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ORIGINAL ARTICLE

Confirmation of the abnormal lipid metabolism as a risk factor for the disease of leukoaraiosis



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Abstract Our purpose is to screen out medical history indicators and test indicators linked to lipid metabolism which is closely correlated to leukoaraiosis (LA), and to build assistant diagnosis model based on support vector machine (SVM), which provided theoretical evidence for genesis and development of LA. One thousand LA patients who underwent magnetic resonance imaging (MRI) examination in Imaging Department was retrospectively analyzed and divided into LA group and non-LA group in accordance with examination results. Detailed clinical statistics of the two groups were collected, including test indicators related to lipid metabolism, such as total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), medical history indicators, age, sex, diabetes, hypertension, hyperlipidemia, history of intracranial infection, history of cerebral hemorrhage, cerebral infarction, lacunar infarction and relevant biochemical indexes. The study shows that patients' incidence of LA was 31.10%; in accordance with Logistic analysis, the incidence of LA is significantly correlated to factors like age, hypertension, history of cerebral hemorrhage, cerebral infarction, lacunar infarction and triglyceride elevation; two SVMs, one including all variables and the other containing all screened variables were successfully established, and the former's accuracy, specificity and sensitivity respectively were 85.0%, 85.0% and 85.0% while the latter's 90.0%, 100.0% and 80.0%. Test indicators and medical history indicators of lipid metabolism correlated to LA were screened out successfully. Meanwhile, an effective SVM model also was built successfully, which is able to predict LA relatively accurately and can be used as assistant diagnostic tool for clinicians.

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1. Introduction

Hyperlipemia, known as dyslipidemia in modern medicine, is characterized by excessive total serum cholesterol and triglyceride (Kagoya et al., 2012). Due to no obvious symptoms and latent onset, hyperlipemia is called “the Silent Killer” in the field of medicine (Zhang, 2016) and it is generally found

in physical examination. At present, serum total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) are often used as test indicators of hyperlipidemia, any of which exceeding normal criteria is recorded as hyperlipidemia. Leukoaraiosis (LA), described in iconography, is a disease of abnormal changes in cerebral white matter. It is proposed in 1986 by the Canadian neurologist Hachinski et al. (1986). LA is often found in the medical examination of the elderly so it was believed that the disease was only related to age and drew little attention from people. But in fact, it is a clinical syndrome caused by a variety of pathogenesis (Huo and Feng, 2015). Pathological studies have shown that LA lesions are mainly caused by the changes of demyelination in white matter, which is expressed in CT as white matter mottling or diffuse low density image in periventricular and semi-oval central area (Huo and Feng, 2015), and in magnetic resonance imaging (MRI) showed isointense or hypointense on T1-weighted image and hyperintense on T2-weighted image. Studies have shown that LA is a biomedical marker for brain aging (Ross et al., 2005) and is closely correlated to Alzheimer (Guo et al., 2004; Pantoni et al., 2007). LA may be a different manifestation pattern of stroke in addition to causing slowed thinking, declined cognitive function and mental status changes (Hassan et al., 2004).

At present, there is no effective therapy for LA, thus how to prevent LA has been a hot research issue (Hassan et al., 2004; Culebras, 2004; Fujita et al., 2005; Altaf et al., 2006; Chen et al., 2004). Through looking for risk factors inducing LA and treating them targetedly can effectively prevent occurrence of dementia, stroke and death. This study established support vector machine (SVM) based on the risk factors inducing LA and provided certain theoretical basis for prevention of LA's genesis and development.

2. Materials and methods

2.1. Subjects

One thousand patients who received enhanced cranial plain scan MRI examination in Imaging Department from September 2010 to September 2015 were enrolled. According to the MRI findings and LA diagnostic criteria, patients were divided into LA group and non-LA group. After reading documents (Culebras, 2004; Fujita et al., 2005), reported pathogenesis of LA was combined with clinical experience to collect the possible factors related to LA. Finally, risk factors included in the study were age, sex, diabetes, hypertension, history of intracranial infection, cerebral hemorrhage, cerebral infarction as well as lacunar infarction, and test indicators linked to lipid metabolism (TC, TG, LDL and HDL). In addition, detailed medical history of each patient was inquired by the same neurologist, and MRI images of cerebral infarction and lacunar infarction were combined to collect materials of patients.

2.2. Variable definitions

① LA: LA is shown as the punctuate, patchy or fusion flaky long T1 and long T2 signals on MRI around the ventricle.

② Infarction: Infarction is shown as long T1 and long T2 signals on MRI with a diameter > 5 mm.

③ Lacunar infarction: Lacunar infarction was shown as long T1 and long T2 signals on MRI with a diameter < 15 mm: level 0 = no; level 1 = 1 ~ 3; level 2 = 4 ~ 10; level 3 = more than 10.

④ History of hypertension: According to the WHO/ISH *Guidelines and Reports of Hypertension* in 2007, Systolic Blood Pressure (SBP) \geq 140 mmHg and/or Diastolic Blood Pressure (DBP) \geq 90 mmHg and/or who are taking antihypertensive drugs are recorded as hypertension history.

⑤ Diabetes: The diagnostic standards of World Health Organization (WHO) about diabetes in 2005 are: showing diabetes symptoms and fasting blood-glucose \geq 7.0 mmol/L (126 mg/dl), or blood glucose \geq 11.1 mmol/L (200 mg/dl) 2 h after meal.

⑥ Hyperlipidemia: According to *Guidelines for Prevention and Treatment of Chinese Adult Dyslipidemia* in 2007, any terms exceeds the four following criteria can be recorded as hyperlipidemia: TC \geq 5.80 mmol/L, TG \geq 1.80 mmol/L, LDL \geq 3.60 mmol/L, HDL \leq 1.00 mmol/L, any index from the above four terms exceeds the standard will be decided as hyperlipidemia.

⑦ Cerebral hemorrhage history: Since a variety of causes lead to cerebral hemorrhage, all patients ever had the disease are recorded as a history of cerebral hemorrhage.

2.3. Statistical analysis

SPSS21.0 software was utilized for statistical analysis, χ^2 test was used for comparison and $P < 0.05$ was considered statistically significant.

2.4. Logistic regression analysis

Several risk factors of LA have been screened out with forward stepwise Logistic regression analysis by SPSS 21.0 software in this study.

2.5. SVM

Two assistant diagnostic models of LA based on all variables and screened variables respectively were established with SVM algorithm. Then the results were divided into two categories and each of them was randomly divided into two groups, one as training set and the other as test set. The SVM models were constructed by MATLAB software and evaluated in terms of accuracy, sensitivity and specificity.

3. Results

3.1. The incidence of LA

According to the analysis of 1000 patients' clinical data, their incidence of LA was 30.10% (311/1000). The percentage of patients who had diabetes, hypertension, hyperlipidemia, history of cerebral hemorrhage, cerebral infarction, lacunar infarction, triglyceride elevation in LA group was greater than that in non-LA group.

3.2. Analysis of LA risk factors

χ^2 test was applied to eight medical history indicators and four test indicators and the test results are shown in Tables 1 and 2 which indicated that differences of the incidence of LA in age, diabetes, hypertension, hyperlipidemia, history of cerebral hemorrhage, cerebral infarction, lacunar infarction and triglycerides elevation were all statistically significant ($P < 0.05$), suggesting that age, diabetes, hypertension, hyperlipidemia, history of cerebral hemorrhage, cerebral infarction, lacunar infarction and elevated triglycerides were correlated to the incidence of LA.

3.3. Logistic regression analysis

Regrading LA as dependent variable and LA risk factors as covariate, this study used forward stepwise Logistic regression analysis to screen out significant indicators for LA diagnosis, and the results are listed in Table 3. It was found that age, hypertension, history of cerebral hemorrhage, cerebral infarction, lacunar infarction, and elevated triglycerides were significantly correlated with the incidence of LA.

3.4. SVM model

All cases were divided into two groups, LA group and non-LA group. 291 cases randomly selected from LA group and 669 cases from non-LA from group were regarded as training sets based on which SVM model was established. Then the rest 20 cases from LA group and 20 cases from non-LA group were taken as test sample and were put into SVM model to perform training and simulating tasks. Two SVM models, one including all variables and the other including screened variables, were established, and their simulation results are shown in Figs. 1 and 2, in which abscissa represents test sample;

ordinate represents, output result of model; “o” represents target output; and “*” represents actual simulation output of SVM. When all variables were included, SVM’s accuracy, specificity and sensitivity respectively were 85.0%, 85.0% and 85.0%; when screened variables were included, SVM’s accuracy, specificity and sensitivity respectively were 90.0%, 100.0% and 80.0%. It can be concluded that SVM including screened variables was better than SVM including all variables in terms of accuracy and specificity. And SVM simulation results had the highest fit level compared with actual results and had good efficacy.

4. Discussion

With the improvement of people’s living standard and the change of dietary structure, the prevalence of dyslipidemia is also gradually increasing, and abnormal lipid metabolism is closely related to the increase of hepatobiliary diseases, diabetes, cardiovascular disease and other biochemical indexes (Zhang et al., 2016; Hu, 1997). LA, an imaging concept, is a clinical syndrome induced by various etiologies and it is correlated to many factors. Most scholars believe that LA’s basic pathological changes are diffuse or localized demyelination in white matter and tissue looseness together with edema, reactive glial cell proliferation around cornu occipitale; intima thickening of subcortical white matter deep perforating artery branches together with lipid deposition, glassy degeneration or abercrombie’s degeneration of small vessel; loss of cells of ependymal layer; increase of extracellular fluid content among intervals around endyma and thinner and less axis cylinder (Chimowitz et al., 1992).

CT outcomes of LA is closely related to age. As seen from Table 1, the incidence rate of LA in each age group was significantly increased with age, which was respectively 2.05%, 20.31% and 53.44%. Logistic regression analysis showed that relative risk odds ratio (OR) of age to LA was 3.535 (95% CI

Table 1 Analysis of medical history indicators on LA.

Factor	Type	LA group	Non-LA group	χ^2	<i>P</i>
Age	≤40	3	143	176.442	0.000
	41–60	91	357		
	61–80	217	189		
Sex	Male	166	400	1.910	0.167
	Female	145	289		
Diabetes	No	254	600	5.031	0.025
	Yes	57	89		
Hypertension	No	195	483	5.376	0.020
	Yes	116	206		
History of intracranial infection	No	308	678	0.620	0.431
	Yes	3	11		
History of cerebral hemorrhage	No	304	684	4.204	0.040
	Yes	7	5		
History of cerebral infarction	No	269	674	51.154	0.000
	Yes	42	15		
History of lacunar infarction	0	28	431	326.423	0.000
	1	39	106		
	2	74	78		
	3	170	74		

Table 2 Analysis of test indicators on LA.

Test indicator	Type	LA group	Non-LA group	χ^2	<i>P</i>
Total cholesterol	≤5.8 mmol/L	255	588	1.814	0.178
	> 5.8 mmol/L	56	101		
Triglycerides	≤1.8 mmol/L	160	447	12.612	0.000
	> 1.8 mmol/L	151	242		
High density lipoprotein	> 1 mmol/L	231	519	0.126	0.723
	≤1 mmol/L	80	170		
Low density lipoprotein	≤3.6 mmol/L	228	504	0.109	0.741
	> 3.6 mmol/L	88	185		

Table 3 Logistic regression analysis of LA.

Factor	Regression coefficient β	<i>P</i>	OR	95% CI	
				Lower	Upper
Age	1.263	0.000	3.535	2.558	4.885
Hypertension	0.495	0.018	1.640	1.089	2.471
History of cerebral hemorrhage	1.891	0.030	6.626	1.206	36.418
Cerebral infarction	1.971	0.000	7.179	2.838	18.156
Lacunar infarction	0.998	0.000	2.712	2.328	3.160
Triglyceride	0.745	0.000	2.106	1.456	3.047

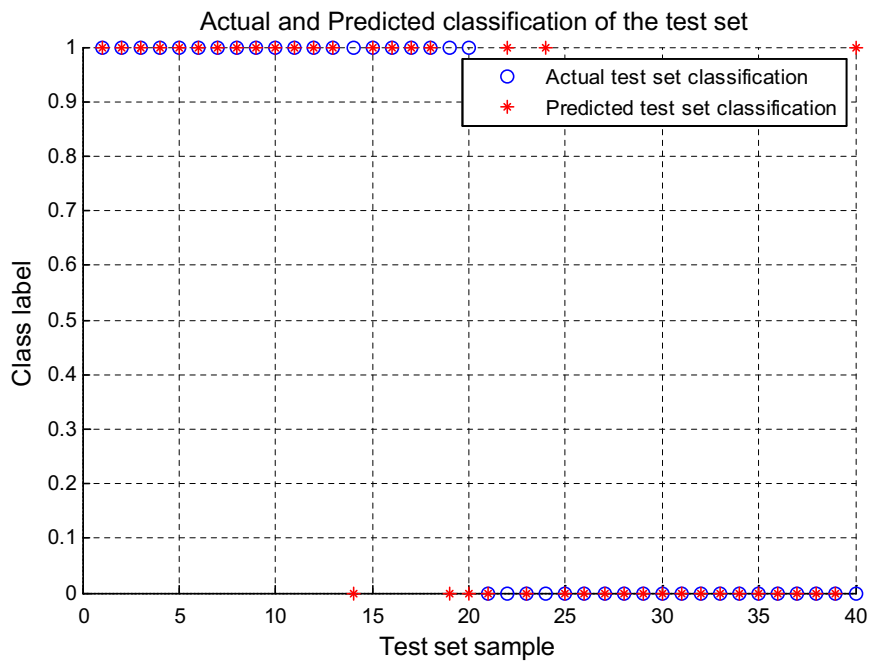


Figure 1 The simulation results of SVM model including in all variables.

2.558 ~ 4.885), indicating that when patient escalated into a higher age group, his risk of LA increased by 3.535 times, which showed that the incidence of LA increased with age. And the study results are in line with those of Zhou and Zhou (2009), indicating a possible association of partial LA with aging.

Among the four indicators causing hyperlipidemia, TC, HDL and LDL were related to the incidence of LA but the

difference among their relations had no remarkable significance. But in Logistic analysis, the OR of triglyceride was 2.106 (95% CI 1.456 ~ 3.047) and the LA incidence on people with high triglyceride was 2.106 times higher than normal people, which indicated that high-triglyceride hyperlipemia was a risk factor for LA, and this result is consistent with the research of Park et al. (2007) on the relations between abnormal metabolism and LA among healthy people. Therefore, the

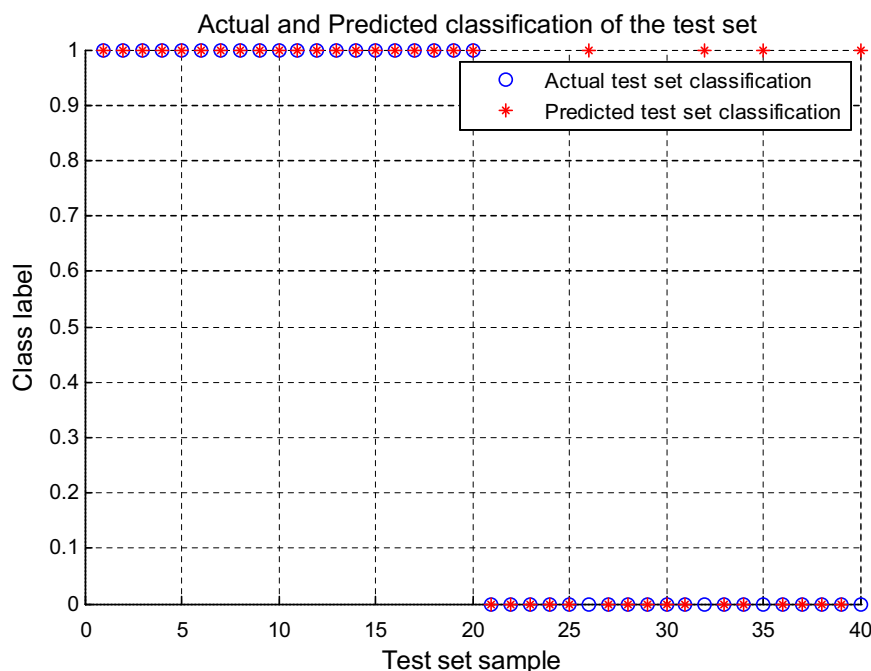


Figure 2 The simulation results of SVM model including in screened variables.

prevention of high triglyceride is effectively helpful for LA's prevention and treatment.

Table 3 shows that OR of the cerebral hemorrhage history was 6.626 (95% CI 1.206 ~ 36.418), illustrating there was a 6.626 times higher risk of LA in people with a history of cerebral hemorrhage than people without cerebral hemorrhage ever; the OR of cerebral infarction was 7.179 (95% CI 2.838 ~ 18.156), showing that the risk of people with cerebral infarction suffering from LA was 7.179 times higher than those without cerebral infarction; the OR of lacunar infarction was 2.712 (95% CI 2.328 ~ 3.160), suggesting that if lacunar infarction increased by one level, the risk of LA would increase 2.712 times. Therefore, the prevention and control of cerebral hemorrhage, cerebral infarction as well as lacunar infarction helps to reduce the incidence of LA.

Hypertension is a risk factor for LA, and compared with normal people, people with hypertension is more likely to have LA, which has been widely recognized (Saba and Mallarini, 2010). In this study, the OR value of hypertension was 1.64 (95% CI 1.089 ~ 2.471), which indicated that the risk of people with hypertension suffering from LA was 1.64 times higher than that of those without hypertension. According to its mechanism, cerebral hemispheres white matter is located in terminal zone of the blood-supply area of middle cerebral artery perforating arteries in cortical layer thus it is easier to get chemia injury than cortex. Therefore, the control and prevention of hypertension helps to decrease the incidence of LA.

Whether diabetes is correlated with white matter changes is controversial now. Longstreth et al. (1999) found that there was no relation between LA degree and fasting blood-glucose, blood insulin levels or history of diabetes, which was not consistent with study results by Baloh and Vinters (1995). And in this study, the incidence rate of LA in diabetes group (39.04%) was still higher than that in non-diabetes group (29.74%). The possible reason is that diabetes causes

cerebral arteriosclerosis inducing blood circulation disorder of white matter in deep brain which leads to hypoxic-ischemic demyelinating and cerebral infarction.

SVM has shown advantages in addressing small sample, nonlinearity and high dimensional mode recognition, and it, to a great extent, overcame problems of "dimension disaster" and "over learning" (Ding et al., 2011). SVM model has been well applied to medicine (Voigt et al., 2016; Wang et al., 2016), but it is rarely used in discussion of LA risk factors and the common method is to adopt Logistic analysis to explore relations between LA and risk factors (Liu et al., 2007; Liu, 2016). In this study, a SVM model containing risk factors screened through Logistic analysis was successfully established. And when including all variables, SVM model's accuracy, specificity and sensitivity were 85.0%, 85.0% and 85.0%, respectively; when including screened factors, SVM model's accuracy, specificity and sensitivity were 90.0%, 100.0% and 80.0%, respectively. It can be seen from the results that the accuracy and specificity of SVM including screened variables increased by 5% and 15%, respectively, while the sensitivity reduced by 5%. Therefore we say SVM including screened variables is superior to SVM including all variables. Moreover, screening out proper character subsets can not only simplify model but also improve its diagnostic efficacy.

The detection rate of LA is increasing year by year. In the case of no specific treatment drugs and methods for LA, effectively controlling various risk factors for LA, slowing the pace of its development, and then postponing a series of functions obstacles can significantly reduce the incidence of LA. This not only can, to some extent, alleviate the burden on patients and families, but also has a positive meaning for all people's healthy development. In the study, patient with elevated triglyceride, hypertension, cerebral infarction, lacunar infarction or history of cerebral hemorrhage is prone to LA, so the result is instructional for prevention of LA to some extent,

and the corresponding preventive measures for different risk factors can be formulated so as to reduce the occurrence of LA. In addition, people without these risk factors can also adopt targeted measures for prevention, thereby indirectly preventing the occurrence of LA caused by the corresponding risk factors.

5. Conclusions

Through Logistic regression analysis, this study screened out test indicators linked to lipid metabolism and medical history that are closely correlated with LA, and the study also shows that control of triglyceride level can reduce LA's incidence. Meanwhile, this study successfully built a SVM model based on the risk factors which can forecast LA relatively correctly and can be regarded as an assistant diagnostic tool for clinician.

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