Matrix metalloproteinase 9 level as an indicator for restenosis following cervical and intracranial angioplasty and stenting

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Abstract
Cervical and intracranial angioplasty and stenting is an effective and safe method of reducing the risk of ischemic stroke, but it may be affected by in-stent restenosis. The present study investigated serum level of matrix metalloproteinase 9 as a predictor of restenosis after 40 patients underwent cervical and/or intracranial angioplasty and stenting. Results showed that restenosis occurred in 30% (3/10) of patients when the serum level of matrix metalloproteinase 9 at 3 days after surgery was 2.5 times higher than preoperative level. Restenosis occurred when the serum level of matrix metalloproteinase 9 at 3 days after surgery was not 2.5 times higher than preoperative level. Restenosis occurred in 12% (2/17) of patients when the serum level of matrix metalloproteinase 9 was higher than preoperative level for more than 30 days after surgery, but only occurred in 4% (1/23) of patients when the serum level of matrix metalloproteinase 9 was higher than preoperative level for less than 30 days after surgery. However, the differences observed were not statistically significant (P > 0.05). Experimental findings indicate that when the serum level of matrix metalloproteinase 9 is 2.5 times higher than preoperative level at 3 days after cervical and intracranial angioplasty and stenting, it may serve as a predictor of in-stent restenosis.

Key Words: nerve regeneration; matrix metalloproteinase 9; cervical and intracranial angioplasty and stenting; restenosis; intracranial artery stenosis; neural regeneration

Funding: This study was supported by the Fund for Distinguished Young Doctors from Fujian Provincial Health Department, No. 2011-1-7.

Liu JP, Wang YZ, Li YK, Cheng Q, Zheng Z (2015) Matrix metalloproteinase 9 level as an indicator for restenosis following cervical and intracranial angioplasty and stenting. Neural Regen Res 10(4):631-635.

Introduction
Ischemic cerebrovascular disease is a disease of high incidence and morbidity in the elderly population all over the world. It is estimated that there are more than 2 million cases of stroke and more than 1.5 million deaths per year in China secondary to ischemic cerebrovascular disease. Among survivors, 66.7% develop disability to varying degrees. Cervical and intracranial angioplasty and stenting is an effective and relatively safe method of reducing the risk of ischemic stroke (Krasniqi et al., 2012; Liu et al., 2013). However, results may be affected by in-stent restenosis (Rutsch et al., 2012; King et al., 2013). Unfortunately, we have no proper indicators to predict and assess the risk of in-stent restenosis and to guide clinical prevention and treatment at present.

Matrix metalloproteinases (MMP) are a family of proteases in which MMP-9 plays an important role in intimal hyperplasia and vascular remodeling (Whatling et al., 2004; Tang et al., 2013; Vandooren et al., 2013; Wu et al., 2013; Zou et al., 2013). A recent study (Rao et al., 2014) has found that MMPs, especially MMP-9, are highly active and expressed at the site of artery in-stent restenosis. MMP-9 promotes smooth muscle cell migration in vessel walls from the media to the intima, proliferating and secreting amounts of extracellular matrix by integrating the degradation and deposition of the extracellular matrix, thereby contributing to artery restenosis (Visse and Nagase, 2003; Silvello et al., 2013; Wang and Cao, 2013; Guo et al., 2014; Yahagi et al., 2014). The formation of artery restenosis is a process of neointimal hyperplasia and vascular remodeling, which is mainly caused by excessive repair after injury. Studies have found that vascular smooth muscle cells do not exist in normal arterial intima. In fact, the rapid degradation of the extracellular matrix around vascular smooth muscle cells is considered to be a prerequisite for their migration (Chaabane et al., 2013). During the degradation of the extracellular matrix, the composition and content of the intima change, which may also influence vascular remodeling when restenosis occurs (Brott et al., 2011).

Neointimal hyperplasia was attenuated and luminal area was reduced in MMP-9 gene knockout mice, which removed the correlation of intimal hyperplasia and vascular remodeling in wild-type mice; while the abilities of migration of vascular smooth muscle cells and collagen contractility declined, indicating that MMP-9 is not only related to matrix...
degradation, but also matrix remodeling (Lee et al., 2011). Another study found that MMP-9 activity in peripheral serum was increased and closely related to postoperative restenosis after coronary stent implantation. However, the correlation between serum MMP-9 levels and incidence of in-stent restenosis after cervical and intracranial angioplasty and stenting is poorly understood (Jones et al., 1999).

The present study aims to investigate the relationship between incidence of in-stent restenosis and serum MMP-9 after cervical and intracranial angioplasty and stenting, and provide laboratory evidence for predicting the risk of in-stent restenosis clinically and improving drug treatment for the prevention of in-stent restenosis.

Subjects and Methods

Subjects

Patients with symptomatic or asymptomatic cervical and/or intracranial artery stenosis who underwent cervical and/or intracranial angioplasty and stenting were recruited retrospectively from the neurology clinical database of Fujian Provincial Hospital (Fuzhou, Fujian Province, China). All patients received interventional treatment for the first time. There were 22 males and 18 females, aged from 39 to 75 years of age (average 51 ± 9 years). Among the patients involved, 24 cases had hypertension, 18 had diabetes, 33 had hyperlipidemia, 9 had hyperhomocysteinemia, and 15 were smokers. For all carotid artery stenoses, we used Aviator Plus balloons (Cordis, Roden, the Netherlands) and Precise stents (Cordis, Miami Lakes, FL, USA). For all vertebral, basal and middle cerebral artery stenosis, we used Apollo balloon expansion stents. All stents were placed correctly using the proper size and residual stenosis was less than 20%.

Patients were required to meet the following criteria: (1) Vascular diameter stenosis in patients with intracranial artery stenosis was more than 70%. (2) Vascular diameter stenosis in patients with cervical artery stenosis was more than 50%. (3) Be less than 80-year-old. (4) Patients with acute cerebral infarction (less than 2 weeks) and cerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage were excluded. (5) Patients with leukemia, aplastic anemia, idiopathic thrombocytopenic purpura, or platelets and coagulation dysfunction were excluded. (6) Patients with multiple organ failure were excluded (Fiotti et al., 2006). The control group was 20 healthy adult volunteers recruited from the Health Examination Centre of Fujian Provincial Hospital in China. All details of the study were explained to all subjects, whereupon written informed consent was obtained.

Detection of peripheral MMP-9 and hypersensitive C reactive protein by enzyme linked immunosorbent assay (ELISA)

Serum samples from the median cubital vein of 40 patients and 20 healthy people were collected in Fujian Provincial Hospital and diluted with PBS (pH 7.4). The serum MMP-9 level was analyzed using the ELISA method. In brief, 100 μL serum specimens were applied to the 96-well plates and incubated overnight at 4°C. After three washes with PBS, each well was blocked with 0.5% skimmed milk at room temperature for 1 hour. After another three washes with PBS containing 0.05% Tween 20, mouse anti-human MMP-9 antibody (1:200; Abcam, Cambridge, UK) was applied to wells and incubated at room temperature for 2 hours. Then horseradish peroxidase-conjugated goat anti-mouse IgG (1:1,000; Dako, Glostrup, Denmark) was added, followed by incubation with SureBlue™ TMB Microwell Peroxidase Substrate (KPL, Gaithersburg, MD, USA). After color development, the reaction was stopped with 1 M HCl and the optical density of the solution was read at a wavelength of 450 nm using a microplate reader (iMark™ Microplate Reader; Bio-Rad, Hercules, CA, USA). The serum hypersensitive C reactive protein level was analyzed using an automatic biochemical analyzer (AU5800, BECKMAN, Brea, CA, USA).

Postoperative follow-up

For all subjects, blood samples were taken 0.5 hours before surgery and 1 day, 3 days, 30 days, 6 months and 12 months after surgery to measure the serum levels of MMP-9. Restenosis was observed by carotid and vertebral artery ultrasound or transcranial doppler at 1, 6, 12 months and computer tomography angiography at 6 and 12 months after surgery (data not shown). If restenosis was observed, digital subtraction angiography was taken immediately for measuring the degree of restenosis. Follow-up rate of subjects was greater than 80% and the standard in-stent restenosis extent was greater than 50%. Blood samples were taken only once from the control group as reference.

Statistical analysis

Data are expressed as the mean ± SD. SPSS 13.0 software (SPSS, Chicago, IL, USA) was used to perform statistical analysis. The distribution of continuous variables was assessed and analyzed with one-way analysis of variance and the Fisher protected least significant difference test. A P < 0.05 value was considered a significant difference.

Results

Change of serum MMP-9 level after cervical and intracranial angioplasty and stenting

The serum level of MMP-9 showed no significant difference between the experimental group and the normal control group before surgery. However, after surgery, the serum level of MMP-9 was significantly increased and reached a peak at 3 days postoperatively. In more than half the patients, the serum MMP-9 level declined to preoperative level at 30 days after surgery. While in some patients, high level of MMP-9 was observed for more than 1 month after surgery, whereupon levels slowly dropped to preoperative amounts within 6–12 months after surgery (Figure 1). The peak of MMP-9 level varied from 1.2 to 3.8 (2.0 ± 0.9) times higher than preoperative levels. To find a better predictor of restenosis after surgery, we divided patients based on the MMP-9 peak level at 3 days after surgery or the duration of high MMP-9 level and analyzed their relationship to the incidence of in-stent
restenosis. There were 10 patients in whom the serum level of MMP-9 was 2.5 times higher than preoperative level at 3 days after surgery (high peak level group), and 30 patients in whom the peak level of serum MMP-9 was not 2.5 times higher than preoperative level at 3 days after surgery (low peak level group). By contrast, 17 patients displayed a serum level of MMP-9 at 30 days still higher than preoperative level (long duration group), and 23 patients in whom the serum level of MMP-9 at 30 days was declined to preoperative level (short duration group).

Change of serum hypersensitive C reactive protein level after cervical and intracranial angioplasty and stenting

The serum level of hypersensitive C reactive protein before and after surgery was similar, but was slightly higher than that in the control group (data not shown). However, there was no significant difference ($P > 0.05$). After surgery, the level of hypersensitive C reactive protein increased and decreased at different time points, but there was no clear trend related to the operation (Figure 2). The level of hypersensitive C reactive protein showed no significant difference among patients who had different MMP-9 levels. Therefore, this study demonstrates that hypersensitive C reactive protein does not have any potential to predict prognosis following surgery.

Follow-up results after cervical and/or intracranial angioplasty and stenting

Follow-up lasted for 18 months and three patients were confirmed to have in-stent restenosis (Figure 3). The three patients belonged to the MMP-9 high peak level group ($n = 10$ patients), while no in-stent restenosis was observed in the MMP-9 low peak level group ($n = 30$ patients). There were significant differences in the incidence of in-stent restenosis between these two groups (30% vs. 0, $P < 0.01$). Two patients with in-stent restenosis belonged to the MMP-9 long duration group ($n = 17$ patients), and one patient with in-stent restenosis belonged to the MMP-9 short duration group ($n = 23$ patients). Unfortunately, the incidence of in-stent restenosis between these two groups was not statistically significant (12% vs. 4%, $P > 0.05$).

Discussion

Endovascular stenting has become one of the main treat-
ment methods of cervical and intracranial artery stenosis due to satisfactory clinical efficacy, but results may be affected by in-stent restenosis (Hou et al., 2014; Li et al., 2014; Sun et al., 2014). Symptomatic intracranial atherosclerotic stenosis can be cured by implanting Wingspan stents (McTaggart et al., 2014). Krasniqi et al. (2012) showed that the restenosis rate of carotid artery stenting was 4.3% at a mean follow-up time of 22 months. Previous studies into symptomatic vertebral artery and intracranial atherosclerotic lesion stenting showed that the rate of restenosis was 32% in 6 months after bare stent implantation (Saati Yaşar et al., 2009). But over the past few years, carotid endovascular techniques have been markedly refined with the availability of wires and stents that are specifically designed for the carotid artery and it is likely that these modifications will improve efficacy and reduce the risks associated with treatment in the future.

It has been reported that the level of MMP-9 significantly increased after atherosclerosis. Previous studies performed in mice, rats, and rabbits have also demonstrated that arterial injury is a potent activator of the MMP system (Bendeck et al., 1994; Zempo et al., 1994; Strauss et al., 1996; Webb et al., 1997; Aikawa et al., 1998; Bassiony et al., 1998; Jenkins et al., 1998; Lijnen et al., 1998). Feldman et al. (2001) provided evidence that MMP activation occurred after stenting, and activation of latent MMP-9 was found in stented arteries. MMP-9 is the main MMP that vascular wall cells secreted, and it plays an important role in neointimal hyperplasia and vascular remodeling (Liu et al., 2009). MMP-9 promotes migration of vessel wall smooth muscle cells from the media to the intima, and also enables proliferation and secretion of the extracellular matrix by integrating its degradation and deposition, thereby contributing to artery restenosis. The formation of artery restenosis is a process of neointimal hyperplasia and vascular remodeling, which is mainly caused by excessive repair after injury. Studies have found that vascular smooth muscle cells do not exist in normal arterial intima, and the rapid degradation of the extracellular matrix of vascular smooth muscle cells is considered to be a prerequisite for their migration. The degradation of the extracellular matrix relates not only to the proliferation and migration of vascular smooth muscle cells, but also to the changes in the composition and content of the arterial intima (Brott et al., 2011).

Intimal hyperplasia and luminal area is reduced in MMP-9 gene deficient mice, which eliminated the correlation of wild-type endometrial hyperplasia and geometric remodeling. Furthermore, migration of vascular smooth muscle cells and collagen contractility declined, indicating that MMP-9 was not only related to matrix degradation, but also matrix remodeling (Lee et al., 2011). Bendeck et al. (2002) found that serum MMP-9 in mice was expressed from the first day after injury of the carotid artery and reached a peak at 6 days. MMP-9 levels then subsequently decreased gradually. Other animal experiments also confirmed that the expression of MMP-9 increased significantly in a time-dependent manner after stent implantation (Hou et al., 2002). Jones et al. (1999) found that MMP-9 activity in the serum increased and was closely related to postoperative restenosis after coronary stent implantation. Other studies also have shown that MMP-9 participated in repair after arterial injury and restenosis. The present study followed patients who underwent cervical and intracranial angioplasty and stenting for 18 months and found that when the level of serum MMP-9 was 2.5 times higher than normal levels at 3 days after surgery, the rate of restenosis was 50%, which showed a high relationship with, and had an important value in predicting, restenosis after cervical and intracranial angioplasty and stenting. Therefore, this study showed that when the level of serum MMP-9 is 2.5 times higher than normal levels at 3 days after surgery, it may be a new indicator for predicting restenosis after implantation of a stent. Since in-stent restenosis is one of the most important factors that affect the outcomes of angioplasty and stenting, our findings help us to determine the high risk patients who are at risk of developing in-stent restenosis allowing intensified medical treatment to be given to reduce this complication. It has been reported recently that the expression of MMP-9 is highly related to the clinical outcomes after stenting. The present study showed that MMP-9 was a powerful indicator of stent restenosis and was highly predictive of clinical outcomes after stenting. The present study showed that MMP-9 was a powerful indicator of stent restenosis and was highly predictive of clinical outcomes after stenting.

**Acknowledgments:** We would like to thank Mr. Tao Zhang from the Second Hospital of Fuzhou Affiliated to Xiamen University in China for his assistance with data collection.

**Author contributions:** JPL was responsible for the concept and design of the study, analyzing experimental data, writing the paper, and performing statistical analysis. JPL was also in charge of the funds. YZW supervised the study and revised the article. YKL, QC and ZZ provided the data and technical information. All authors approved the final version of the paper.

**Conflicts of interest:** None declared.

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