of vascular events, but not to the history of hypertension or smoking(Table 3). There was significant difference in cognitive function in each LA grade. LA severity was found to be positively correlated with P300 latency and negatively correlated with MMSE score(Table 2). Even after we adjusted for age and sex, LA grade was significantly related to P 300 latency and MMSE score(Table 4). However, we found no evidence for a relation between MMSE score and P300 latency, even afteradjusted for age and sex(partial correlation coefficient=-.348, $p>0.5$).

Discussion

With the technical developments of neuroimaging, the frequent appearance of white matter lesions of unknown origin is common in older people. In 1987 Hachinski suggested the term "leuko-araiosis" for such lesions of white matter whose pathogenesis requires clarification[1]. These lesions increase in frequency and severity with age[13], but there is controversy regard-

ing their pathologic significance.

It is now well-documented that there are several risk factors that cause white matter lesion such as advanced age[13], hypertension, occlusive disease of the internal carotid artery 14), and history of stroke, particularly of the lacune type[15]. In our study, history of cerebrovascular events or myocardial infarction was considered as a statistically significant predictive factor of the severity of LA. Breteler, et al[12] found previous cardiovascular events to be related to white matter lesion in a population based study. In some previous studies, arterial hypertension[16] and diabetes mellitus[17] have been found to be statistically linked to LA. In our study, although LA free subjects were not included, arterial hypertension and diabetes mellitus were not found to be a predictor factor of the severity of LA. A possible explanation for these results regarding LA severity in our study may be that the relative importance of various atherogenic factors related to white matter lesion could actually differ. Another explanation is that they could be the selection bias.

Although some investigators have found a relationship between the white matter lesions and cognitive deficit[5][6], others have not[14][18]. Our findings regarding LA establish the link to date between decline in cognition and changes in white matter on MRI, although our neuropsychological testing was not especially extensive. Rather we studied subjects with LA using both neuropsychological and neuropsychological test. Cognitive evoked potential is the result of endogenous brain response following cognitive stimulus[7]. Only P3(00) wave is widely applicated in clinical fields among several kinds of waves. In some studies a relationship between the P300 latency and dementia was found[8][9], but not in others[19]. In our study, we found no evidence for a relation between neuropyschogical test MMSE and neurophysiological study P300. The lack of correlation is not surprising ; indeed the P300 are the final product of a set of mental processes[7], which are hard to evaluate by means of a few neuropsychological tests. Even though the precise relationship between P300 values and neuropsychologic function is not yet clear, the simplicity and the rapidity of execution of the P 300 latency has demonstrated considerable utility in the study of cognitive aging. Recent studies about the relationship among P300, neuroimaging and neuropyschologic test revealed the significant association between neurophysiological and neuropsychological measurement[20][21]. The significant association between MMSE, P300 latency and LA grade in our study reflects a disrupted aspect of cognitive function in patients with LA. The dementia associated with LA is predominantly of the subcortical type[22], and P300 may be a useful means to assess the degree of subcortical cognitive deterioration.

Conclusions

LA, as identified by MRI, embraces common and subtle changes of unclear cause. The purpose of this study was to investigate potential risk factors for and cognitive correlates of LA. The relationships among LA grade, conventional vascular risk factors, MMSE score and P300 latency were studied. P300 was measured at Cz site using an oddball paradigm. LA severity was significantly related to the history of cerebrovascular events or myocardial infarction. There was significant difference in cognitive function in each LA grade. LA severity was found to be positively correlated with P300 latency and negatively correlated with MMSE. Although heterogeneity of LA and often-limited extent render assessment of its effect difficulty, this study suggest that severe LA can produce cognitive impairment. Also, the P300 measurement reflects a disrupted aspect of cognitive function in patients with LA.

If LA is marker for impaired cognitive function, as suggested by this and other studies, the search for causal risk factor is important because modification of them might reduce the risk of cognitive dysfunctions in the elderly. Longitudinal studies will be needed to determine a causal relationship between LA and cognitive function.

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