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## Risk factors of brain herniation in patients with acute middle cerebral artery occlusion

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**Background** : *In acute massive hemispheric infarction caused by middle cerebral artery occlusion, 40 - 50 % of the cases progress to edema and herniation of the brain (malignant MCA infarction) a condition which has high mortality rate (40 -100 %). Identifying the risk factors of brain herniation in this group of patients may change the outcome by some kinds of procedure such as decompressive craniectomy operation to receive early treatment which will benefit them most.*

**Methods** : *This is a retrospective analytical study in patients with acute massive hemispheric infarction from middle cerebral artery occlusion who were admitted to King Chulalongkorn Memorial Hospital from January 1<sup>st</sup> 2004 (2547BE) to June 30<sup>th</sup> 2005 (2548 BE). In total there were 48 cases who were divided into two groups: patient group, i.e., patients who had brain edema that caused brain herniation, and control group, i.e., patients who had no brain edema and brain herniation. Analysis was based on clinical data of symptoms and signs and laboratory findings collected from hospital and in-patient records.*

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**Results** : In the patient group, there were 8 cases (16.7 %) and in the control group, 40 cases (83.3 %). The risk factor that was associated with brain herniation with statistical significance was the heart rate (OR = 1.08, 95 % CI 1.02-1.15,  $p = 0.011$ ). As for the risk factors of brain herniation which were not associated with statistical significance were: 1) diastolic blood pressure on admission (OR = 1.02, 95 % CI 0.98-1.05,  $p = 0.384$ ); 2) history of diabetes (OR = 1.4,  $p = 0.692$ ); 3) history of hypertension (OR = 4.2,  $p = 0.240$ ) 4) high blood cholesterol (OR = 1.01, 95 % CI 0.99-1.02,  $p = 0.799$ ); 5) fasting blood sugar (OR = 1.01, 95 % CI 0.99-1.02,  $p = 0.120$ ); 6) level of blood HDL (OR = 1.05, 95 % CI 0.99-1.12,  $p = 0.079$ ); and, 7) atrial fibrillation (OR = 1.52,  $p = 0.356$ ).

**Conclusion** : Risk factors to brain herniation manifest in clinical symptoms and signs and laboratory findings are: heart rate, diastolic blood pressure, history of diabetes and hypertension, level of fasting blood sugar, and blood cholesterol, number of white cells in the blood and atrial fibrillation. The collected data correspond with previous studies. However, there is still the need to have prospective, multi-centered studies that recruit more number of patients to confirm the result and to acquire risk factors with statistical significance.

**Keywords** : Brain herniation, Acute brain infarction, Middle cerebral artery.

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**ฐกรรต์ ชัยสาม, นิจศรี ชาญณรงค์. ปัจจัยเสี่ยงของการเกิดสมองเลื่อนในผู้ป่วยสมองขาดเลือดเฉียบพลันจากการอุดตันของหลอดเลือดแดง middle cerebral. จุฬาลงกรณ์เวชสาร 2550 ก.ค. - ส.ค; 51(7): 317 - 26**

**หลักการและเหตุผล** : ภาวะสมองขาดเลือดเฉียบพลันเป็นบริเวณกว้างจากการอุดตันของหลอดเลือด middle cerebral (massive hemispheric infarction) เป็นภาวะที่มีการดำเนินโรคเกิดการบวมและเลื่อนที่ของสมอง (malignant MCA infarction) ได้ร้อยละ 40-50 ซึ่งเป็นภาวะที่มีอัตราตายสูง (ร้อยละ 40 -100) การค้นหาปัจจัยเสี่ยงของการเกิดการเลื่อนที่ของสมองในผู้ป่วยกลุ่มนี้จะทำให้สามารถนำผู้ป่วยที่คาดว่าจะได้รับประโยชน์จากการรักษาบางอย่างเช่นการผ่าตัด decompressive craniectomy ไปรับการรักษาตั้งแต่ในระยะแรก อันจะเกิดประโยชน์สูงสุดแก่ผู้ป่วยต่อไป

**วิธีการศึกษา** : เป็นการศึกษาระบบ retrospective case-control ในผู้ป่วยโรคสมองขาดเลือดเฉียบพลันจากการอุดตันของหลอดเลือด middle cerebral ที่เข้ารับการักษาในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่วันที่ 1 มกราคม 2547 ถึงวันที่ 30 มิถุนายน 2548 ทั้งสิ้น 48 ราย กลุ่มผู้ป่วยหมายถึงผู้ป่วยที่มีการบวมของสมองและเกิดการเลื่อนที่ของสมอง กลุ่มควบคุมหมายถึงผู้ป่วยซึ่งไม่มีการบวมและการเลื่อนที่ของสมอง มีการวิเคราะห์ข้อมูลของผู้ป่วยทั้งอาการและอาการแสดงทางคลินิก และผลการตรวจทางห้องปฏิบัติการ โดยเก็บรวบรวมข้อมูลทั้งจากเวชระเบียนผู้ป่วยนอก และผู้ป่วยใน

**ผลการศึกษา** : มีจำนวนผู้ป่วยในกลุ่มผู้ป่วยทั้งสิ้น 8 ราย (ร้อยละ 16.7) และในกลุ่มควบคุม 40 ราย (ร้อยละ 83.3) ปัจจัยเสี่ยงต่อการเกิดการเลื่อนที่ของสมองอย่างมีนัยสำคัญทางสถิติคืออัตราการเต้นของหัวใจ (OR = 1.08, 95 % CI 1.02-1.15, p = 0.011) สำหรับปัจจัยเสี่ยงต่อการเกิดการเลื่อนที่ของสมองแต่ไม่มีนัยสำคัญทางสถิติได้แก่ 1) ความดันโลหิตไดแอสโตลิกแรกรับ (OR = 1.02, 95 % CI 0.98-1.05, p = 0.384) 2) ประวัติโรค เบาหวาน (OR = 1.4, p = 0.692 ) 3) ประวัติโรคความดันโลหิตสูง (OR = 4.2, p = 0.240 ) 4) ระดับคอเลสเตอรอลในกระแสเลือด (OR = 1.01, 95 % CI 0.99-1.02, p = 0.799 ) 5) ระดับน้ำตาลในกระแสเลือดขณะงดอาหาร (OR =1.01, 95 % CI 0.99-1.02, p = 0.120) 6) ระดับเฮมตีแอลในกระแสเลือด (OR = 1.05, 95 % CI 0.99-1.12, p = 0.079) และ 7) atrial fibrillation (OR = 1.52, p = 0.356)

- บทสรุป** : ปัจจัยเสี่ยงต่อการเกิดการเลื่อนที่ของสมอง ในทางอาการและอาการแสดงทางคลินิก และการตรวจทางห้องปฏิบัติการ ได้แก่ อัตราการเต้นของหัวใจ ความดันโลหิตไดแอสโตลิก ประวัติโรคเบาหวานและความดันโลหิตสูง ระดับน้ำตาลขณะงดอาหารและคอเลสเตอรอลในกระแสเลือด ปริมาณเม็ดเลือดขาวในกระแสเลือด และการมี atrial fibrillation ซึ่งข้อมูลเหล่านี้มีความสอดคล้องกับผลการศึกษาที่ผ่านมา อย่างไรก็ตาม ยังจำเป็นต้องมีการศึกษาแบบ prospective, multi-centered ที่ใช้จำนวนผู้ป่วยในการศึกษามากกว่านี้ เพื่อยืนยันผลการศึกษา และเพื่อให้ได้ปัจจัยเสี่ยงที่มีนัยสำคัญทางสถิติมากขึ้น
- คำสำคัญ** : สมองเลื่อน, ผู้ป่วยสมองขาดเลือดเฉียบพลัน, หลอดเลือดแดง middle cerebral.

The prevalence of massive hemispheric infarction is about 5% of all acute brain ischemia<sup>(1)</sup>, and it is found 10-15 % of acute brain ischemia from middle cerebral artery occlusion.<sup>(2)</sup> In this category of patients, the course of disease is malignant MCA infarction which is 40 - 50 %<sup>(3,4)</sup> (Malignant MCA infarction means local brain edema and which causes brain herniation which has the mortality rate of 40 -100 %).<sup>(1, 5-9)</sup> The natural cause of death is brain edema which increases the intracranial pressure and subsequently herniation of the brain. Brain herniation manifests by symptom and signs, i.e., the patient's level of consciousness decreases and symptoms of brainstem compression which usually occurs in the first 2 - 5 days.<sup>(10)</sup> Patients who survive from the condition have a high rate of morbidity. Treatments that are commonly provided for the patients in this condition are symptomatic, e.g., controlled hyperventilation, intravenous osmotherapy, mild to moderate hypothermia or deep barbiturate coma which has limited outcome and cannot prevent brain herniation and mortality rate is about 80 %.<sup>(5,8)</sup> Currently, there is no standard treatment for patients whose clinical conditions are deteriorating as mentioned. So far, decompressive craniectomy is one of the treatments which give a satisfactory result and known to decrease the mortality and increase the long-term well being of the patient (conclusion from case series reports).<sup>(9, 11)</sup> The primary objective of the operation is to decrease intracranial pressure, increase cerebral perfusion pressure, and to prevent secondary neural injury. Therefore, it is suggested for this group of patients.

Identification of patients who are of high risk to brain herniation makes them candidates for

decompressive craniectomy at the early state is essential for reduction of mortality and morbidity as well as decreasing the number of patients to receive unnecessary surgical operations. Previous studies have found many risk factors to brain herniation in patients with acute brain ischemia from occlusion of the middle cerebral artery. Most of the identified risk factors require advanced investigations which are time-consuming, costly, and sometimes invasive. For example; the computerized X-ray of the brain which illustrates areas of the ischemic brain tissue more than 400 ml<sup>(12)</sup>, areas of ischemia over 50 % of the brain supplied by middle cerebral artery<sup>(4,13-15)</sup>, hyperdense MCA sign<sup>(14)</sup>, local brain edema<sup>(15)</sup> or shifting of the brain crossing the midline<sup>(12)</sup>, carotid artery occlusion proved by angiography<sup>(11)</sup>, MRI reveals the amount of diffusion lesion more than 145 ml in the first 14 hours and the decrease of apparent diffusion coefficient (ADC)<sup>(16)</sup>; the measurement of cerebral blood flow by xenon CT<sup>(17)</sup> or 99m technetium-ethylcysteinate-dimer single-photon emission computerized tomography.<sup>(18)</sup> Indisputably, they are not generally applicable in most hospitals. The study is, therefore, focused on the use of history of symptoms and signs as well as laboratory tests that are available in most hospitals to search for risks of brain herniation in patients with acute brain ischemia from occlusion of the middle cerebral artery.

## Methods

### Methodology and subject recruitment

This is a retrospective analytical study in patients who were admitted into King Chulalongkorn Memorial Hospital with the diagnosis of acute brain ischemia from middle cerebral artery occlusion from January 1<sup>st</sup>, 2004 to June 30<sup>th</sup>, 2005. Their data from

medical archive of the Outpatient Department and inpatient history files were collected.

Inclusion criteria are as follows:

1) Acute brain ischemia from middle cerebral artery occlusion.

2) Having periods of awareness or stupor but reactive to stimuli and able to respond to command or responds to questions within first 5 days of hospital admission.

3) Arrival to hospital within 48 hours from the onset of the symptom.

The study did not recruit patients who were semi-unconscious or in coma as these patients might have suffered from brain herniation from the beginning, or those with bad prognosis and unfit for decompressive craniectomy or other treatments. Patients who did not fit in with the inclusion criteria are those who had large haematoma in the brain over 30 % of ischemic area causing brain edema or mass effect.

The patient group means patients with edema and herniation of the brain after acute ischemia from occlusion of the middle cerebral artery. The control group means the rest of the patients who suffered from acute brain ischemia from occlusion of the middle cerebral artery but had no brain herniation. Neurological death means death which was caused by brain herniation that was displayed by symptoms of brainstem compression (dilated pupils, unconsciousness, having no brainstem reflexes) before dying which included cardiac arrest caused by compression of the brainstem from brain herniation. Other causes of death such as pneumonia, sepsis, pulmonary embolism were taken as non-neurological death.

### Data collection

Demographic data of the patients such as age and their clinical information on admission, for example, risk factors of occlusion of cerebral vessels, vital signs on admission, type of occlusion as well as laboratory findings, e.g., number of leukocytes, level of fasting blood sugar, level of blood cholesterol, triglyceride, HDL, level of electrolytes, ESR and CRP taken from the patients' records history of patient described, e.g., medical procedures or other treatments in some cases such as tracheal intubations and administrations of anticoagulant.

Every patient received diagnostic X-ray with computerized X-ray of the brain from the admission time, focusing on the characteristics of acute brain ischemia, location of the occluded artery and location of occlusion and bleeding in the brain tissue and measurement of mass effect. Apart from this, patients who showed symptoms and signs / or signs of brain herniation are re-investigated by computerized X-ray of the brain.

### Statistical methods

The patient group and the control group were equivalent in terms of their demographic characters, underlying diseases, or past history of illnesses, clinical symptoms and signs, laboratory results as well as findings from computerized X-ray of the brain.

Bivariable analysis, dichotomous and categorical variables were compared using chi-square test.

Their continuous variables were compared by unpaired t test, binary logistic regression test.

Calculation of risk factors was based on odd ratio and the level of statistical significance is taken when  $p < 0.05$ .

Statistical calculation is performed by SPSS for Windows version 13.0.

## Result

### Patients' data

Forty-eight patients with acute brain ischemia from occlusion of the middle cerebral artery were recruited into the study. They were divided into two groups: 8 in patient group (16.7 %) and 40 in control group (83.3 %).

There was no statistical significance in the difference of their age, gender between the two groups. The patient group had the ratio of history of hypertension: diabetes higher than the control group, whereas the control group had the ratio of history of

ischemic heart disease history of smoking: alcohol consumption higher than the patient group. Both groups had equivalent systolic and diastolic pressures at their admissions, whereas the patient group had the ratio of atrial fibrillation: average heart rate higher than the control group.

### Laboratory findings

Both groups had almost similar levels of blood cholesterol, triglyceride HDL and sodium. However, the patient group had higher fasting blood sugar than the control group, whereas the control group had higher number of leukocytes than the patient group. Patients' data, laboratory findings at admission and bivariable analysis are showed in Table 1.

Table 1. Patients' data and Bivariable Analysis.

	Cases (n=8)	Controls (n=40)	p value	OR	95 % CI
Age, mean $\pm$ SD (Yr)	66.63 $\pm$ 14.42	63.18 $\pm$ 14.22	0.550		
Diabetes (%)	37.5	30	0.692	1.4	
Hypertension (%)	87.5	62.5	0.240	4.2	
Ischemic heart dis. (%)	12.5	15	1.000	0.8	
Smoking (%)	25	37.5	0.694	0.55	
Alcohol consumption (%)	0	10	1.000	0	
Atrial fibrillation (%)	37.5	28.2	0.356	1.52	
Systolic BP (mmHg)	152.38 $\pm$ 38.14	162.55 $\pm$ 29.84	0.401	0.99	0.96-1.02
Diastolic BP (mmHg)	98.25 $\pm$ 26.04	91.18 $\pm$ 19.72	0.384	1.02	0.98-1.05
Heart rate (BPM)	100.43 $\pm$ 21.21	80.61 $\pm$ 13.57	0.011	1.08	1.02-1.15
Cholesterol (mg/dl)	209.57 $\pm$ 44.85	203.79 $\pm$ 58.04	0.799	1.01	0.99-1.02
Triglyceride (mg/dl)	102.43 $\pm$ 42.43	117.76 $\pm$ 49.71	0.440	0.99	0.97-1.01
HDL (mg/dl)	55.50 $\pm$ 21.17	44.95 $\pm$ 10.76	0.079	1.05	0.99-1.12
LDL (mg/dl)	131.00 $\pm$ 26.03	142.87 $\pm$ 52.79	0.653	0.99	0.97-1.02
FPG (mg/dl)	153.50 $\pm$ 68.9	121.58 $\pm$ 45.56	0.120	1.01	0.99-1.02
Serum Na (mEq/dl)	138.43 $\pm$ 4.18	138.65 $\pm$ 7.04	0.838	0.98	0.85-1.14
WBC count	8,908.0 $\pm$ 5,051	11,403.64 $\pm$ 4,966.54	0.321	1.00	1.00-1.00



### Bivariable Analysis

The risk factor that was related to brain herniation with statistical significance is heart rate (OR = 1.08, 95 % CI 1.02-1.15,  $p = 0.011$ ). Regarding other proposed risk factors of brain herniation but were not found related with statistical significance are, namely: 1) diastolic pressure on admission (OR = 1.02, 95 % CI 0.98-1.05,  $p = 0.384$ ); 2) history of DM (OR = 1.4,  $p = 0.692$ ); 3) history of hypertension (OR = 4.2,  $p = 0.240$ ); 4) level of blood cholesterol (OR = 1.01, 95 % CI 0.99-1.02,  $p = 0.799$ ); 5) level of fasting blood sugar (OR = 1.01, 95 % CI 0.99 -1.02,  $p = 0.120$ ); 6) blood level of HDL (OR = 1.05, 95 % CI 0.99 -1.12,  $p = 0.079$ ); and, 7) atrial fibrillation (OR = 1.52,  $p = 0.356$ ).

### Discussion

This study is designed to identify risk factors of brain herniation in patients with acute brain ischemia from middle cerebral artery occlusion. Collected data in the study are from demographic records, clinical symptoms and signs of the patients and laboratory findings which are commonly used in most hospitals using study population which is diverse. There is a limitation of the study, however, due to its design as a retrospective case-control which has small number of recruited patients like most of the studies in the past (the prevalence of acute brain ischemia from middle cerebral artery occlusion at King Chulalongkorn Memorial Hospital during the study period was 21 % and the prevalence of brain herniation was 16 % of ischemia from middle cerebral artery occlusion, and 3.5 % of all cases of acute brain ischemia which is close to the study of Kasner *et al.* in 2001(2544BE).<sup>(3)</sup>

The risk factor that related to brain herniation with statistical significance is heart rate. Apart from this, the risk factors which are not statistically significant are: diastolic blood pressure, history of diabetes, history of hypertension, level of blood cholesterol and HDL, fasting blood sugar and atrial fibrillation. These correspond to the study of Kasner *et al.* in 2001 (2544 BE) which identified risk factors of brain herniation that are associated with statistical significance are history of hypertension and heart failure, leukocytosis, ischemia with more than 50 % of the brain supplied by middle cerebral artery and occlusion of other vessels of the brain. However, the relationship between the risk factors and brain herniation are not clearly understood. It is possible that the detected higher heart rate in the patient group indicated higher activities of sympathetic nervous system which could have caused from higher severity of the disease which subsequently caused higher stress. History of hypertension, history of diabetes, high blood sugar and high blood cholesterol may be related to chronic impairment of cerebral collateral flow and autoregulation.<sup>(19)</sup> The condition of ischemic brain tissue with more than 50 % of the brain supplied by middle cerebral artery and occlusion of other vessels of the brain such as anterior cerebral, anterior choroidal are indications of poor hemispheric collateral flow, occlusion of large brain vessels or vessels that are more proximal (e.g., intracranial internal carotid artery) and wide area of brain edema.<sup>(20, 21)</sup>

The study has certain limitation as it is a retrospective analytical with small number of patients as well as clinical data and laboratory findings of some patients not recorded. Therefore some risk factors are not found related to brain

herniation. This might have been caused by limited statistical power. Besides, there was no continued data collection of the survivors regarding the impacts of arterial occlusion on their daily living, disability and dependency.

In conclusion, the study was focused on searching for risk factors in terms of symptoms and signs, and clinical manifestations, as well as laboratory findings that might be useful to determine the prognosis of brain herniation in patients with acute brain ischemia. The patients in this category might benefit from decompressive craniectomy in their early phase. However, prospective studies are necessary; they should have sufficient number of patients recruited from diverse population more than this in order to precisely identify risk factors at the early admission of the patient.

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