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ORIGINAL ARTICLE

Blood pressure variability and prognosis in acute ischemic stroke with vascular compression on the rostral ventrolateral medulla (RVLM)

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One of the known causes of hypertension is vascular compression on the rostral ventrolateral medulla (RVLM). However, it remains unknown whether RVLM vascular compression causes the significant variability in blood pressure observed during acute ischemic stroke. The purpose of this study was to evaluate differences in blood pressure variability and prognosis in acute ischemic stroke patients based on the presence or absence of RVLM vascular compression. We evaluated 56 patients with acute ischemic stroke. Blood pressure was measured every 6 h for 72 h after admission and evaluated with successive variation (SV). The presence of RVLM vascular compression was evaluated using time-of-flight 3D magnetic resonance imaging. Neurological severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at admission and 14 days after admission, and clinical improvement was determined by taking the difference in the NIHSS scores between admission and at 14 days. Patient clinical outcome was evaluated with the modified Rankin scale on discharge. Vascular compression of the RVLM was identified in 15 patients (26.8%). The proportion of patients showing clinical improvement was significantly higher in the non-compression group (odds ratio, 0.21 (95% CI=0.06–0.78); *P*=0.01). The SV value for systolic blood pressure was significantly higher in the compression group (*P*<0.0001). We found that patients with RVLM vascular compression had a greater variability in blood pressure during the acute ischemic stroke phase, which may be related to poorer prognosis.
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Keywords: acute ischemic stroke; blood pressure; rostral ventrolateral medulla

INTRODUCTION

Regardless of nationality or ethnicity, hypertension is a lifestyle-related disease afflicting patients throughout the world and is a major risk factor for stroke. Hypertension is a multifactorial disease. It has been reported that a large population of patients with vascular compression on the rostral ventrolateral medulla (RVLM) have hypertension.[1–4] Surgical decompression of the RVLM reduced sympathetic nerve activity and normalized systemic blood pressure.[5,6] Therefore, it is suggested that vascular compression on the RVLM influences the development or maintenance of hypertension. The RVLM has been experimentally shown to be a site of cardiac and vasomotor regulation. The mechanism of increased blood pressure in patients with vascular compression on the RVLM remains to be completely elucidated. It is currently hypothesized that chronic stimulation of this region with vascular compression can cause constitutive activation of the sympathetic nervous system and the development of hypertension.[7,8]

More than 80% of acute stroke patients have elevated blood pressure. Several days following the incidence of stroke, however, the blood pressure in these patients returns to baseline levels.[9] This blood pressure elevation varies depending on the subtype of ischemic stroke and on the patient's medical history.[10] In general, the cause of elevated blood pressure during the acute phase of ischemic stroke is presumed to be an increase in sympathetic nerve activity and stress from the ischemic insult that disrupts intracerebral autoregulation to maintain cerebral blood flow.[11] During acute ischemic stroke, the rapid decrease in blood pressure reduces cerebral blood flow in parallel to a decrease in the perfusion pressure that is sufficiently large to expand infarct volumes and worsen neurologic symptoms. Therefore, such an excessive lowering of blood pressure during acute ischemic stroke is not desirable. Even in studies examining the correlation between blood pressure and prognosis in the acute ischemic stroke phase, the variability in blood pressure has been shown to be an independent prognostic factor for a poor outcome.[12,13]

RVLM vascular compression may cause significant variability in blood pressure during acute ischemic stroke by sympathetic nerve activation.[14] However, to our knowledge, it remains unclear whether RVLM vascular compression influences blood pressure during acute ischemic stroke. Therefore, the purpose of this study was to evaluate differences in blood pressure variability and prognosis during acute ischemic stroke in the presence or absence of RVLM vascular

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compression and to examine the influence of chronic sympathetic nerve activation on acute ischemic stroke.

METHODS

Subjects and study design

This study was conducted in consecutive patients with acute ischemic stroke admitted between April 2008 and March 2010 to Hiroshima University Hospital within 24 h of stroke onset. Exclusion criteria included the inability to undergo magnetic resonance imaging (MRI) examination, the administration of thrombolysis, an National Institutes of Health Stroke Scale (NIHSS) score ⩾23 on admission, the use of anti-hypertensive or vasopressor medicines within 72 h after admission, and surgery within 72 h after admission. In addition, we excluded patients with medullary infarctions, which might have effects on RVLM. The stroke subtype was determined based on MRI findings, electrocardiography, and carotid artery and cardiac ultrasound findings by at least two stroke specialists according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[15] The acute treatment was determined based on the stroke subtype in accordance with the established guidelines. Neurological severity was evaluated using the NIHSS upon admission and 14 days after admission.[16] Their clinical outcome was evaluated with the modified Rankin scale at the time of discharge.[17] The study was approved by the institutional review board of Hiroshima University Hospital.

Hypertension was defined as the use of any anti-hypertensive medicines before admission or a confirmed blood pressure of ⩾140/90 mm Hg at rest after 2 weeks from stroke onset. Diabetes mellitus was defined as HbA1c ⩾6.5%, fasting blood sugar ⩾126 mg dl^{-1}, or the use of any anti-diabetic medicines. Hyperlipidemia was defined as total cholesterol ⩾220 mg dl^{-1}, low-density lipoprotein cholesterol ⩾140 mg dl^{-1} on admission, or the use of any anti-hyperlipidemic medications. For 72 h after admission, blood pressure and pulse rate were measured every 6 h on the unaffected arm in a resting supine position using a standard automated sphygmomanometer without any anti-hypertensive medicines. Blood pressure and pulse rate variability was evaluated with successive variation (SV), defined as the square root of the averaged squared differences between two successive measurements.[18]

The presence or absence of RVLM vascular compression was evaluated on a 3T MRI unit (GE, Fairfield, CT, USA) using 3D time-of-flight (slice thickness of 1.0 mm, TR/TE/flip angle, 23/3.4/18°). The RVLM was located at the root-entry zone of cranial nerves IX and X (Figure 1). The location was defined as follows: upper and lower borders of the root-entry zone were determined by the uppermost and lowest fibers of the IX/X nerve bundle entering the medulla; the anterior border of the root-entry zone was defined as the transition of the olivary convexity to the concavity of the retro-olivary sulcus; and the posterolateral border was located at the junction of parenchymal brain tissue and individual nerve fibers.[2] Arterial compression (vertebral artery or posterior-inferior cerebellar artery) within this defined area was considered 'positive' for RVLM, and patients with no arterial compression were considered 'negative.' We defined arterial compression as deformation of the medulla surface. Therefore, instances in which the artery just contacted the surface of the medulla were excluded from the criteria for RVLM vascular compression. The presence of RVLM vascular compression was evaluated by two neurologists who were unaware of each patient's medical history.

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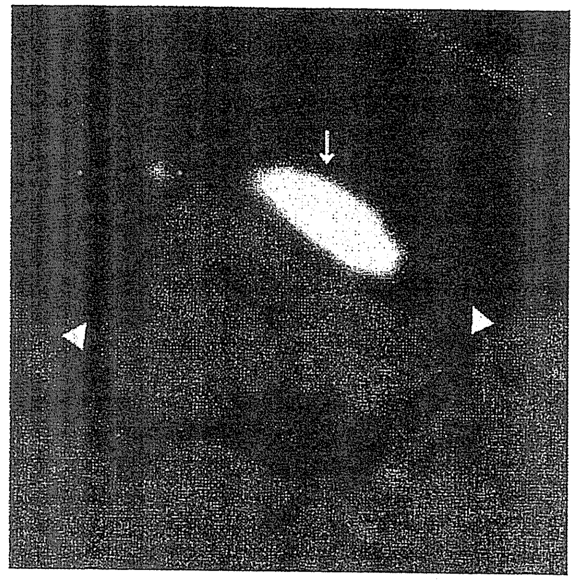
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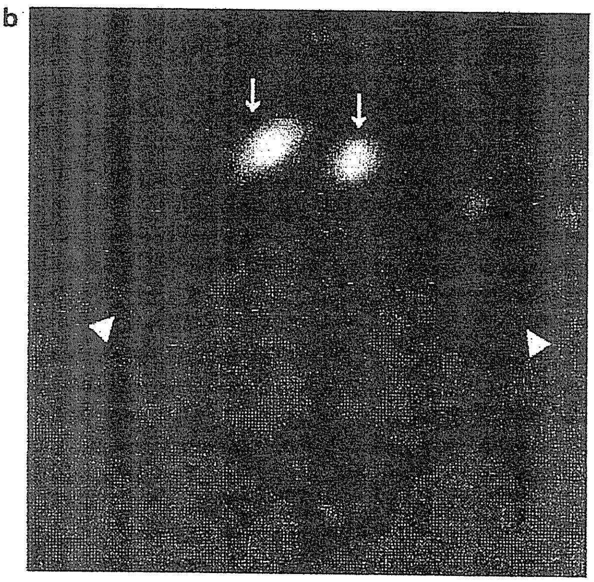

Figure 1 Axial 3D time-of-flight (TOF) images are shown (**a**) compression case, (**b**) non-compression case. The RVLM extends in a craniocaudal direction from the root entry zone of cranial nerve IX down to the upper part of cranial nerve XI. The RVLM is dorsolateral to the olive and medioventral to the root entry zone of cranial nerves IX and X (arrowhead). The compression of vertebral artery (arrow) or posterior-inferior cerebellar artery within this defined area was considered 'positive' for RVLM.

Statistical analysis

Data are shown as the mean ± s.d. or median (minimum-maximum) for continuous variables. Statistical analysis for comparison of the two groups was performed using Student's *t*-test or the Mann–Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. *P*-values <0.05 were considered statistically significant. Receiver operating characteristic curves were configured to establish cut-off points for SV that optimally predicted RVLM compression.

RESULTS

Of the 86 enrolled patients, 11 did not undergo MRI, 4 had missing data, 3 received thrombolysis, 4 had an NIHSS score ⩾23 on admission, 5 received anti-hypertensive or vasopressor medicines, and 3 had surgery within 48 h of hospital admission. Thus, all analyses were performed on the remaining 56 patients. MRI was performed at a mean time of 32.3 h after symptom onset (range, 4–50 h). Table 1 shows the baseline characteristics of all patients. Vascular compression on the RVLM was identified in 15 (26.8%) patients (hereafter, referred to as the compression group). Age was not significantly different between the patients with and without RVLM vascular compression. In the compression group, the proportion of males was significantly higher (93.3 *vs.* 63.4%, *P*=0.03). The prevalence of hypertension was significantly higher in the compression group (93.3 *vs.* 61.0%, *P*=0.02). At the time of admission, there was no significant difference

Table 1 Baseline characteristics, blood pressure and NIHSS on admission, and ischemic stroke subtypes

Variables	*Compression (n=15)*	*Non-compression (n=41)*	*P-value*
Age, mean years ± s.d.	71.6 ± 9.37	73.2 ± 9.5	0.59
Male, n (%)	14 (93.3%)	26 (63.4%)	0.03
Risk factors			
Hypertension, n (%)	14 (93.3%)	25 (61.0%)	0.02
Diabetes mellitus, n (%)	9 (60.0%)	17 (41.5%)	0.22
Hyperlipidemia, n (%)	7 (46.7%)	27 (65.9%)	0.19
Baseline NIHSS	4 (0–8)	4 (0–20)	0.29
Baseline SBP, mean mm Hg ± s.d.	159.1 ± 8.9	149.5 ± 26.1	0.17
Baseline DBP, mean mm Hg ± s.d.	81.1 ± 14.7	75.4 ± 15.2	0.88
Ischemic stroke subtype			
Atherothrombotic, n (%)	5 (33.3%)	13 (31.7%)	
Cardioembolic, n (%)	2 (13.3%)	17 (41.5%)	
Small vessel, n (%)	3 (20.0%)	5 (12.2%)	0.17
Other etiology, n (%)	5 (33.3%)	6 (14.6%)	

Abbreviations: DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Table 2 Relationship between RVLM vascular compression and clinical improvement at 14 days

	Improved (NIHSS ⩾4 improvement or NIHSS=0)	*Unimproved*	*OR (95% CI) probability*
Compression	4 (26.7%)	11 (73.3%)	0.21 (0.06–0.78)
Non-Compression	26 (63.4%)	15 (36.6%)	P=0.01

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; RVLM, rostral ventrolateral medulla.

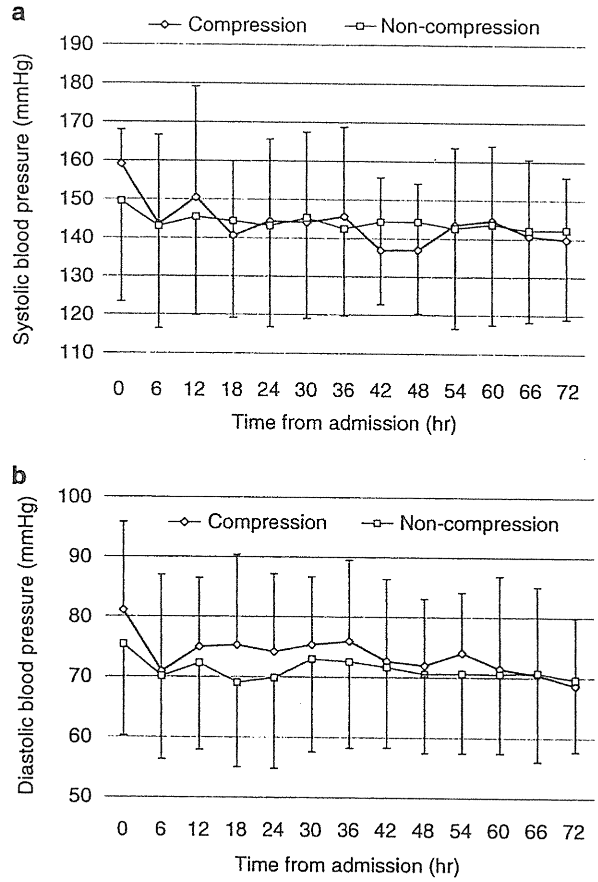

Figure 2 Average blood pressures during 72 h of hospitalization in the compression group (n=15) and the non-compression group (n=41). (**a**) Systolic blood pressure, (**b**) diastolic blood pressure.

in NIHSS scores, and no significant difference was observed in systolic or diastolic blood pressure between the groups. In addition, the subtype of ischemic stroke was not significantly different between the groups (P=0.17).

The patients were defined as clinically improved when their NIHSS score decreased more than four points or recovered to 0 on day 14 (ref. 19). The proportion of clinically improved patients was 26.7% in the compression group and 63.4% in the non-compression group (Table 2), with a significantly lower rate of improvement in the compression group (odds ratio, 0.21 (95% CI=0.06–0.78); P=0.01).

Figures 2 and 3 show the systolic and diastolic blood pressures and the SV values of the patients up to 72 h after admission. At all time points, no significant differences were observed in mean systolic or diastolic blood pressures between the two groups. However, the SV value of the systolic blood pressure was significantly higher in the compression group during the first 24 h after admission ($P<0.0001$) and during the 72 h period after admission ($P<0.0001$). Conversely, there were no significant differences in the diastolic blood pressure SV value between the groups at any time point. The pulse rate SV value was significantly higher in the compression group during the 72 h period after admission (8.7 ± 2.7 b.p.m. *vs.* 7.3 ± 2.2 b.p.m., $P<0.05$)

In the explanatory analysis, the best cutoff SV value of the systolic blood pressure during the 72 h period after admission obtained from the Receiver operating characteristic curve was 15.3 mm Hg, which predicted RVLM compression with a sensitivity of 67% and a specificity of 88% (area under the curve=0.783; P=0.0002). In the compression group, the patients with SV <15.3 mm Hg tended to show a more favorable outcome, defined using modified Rankin scale, than the patients with SV ⩾15.3 mm Hg (P=0.10) (Figure 4).

DISCUSSION

This study found that blood pressure variability during the acute ischemic stroke phase was significantly greater in patients with RVLM vascular compression than in those without. In addition, decreased improvement in neurologic symptoms was observed in patients with RVLM vascular compression compared with patients without RVLM vascular compression. In the compression group, patients with high SV values were more likely to have unfavorable outcomes. The association between blood pressure variability and acute ischemic stroke outcome has previously been reported.[12,13] To our knowledge, this study is the first to clearly show an association between RVLM vascular compression, blood pressure variability and functional prognosis.

It has been reported that a large proportion of patients with RVLM vascular compression have hypertension.[1–4] Mechanical stimulation of the RVLM causes glutamate release from RVLM vasomotor neurons, thereby increasing sympathetic nerve activity.[20] RVLM vascular compression was observed in 7–22.2% of healthy individuals without

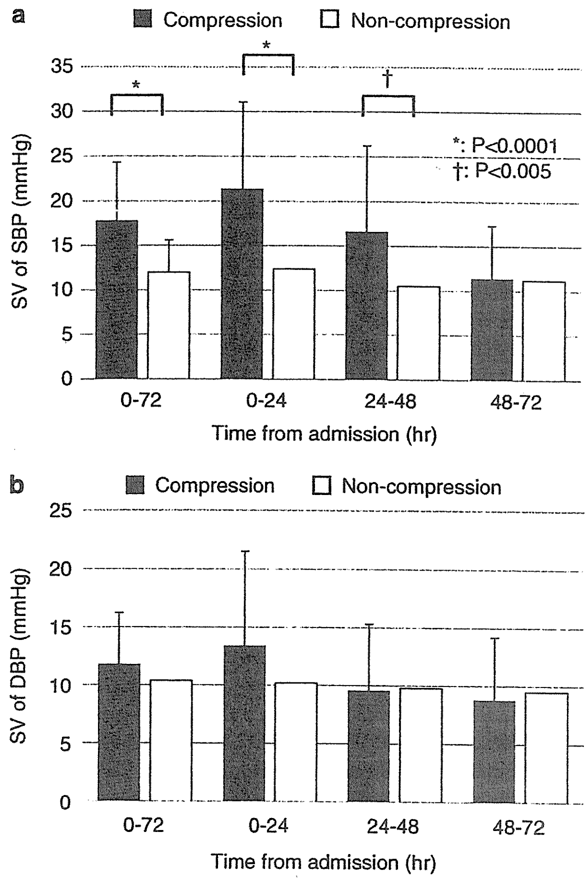

Figure 3 Successive variation (SV) of blood pressure during 72 h of hospitalization in the compression group (n=15) and the non-compression group (n=41). (a) Systolic blood pressure (SBP), (b) diastolic blood pressure (DBP).

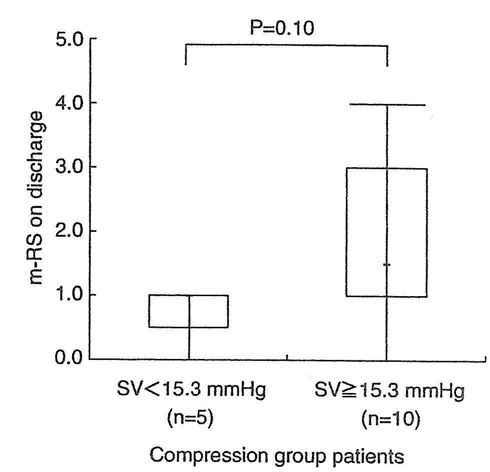

Figure 4 Box plot showing median modified Rankin scale (m-RS) on discharge (solid bar), interquartile range (bar width), and minimum/maximum values across SV<15.3 mm Hg or ⩾15.3 mm Hg in compression group.

hypertension and in 74–90% of patients with hypertension.[3,4,21,22] Our results demonstrated that the prevalence of hypertension was 93.3% (14/15) in patients with RVLM vascular compression, and it was higher than that in patients without RVLM vascular compression, which is consistent with previous studies. The prevalence of hypertension was 60.5% (25/41) in patients without RVLM vascular compression, which is similar to other previous population-based studies of ischemic stroke.[23,24] We propose that RVLM vascular compression is one of the important factors related to hypertension. However, it is still unknown whether RVLM vascular compression is the cause of hypertension because no study has prospectively followed young normotensive subjects with RVLM vascular compression to evaluate the incidence of hypertension. Conversely, several reports have demonstrated that surgical decompression of the RVLM reduced sympathetic nerve activity and normalized systemic blood pressure.[5,6] In addition, in our study, the patient with RVLM vascular compression who did not show hypertension (n=1) had higher blood pressure variability than patients without RVLM vascular compression and had a poor prognosis on discharge. In the other target organs (the heart), it has been reported that the regression of left ventricular hypertrophy depends on not only blood pressure levels, but also the reduction of cardiac sympathetic drive.[25] Therefore, we think that chronic sympathetic nerve activation influences target organ damage even when patients are not hypertensive.

In the present study, the compression group had a significantly higher SV value and a significantly lower proportion of clinically improved patients. In the compression group, the sympathetic nerve may be chronically activated. Hypertension is likely one of the markers of this chronic sympathetic nerve activation, which explains the significantly higher rate of hypertension in the compression group. In patients with chronic hypertension, cerebral blood flow decreases rapidly with cerebral ischemia in association with an increasing cerebral oxygen extraction fraction.[26] Therefore, blood pressure variability may change cerebral blood flow. This pathological response may deteriorate the improvement of neurological symptoms in patients with RVLM vascular compression.

Our findings demonstrated that the difference in blood pressure between the groups was not significant, although it tended to be slightly higher in the compression group. Interestingly, the variability in blood pressure was significantly greater in the compression group. The sympathetic nervous system is generally persistently activated during acute ischemic stroke, leading to increased blood pressure regardless of the presence or absence of RVLM vascular compression. Therefore, it is difficult to detect a difference in blood pressure with or without RVLM vascular compression during the acute ischemic stroke phase. By contrast, RVLM vascular compression clearly activates the sympathetic nervous system, leading to increased burst-like firing of sympathetic nerves,[27] which is thought to have a role in blood pressure variability.

It has been reported that patients with RVLM vascular compression have increased sympathetic nerve activity.[8] In addition, the increased sympathetic nerve activity may induce high blood pressure variability because it was reduced after ganglion blockade with trimethaphan.[28] In parallel to this response, when sympathetic nerve activity increases, the baroreflex counteracts this activation in normal subjects. However, it is still unknown whether the increase in sympathetic nerve activity is caused by increased sympathetic nerve traffic, increased vascular sensitivity, or impaired baroreflex buffering in patients with RVLM vascular compression. It has been reported that baroreflex buffering and baroreflex-mediated vasopressin release are severely impaired in patients with RVLM vascular compression.[7] When the impaired baroreflex is associated with RVLM vascular compression, blood pressure variability may increase with increased sympathetic nerve activity. It has been suggested that restoration of baroreflex sensitivity may prevent stroke in the animal model.[29] It is possible that the restoration of baroreflex sensitivity reduced blood pressure variability and, therefore, stroke incidence. However, blood pressure variability was not examined in the experiment by Liu *et al.* Therefore, it is unknown whether stroke prevention with the restoration of baroreflex sensitivity was mediated by the reduction of blood pressure variability. In our study, we evaluated the association of blood pressure variability at the acute ischemic stroke phase and its prognosis for patients with or without RVLM vascular compression. However, we were unable to evaluate blood pressure variability at the pre-ischemic stroke period. Therefore, further studies are needed to clarify the association between blood pressure variability and the occurrence of stroke in patients with RVLM vascular compression.

Various measures of variability of individual blood pressure profiles have been used. The most common measures of variations are the extreme values, such as maximum, minimum, range (difference between maximum and minimum), s.d., or coefficient of variation (s.d. over mean).[30] In the present study, we selected SV as a parameter of within-patient blood pressure variability. This parameter includes the serial variation on a time sequence, whereas other measures, such as s.d. and coefficient of variation, ignore the sequential nature of such a data set. Therefore, when analyzing the sequential nature of data, as in the present study, it is better to use SV. If not, time-invariant measures, such as s.d. or coefficient of variation, can result in a misleading prediction of prognosis and is less informative for blood pressure management.

In the present study, we evaluated RVLM vascular compression with MRI images. However, it is possible that cases in which there appeared to be RVLM vascular compression had a low degree of compression that did not result in sympathetic nerve activation. Thus, we examined the association between SV and prognosis in the compression group, which was divided into two groups using the best cutoff SV value of the systolic blood pressure during the 72 h period after admission. As a result, the patients with high SV values tended to show more unfavorable prognosis than the patients with low SV values. Therefore, large-scale studies are required to confirm the influence of the SV value on the compression group prognosis.

The present study has several limitations. First, a selection bias may exist because of the small sample size at a single institution. Therefore, it will be necessary to conduct a similar multi-center study to confirm whether these results can be generalized. In addition, our results may not reflect all ischemic stroke patients because of the frequent exclusion of severe cases. It is highly possible that the severe cases have poor prognoses regardless of the presence of RVLM vascular compression or that the influence of RVLM vascular compression might be low. To study these issues, we are planning a multi-center, large-scale trial to define the association of RVLM vascular compression with the prognosis of ischemic stroke patients. Another limitation of the current study is that we did not examine the correlation between RVLM vascular compression and SV value with the use of anti-hypertensive medications before stroke onset. In particular, medications that inhibit sympathetic nerve activation may influence blood pressure and blood pressure variability. However, the half-lives of these anti-hypertensive medications are not more than 24 h, and their effects decrease with time. In our study, the SV value for blood pressure variability was calculated at 72 h after admission. Therefore, pre-medication with anti-hypertensives should have had a limited effect on the SV value. Finally, the correlation with ischemic location was not fully investigated. A previous study demonstrated that patients with infarctions involving the insular cortex tended to suffer from autonomic dysfunction,[31] which may influence blood pressure. However, in the present study, few patients had infarctions involving the insular cortex, and the proportion of patients with infarctions involving the insular cortex was similar between the compression and non-compression groups (two in the compression group (13.3%) and five in the non-compression group (12.2%)). Thus, the influence of ischemic location in the present study may also be limited.

In conclusion, this study found that patients with RVLM vascular compression had greater variability in blood pressure during the acute ischemic stroke phase, which may be a factor related to poorer prognosis. In the future, larger scale prospective studies are required to confirm the influence of RVLM vascular compression in acute ischemic stroke.

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potential candidates for the optimum surgical technique in the current guidelines.

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1. Prevention of Intracerebral Hemorrhage

Recommendations

1. Treating hypertension is the most vital step to reduce the risk of intracerebral hemorrhage (ICH) (Grade A).
2. People should be encouraged to take a moderate amount of vegetables and fruits every day (Grade B).

Recommendations, *continued*

3. Heavy alcohol consumption leading to abnormal blood γ-GTP levels should be discouraged (Grade B).
4. In the case of hypocholesterolemia, it has generally been agreed that the its underlying hepatic disease and coexisting hypertension should be treated. Lowering serum cholesterol level with statins does not increase the incidence of ICH, but some data have implied that intervention for stroke patients may increase the recurrence of ICH (Grade B).
5. We recommend the very careful consideration of an appropriate dose of each antithrombotic drug and its dual medications, that are required to control concurrent hypertension (Grade B).

Evidence

The prevention of ICH consists of collective intervention for the improvement of lifestyle habits, primary prevention in a high-risk group such as hypertensives and secondary prevention in stroke patients. Adherence of individual patients to identified risk factor reduction is a prerequisite for the prevention of ICH which has high morbidity and mortality rates.

The higher the blood pressure, the higher the incidence of ICH. Hypertension is a risk factor to which the utmost attention should be paid for Asian people in whom ICH occurs more frequently than in Caucasians[14,15] (IIb). A meta-analysis has demonstrated the usefulness of antihypertensive therapy for the prevention of stroke and recurrent stroke[16] (Ia). The Perindopril Protection against Recurrent Stroke Study (PROGRESS) showed that an antihypertensive regimen decreased the incidence of ICH by half for over 3.9 years of follow-up in 6105 patients with previous cerebrovascular events[17] (Ib). A surge of blood pressure in the early morning has been identified to be an independent risk factor for ICH[18] (IIa); thus, to control hypertension strictly all day long is the most important action to reduce the risk of ICH.

A meta-analysis of epidemiologic surveys demonstrated that the incidence of stroke decreased in a group with a high consumption of green and yellow vegetables and fruits[19] (IIb). In Japanese people, the incidence of ICH was lower when the general population were in the habit of eating fruits and vegetables every day[20] (IIb).

It is generally agreed that heavy alcohol consumption increases blood pressure and causes hepatic dysfunction thereby decreasing the serum levels of blood coagulation factors and cholesterol, thus elevating the risk of ICH[21,22] (IIb). In a group with increased γ-GTP levels, which are an index of hepatic dysfunction associated with heavy alcohol consumption, the incidence of ICH increased regardless of blood pressure or lipid levels[23] (IIb).

There was indeed a concern that hypocholesterolemia raised the risk factor for ICH, but it has been shown that the hazard arises only when low cholesterol levels are combined with hypertension[23] (IIb). It is generally agreed to treat concurrent hypertension with hypocholesterolemia, although there are no clinical data regarding any relationship between the attenuation of serum cholesterol and the lower incidence of ICH.

A meta-analysis showed that statin treatment for improving hyperlipidemia did not increase the incidence of ICH[24] (Ia). In contrast, analyses including the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that improving the lipid profile in patients with previous stroke elevated the incidence of ICH[25,26] (Ia). No correlation was observed between levels of LDL cholesterol and the occurrence of ICH[27] (IIb). It is generally agreed that lipid-improving statins should be administered with care to male, elderly, hypertensive and chiefly hemorrhagic stroke patients, and that their physicians have been educated as to the need for blood pressure reduction as a feasible countermeasure[28] (IIb).

Antithrombotic therapy increases frequency of ICH onset and the subsequent hematoma expansion. Whenever 2 different antiplatelet drugs are administered or an antiplatelet is combined with an anticoagulant over the long term, it is generally agreed that the clinicians of such patients should weigh the advantage of the antithrombotic actions against the disadvantage of bleeding complications[29] [*See also additional remarks for the English version]. The appropriate adjustment of the blood anticoagulation intensity and uninterrupted stabilization of blood pressure with antihypertensive medication are recommended[30,31] [*See also additional remarks for the English version] (Ia).

Not only chronic renal failure requiring hemodialysis[32] but also chronic kidney disease with a low glomerular filtration rate (GFR) elevate the risk of ICH[33] (IIa). A subanalysis of the PROGRESS reported that antihypertensive therapy with an angiotensin-converting enzyme inhibitor prevented recurrent stroke in renal disease patients,[34] but they have no available data regarding how renal protection works well against ICH.

Diabetes mellitus (DM) increased the incidence of stroke; type 1 DM elevated the incidence of ICH, whereas type 2 DM did not[35] (IIa). The treatment of DM with hypoglycemic drugs, such as insulin and insulin-resistance improving drugs, has not been reported to prevent ICH.[36] Concurrent hypertension remains the most important target[37] (Ib).

Asymptomatic cerebral microbleeds detected in T2*-weighed MRI in patients with acute cerebral infarction are a risk factor for stroke recurrence, particularly symptomatic ICH for Japanese people[38,39] (IIa). No research on the efficacy of antihypertensive therapy and safety of antithrombotic therapy in patients with hemorrhage-prone microangiopathy is currently under way.

No data are available to help develop preventive measures specific to non-hypertensive ICH associated with cerebral amyloid angiopathy that frequently occurs and recurs in the late elderly.

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***Additional remarks for the English version**

A Japanese prospective observational study of 4009 patients who were taking antithrombotic agents for stroke and cardiovascular disease provided us with the information that adding an antiplatelet agent to either another antiplatelet or warfarin increased the events of life-threatening major bleeding, including intracranial hemorrhage, over a 19-month follow-up.[40] An increase in blood pressure during antithrombotic medication was positively associated with the occurrence of hemorrhagic stroke; the optimal cutoff was 130/81 mmHg to predict imminent danger.[41]

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2. Nonsurgical Treatment of Hypertensive Intracerebral Hemorrhage

2-1. Administration of a hemostatic

Recommendations

1. When there is no abnormality with the blood coagulation system in patients with a normal hypertensive intracerebral hemorrhage (ICH) in the acute phase, administration of blood products including blood coagulation factors is not recommendable (Grade C2).
2. Even if the ICH is the hypertensive type, administration of blood products such as platelets, prothrombin complex and fresh frozen plasma should be considered for patients with concurrent abnormal platelets or blood coagulation system and a bleeding tendency according to their clinical conditions (Grade C1).
3. There is no adequate scientific evidence supporting the use of capillary stabilizers or antiplasmin agents for the treatment of acute ICH (Grade C1).

Evidence

The usefulness of the recombinant activated coagulation factor VIIa (rFVIIa) for acute ICH was evaluated first in 2 small-scale studies[42,43] and a medium-scale study.[44] In the latter medium-scale study, 399 patients with ICH within 3 hours after onset were randomized into a placebo or rFVIIa group. The results showed that rFVIIa treatment significantly inhibited increases in the bleeding volume, decreased mortality, and improved the dysfunction level at 90 days after onset (Ib). In the subsequent Phase III, large-scale study,[45] 841 patients were treated with rFVIIa or a placebo within 4 hours after onset in a randomized, double-blind manner. Compared with the placebo, the rFVIIa treatment significantly inhibited increases in ICH and improved the level of functional care and the level of neurological disorder by 15 days after hemorrhage, whereas the primary endpoint defined as the frequency of deaths and serious sequelae (mRS score 5-6) at day 90 did not improve (Ib).

Even if the main cause of ICH is hypertension, administration of blood products such as platelets, prothrombin complex and fresh frozen plasma should be considered for patients with concurrent abnormal platelet or blood coagulation system and a bleeding tendency according to individual clinical conditions.[46,47]

There is no large-scale clinical study on the use of capillary stabilizers or antiplasmin agents in patients with acute ICH as compared with a placebo. Only reports on a small-scale controlled study[48] and use of these drugs without comparators[49] are available[50] (IIb-III).

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B 脳梗塞慢性期治療
——1　危険因子の管理と再発予防

Point

1　脳卒中再発予防には，その病態生理を考慮し危険因子に優先順位をつけて治療を行うことが推奨される．
2　脳梗塞に対する適切な抗血栓療法，高血圧性脳内出血に対しては，急性期から継続される降圧療法が第一である．
3　脳梗塞に対して発症2～3週後から慢性期にかけて高血圧に対する降圧療法が推奨される．
4　さらに動脈硬化を基盤とする脳梗塞に対して，糖尿病や脂質異常症に対する治療が追加される．

1　高 血 圧

疫学調査から，血圧値が正常域を超えると脳卒中の発症率が急に上昇し，降圧療法により脳卒中予防効果を得ることができる．必ずしも旧来の β-遮断薬や降圧利尿薬に比べ，新しいカルシウム拮抗薬やACE（angiotensin converting enzyme）阻害薬の優位性は著明ではない[1,2]．すべての脳卒中は高血圧が最大の危険因子であるため治療は必須であるが，どのクラスの降圧薬を用いても“降圧度に相応した”予防効果が期待できると考えられる（**図1**）[1]．降圧目標は140/90 mmHg以下と設定されるが，後期高齢者では160/95 mmHg以下の穏やかな目標として，合併する疾患，危険因子に応じて適切なクラスの降圧薬を選択し，さらに厳格な降圧目標を設定する．

脳梗塞慢性期の降圧治療に関しては，「高血圧治療ガイドラインJSH 2009」では，通常発症1か月を経過してから140/90 mmHg未満を降圧目標として，少なくとも1～3か月かけて緩徐な降圧を導入することを推奨している．頭蓋内主幹動脈に閉塞性病変を認め脳血流SPECTなどで広範囲な低灌流を認め，かつ血管予備能が低下している状況では，降圧による血行力学性脳虚血のリスクが危惧されるので，症状を観察しながら発症1～2か月後から降圧を導入，3～6か月かけて目標値まで降圧する．

慢性期の脳卒中患者に推奨される降圧薬として，「JSH2009」では長時間作用型カルシウム拮抗薬，ACE阻害薬，降圧利尿薬とARB（angiotensin receptor blocker）があげられている．PROGRESS研究のサブ解析によると，脳卒中既往症例の高血圧に関しては，収縮期120 mmHgまでの降圧には安全性と予防効果が期待でき，いわゆるJカーブ（降圧に応じた有用性があるが，閾値以下では逆に脳卒中発症率が増加する現象）はないと示された[3]．前期高齢者，糖尿病，慢性腎疾患合併症例や後期高齢者における脳梗塞患者では120/80 mmHgを目標とする厳格な降圧

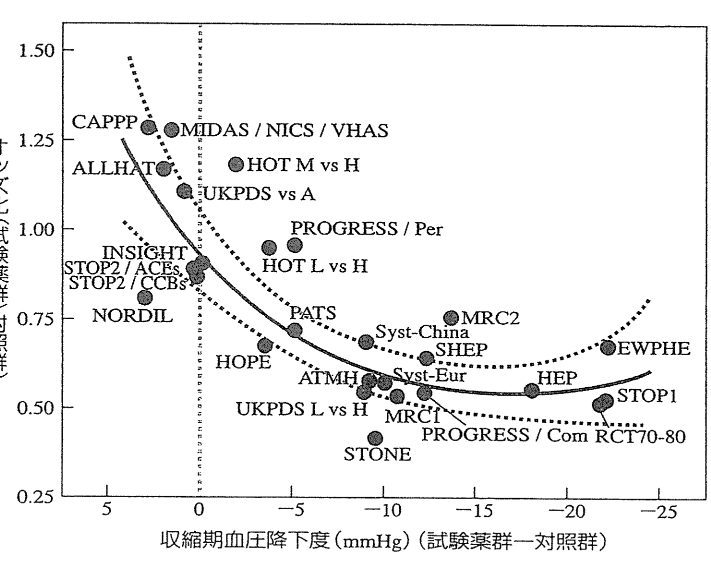

図1　収縮期血圧値降下度による脳卒中発症オッズ比低下
降圧すればするほど，脳卒中発症率は低下する（The lower, the better）．
（Staessen JA, Wang JG, Thijs L : Cardiovascular protection and blood pressure reduction ; a meta-analysis. *Lancet* 2001 ; **358** : 1305-1315 より改変）

管理が，両側内頸動脈有意狭窄症では160/90 mmHg以下を目標とする緩やかな降圧管理が推奨される．

ARBであるエプロサルタンが，同等の降圧度を呈したカルシウム拮抗薬ニトレンジピンに比し脳卒中再発が有意に予防できたMOSES研究を踏まえ[4]，一部のクラスの降圧薬は，降圧を超えた脳保護作用の存在が推定される．ACCESS研究では主幹動脈病変を有さない神経徴候の安定した脳梗塞急性期に早期からARBであるカンデサルタンを投与すると1年後の生命予後が良好であることが示され，臨床的解釈が容易ではないが，レニン·アンジオテンシン系の抑制や抗酸化による急性期における抗動脈硬化作用等多面的効果としての脳保護作用が予測された[5]．基本原則は，早朝を含む24時間にわたる降圧効果の持続，新規糖尿病発症予防，新規心房細動発生予防，動脈硬化の退縮等のクラス特有の利点によるものと考えられる．

また，脳卒中症例に合併するその他の危険因子を層別化し，単剤大量療法に固執せず，クラス特有の副作用を分散させるべく多剤併用療法を試みるほうが得策である．長年高血圧を罹患した後期高齢者や頭蓋内主幹動脈病変を有する症例では通常量半分の降圧薬から投与し，緩徐な増量を行うべきである．また，脳卒中や心筋梗塞は，早朝や午前中に多発するので夜間と早朝高血圧の管理が重視される．家庭血圧を参考にしてこれに対して，長時間作動型カルシウム拮抗薬やARB，またその併用療法が選択される．

高齢者脳卒中患者は軽度の認知機能低下を有することも多く，長年の生活習慣を急に変えることは困難なうえに，心身のハンディキャップにより，無理な塩分制限や運動療法を強いることは逆効果になることもあるので，まずは降圧療法を並行して開始するのも得策となるだろう．

頸部超音波検査による内膜中膜複合体厚(intima-media complex thickness；IMT)は虚血性心疾患や脳卒中の独立した予測因子となり，降圧療法の代替エンドポイントとなる[6]．カルシウム拮抗薬，ACE阻害薬，α・β-遮断薬はIMT進展を抑制することが可能である[7]．このIMTは，ベッドサイドで非侵襲的かつ反復して患者に提示でき，治療へのアドヒアランスや服薬コンプライアンス向上に有用である．

2 糖尿病

糖尿病により脳梗塞の相対危険率は1.8～6倍となる．しかし，UKPDS 33研究によると，標準的な血糖降下治療だけでは脳卒中発症率を低下させることはできなかった(図2)[8]．腎症，網膜症，末梢神経障害等マイクロアンギオパチーやマクロアンギオパチーである心筋梗塞が，血糖降下療法により発症が減少したのとは対照的である．しかし，UKPDS 38研究では血糖管理に厳格な降圧療法を上乗せして初めて脳卒中が予防できたことが示された(図2)[9]．脳卒中の約半分を占める動脈硬化を基盤とするラクナ梗塞とアテローム血栓性脳梗塞では，血糖・血圧値の両管理により初めて動脈硬化の進行予防が得られ，脳卒中予防に寄与できた．

耐糖能異常から2型糖尿病への進展や動脈硬化性心疾患の予防に食後高血糖，糖毒性，インスリン抵抗性が重要であるが，STOP-NIDDM試験によるとαグルコシダーゼ阻害薬アカルボースにより，糖尿病への進展の予防，脳卒中・心筋梗塞狭心症の複合エンドポイントの減少が示された[10]．食後血糖管理，糖尿病への進展予防が脳卒中一次予防に強く寄与したと考えられる．

また，PROactive試験によると，インスリン抵抗性改善薬ピオグリタゾンは，心筋梗塞・脳梗塞・総死亡の複合エンドポイントの有意の低下を示した[11]．脳卒中二次予防に着目したPROactive研究サブ解析によると，脳卒中既往症例に対してピオグリタゾン

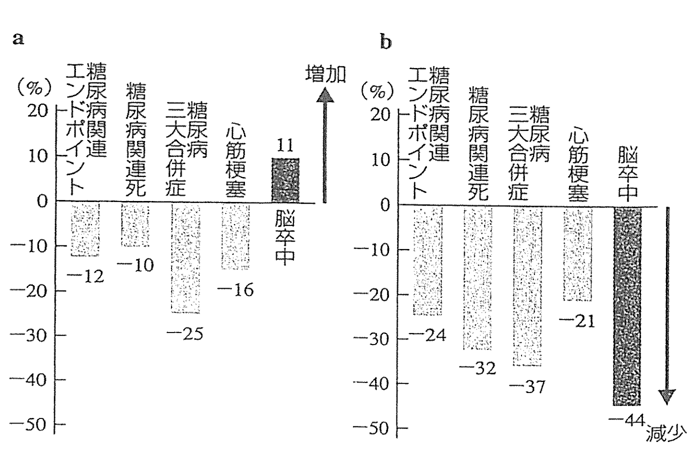

図2 UKPDS 33研究とUKPDS 38研究・脳卒中予防
a：UKPDS 33．厳格な血糖コントロール(HbA_{1c} 7.0%対7.9%)，b：UKPDS 38．厳格な血圧コントロール(144/82対154/87 mmHg)．厳格な血糖降下では脳卒中発症率は軽減できなかったが，降圧療法は著明に脳卒中を軽減した．図1より鑑みると，降圧度から順当な相対危険率低下である．
(Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998；**352**：837-853より改変)
(Tight blood pressure control and risk of macrovascular and microvascular complication in type 2 diabetes；UKPDS 38. UK Prospective Diabetes Study (UKPDS) Group. *BMJ* 1998；**317**：703-713より改変)

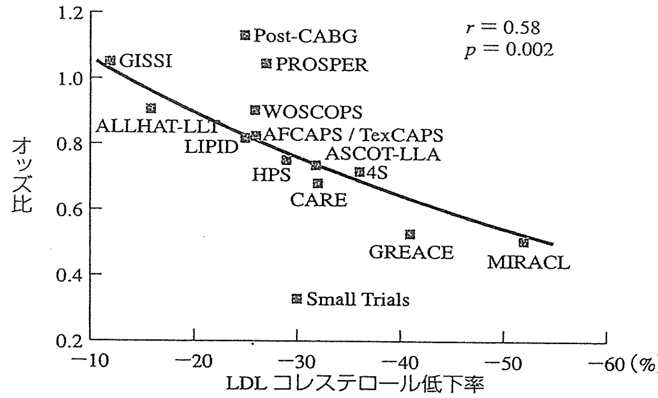

図3　LDLコレステロールの低下率と脳卒中発症率抑制との関係

LDLコレステロールを10%低下させると15.6%脳卒中リスクが軽減されると推定された(The lower, the better).
(Amarenco P, Labreuche J, Lavallee P, *et al.* : Statins in stroke prevention and carotid atherosclerosis ; systematic review and up-to-date meta-analysis. *Stroke* 2004 ; 35 : 2902-2909より改変)

は著明に再発を抑制することができた[12]. 脳卒中再発予防における糖尿病治療薬の有用性がサブ解析研究ではあるが初めて示された. アカルボースやピオグリタゾンは, 食後高血糖による活性酸素産生亢進の低下, 平滑筋や内皮の増殖因子であるインスリンの低下が, 動脈硬化すなわちIMT進展を抑制し, 動脈硬化性脳卒中の発症予防に寄与したと考えられた[13, 14].

3　脂質異常症

高血圧,糖尿病等を合併する脂質異常症症例では, HMG-CoA (3-hydroxy-3-methylglutary-coenzyme A) 還元酵素阻害薬アトルバスタチンの心筋梗塞・脳卒中一次予防の有用性が示され[15], プラバスタチンも日本人での有用性を示した[16]. 日本人は総コレステロール値が高くてもHDLコレステロールが高値, LDLコレステロールを主とするnon-HDLコレステロールが低値がありうるので, 脂質管理上ぜひ両者の測定を勧める.

脳卒中予防として虚血性心疾患既往症例にはスタチンの使用が推奨され, LDLコレステロールの低下に相応して脳卒中の発症リスクが軽減した(図3)[17, 18].

また, 脳卒中既往症例に対する脳梗塞二次予防にアトルバスタチンの有用性が示された[19]. わが国でも脳血栓症既往例の再発予防目的のプラバスタチンの効果を検討するJ-STARS研究が進行中である. アテローム血栓性やラクナ梗塞に対してスタチンは特に有用であると想定される. しかし, 高血圧性脳内出血既往症例や高齢者高血圧症例では, 極端な脂質低下療法では脳出血の発症の危惧がある[19]. 降圧療法を併用して初めて脂質低下療法は脳卒中発症の抑制効果を発揮すると考えられる[20]. 糖尿病合併脂質異常症に対しても, 脂質低下療法の脳卒中発症予防効果が期待できる[21].

最近発表された, ω(n)-3系多価不飽和脂肪酸の一つであるEPA (eicosapentaenoic acid〈イコサペント酸エチル〉) の閉塞性血管障害に対する発症予防を検証した大規模臨床試験JELIS (Japan EPA Lipid Intervention Study) の結果では, EPA (エパデール®) (1,800 mg/day) を, 脳卒中の既往を有する高コレステロール血症患者 (≧250 mg/dL) に, スタチン製剤とともに5年間投与することで, スタチン製剤単独服用患者と比較して, 脳卒中(おもに脳梗塞)の再発を有意に20%抑制することが明らかになった[22]. 5年間におけるNNT (number needed to treat) は27であった. このJELISの結果により,「脳卒中治療ガイドライン2009」[23]では, 高コレステロール血症を示し脳卒中の既往のある患者では, スタチン製剤によって血清LDLコレステロール値や総コレステロール値を正常化するとともに, EPA (1,800 mg/day) を追加投与することが推奨されている.

一方, イオン交換樹脂薬やフィブラート系脂質低下薬の有用性も期待されるが, 現在脳卒中予防の観点からの十分な科学的根拠はない[24]. また, 脳血管の動脈硬化の指標IMTの進展に関してもnon-HDL (LDL) コレステロール値低下度と相関し, 動脈硬化の最上流のステップでの抑制が有用かつ優先治療であることを示している[18].

4　心房細動

僧帽弁狭窄症等流出路障害の弁膜症に伴う心房細動は, 抗凝固療法が必須である. 非弁膜症性心房細動の患者で, 糖尿病, 高血圧, 虚血性心疾患や心不全, 70歳以上の高齢者のうち一つでも有するものは, 抗凝固療法による脳塞栓を含めた動脈塞栓症の予防方策をとることが推奨される. これ以外の条件ではアスピリンの投与が勧められる. また, 脳梗塞, 一過性脳虚血発作 (transient ischemic attack ; TIA) を既往とする心房細動に対しては, 脳梗塞再発率を年間12%から4%まで下げることができる抗凝固療法が, 消化管出血や癌合併がない限り再発予防に必須である. PT-INR (prothrombin time-international normalized ratio) が2.0〜3.0になるようにワルファリン

カリウムを微調整し，70歳以上の高齢者では出血性合併症が多くなるため1.6～2.6に維持する．

持続性心房細動に関しては，ジギタリスや非ジヒドロピリジン系カルシウム拮抗薬(ベラパミルやジルチアゼム)による心拍管理を主とする．発作性心房細動に対しては，心機能維持，心不全予防のため薬物による調律管理や洞調律化が勧められる[25]．しかし，現時点では脳卒中再発予防の観点から調律管理が心拍管理に比較して優位性を示すことはできず[26]，やはり抗凝固療法が基本である．左心房肺静脈入口部のアブレーションによる心房細動抑制が直接脳塞栓予防につながるか否かは現時点では不明である[27]．

また，高度の高血圧や高血圧性脳内出血の既往が合併している場合，抗凝固療法は慎重に行うべきである．また抗血小板薬との併用療法も含めて出血性合併症を予防するべく降圧療法の重要性，とりわけ24時間にわたる厳格な降圧療法の併用が必須であることを強調したい[28, 29]．

5 卵円孔開存

卵円孔開存に対して下肢静脈血栓や肺塞栓があれば，脳塞栓予防のため抗凝固療法が必要となる．心房中隔瘤をさらに伴う場合，脳塞栓発症率が高く抗凝固療法が推奨される．心房中隔瘤を伴わない卵円孔開存単独の脳梗塞既往例に対しては，病型分類上心原性脳塞栓症であるが，抗血小板薬アスピリンの単独使用も選択されうる[30]．欧米人によく観察される直径の大きい卵円孔開存に対するカテーテルによる閉鎖術の臨床治験(Evaluation of the STARflex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO ; CLOSURE)が現在行われているが，開存卵円孔径が小さくValsalva負荷時にのみシャントが観察される日本人に対して，この外科治療の利点は大きくないと思われる．

奇異性脳塞栓の原因としての肺動静脈瘻に対しては，カテーテル塞栓術の適応となりうるが，脳・肺塞栓予防として下肢静脈血栓があれば抗凝固療法が必要となる[31]．

6 喫　煙

喫煙は易血栓性と動脈硬化作用から，動脈硬化性脳梗塞や脳出血の危険因子となる．禁煙が脳卒中の危険率を下げる[32]．それゆえ，二次予防の観点からも禁煙が発症率を低下させるであろう．危険因子が喫煙だけの頭蓋内主幹動脈狭窄や閉塞による脳梗塞症例も散見される．禁煙のためには，カウンセリング，バレンクリン酒石酸の内服療法やニコチンパッチ塗布が用いられる．受動喫煙も脳卒中の危険因子となる．

7 飲　酒

過剰な飲酒は脳卒中発症の危険因子となるので避けるべきである．少量飲酒(アルコール換算1日12 g未満)までは脳梗塞発症を低下させうる[33, 34]．同時に少量の飲酒による頸動脈IMTの進展抑制効果が示されている[35]．しかし，多量飲酒(1日60 g以上)により脳梗塞のリスクは高まり，飲酒量と脳卒中発症率との関係のJカーブ現象が示されている[36]．脳出血に関してもアルコール摂取量とともに脳出血発症率が増加するが，高血圧患者の多量飲酒者では，血圧値のさらなる上昇や肝機能障害，低コレステロール血症等が関与していると推定される．非飲酒者に比較し約3倍高い脳出血発症率が示されたことから[34]，高血圧性脳内出血の再発予防にはγ-GTPが正常値を超えて異常値を示すような過剰な飲酒は禁止すべきと考えられる[36]．

赤ワインは抗動脈硬化・抗酸化作用のあるポリフェノールを多く含有するが，脳梗塞再発予防効果に関しては不明である[37]．また，急激な大量飲酒は，一過性心房細動の誘発，心筋障害，睡眠時無呼吸の増悪により脳塞栓を誘発する可能性が示唆されており，飲酒後の血圧値の急激な上昇が脳卒中発症に関係する可能性もあるので禁止すべきである[38]．

8 多血症

高ヘマトクリット血症は，脳梗塞の危険因子であると思われる．ヘマトクリット値46%以上で脳梗塞の出現頻度が増加した[39]．しかし，治療により脳梗塞再発予防を検討した報告はないが，再発とヘマトクリット値との関連はないとの報告がある[40]．

ストレス多血症に対しては，喫煙，肥満，ストレスを軽減し，ヘマトクリット値を改善させることを考慮する．瀉血の有用性は不明である．真性多血症に対しては，脳梗塞を含む血栓症の再発リスクを軽減できることを期待して化学療法を行うことが多い[41]．

9 出血凝固系異常

先天性血栓性素因であるアンチトロンビンIII，プロテインC，プロテインS，およびプラスミノゲン異常症・欠損症では静脈血栓症が多い[42]．原因不明の脳塞栓では，上記の血栓性素因の検索と，下肢深部静脈血栓症を静脈超音波検査，卵円孔開存等右左短絡を経食道心エコーで評価すべきである[43]．明らかな静脈血栓症がない場合でもワルファリンカリウム等の抗血栓療法を行うことを考慮してもよいが，十分な科学的根拠はまだない．

高フィブリノゲン血症も脳梗塞の危険因子であるが，フィブリノゲンを低下させるフィブラート系薬剤の脳梗塞発症予防効果は十分検討されていない[44]．

若年女性の脳梗塞等血栓症症例においては，抗リン脂質抗体(ループスアンチコアグラント，抗カルジオリピン抗体)を検索するべきであり，陽性者で脳梗塞発症リスクが高い[45, 46]．ワルファリンカリウム投与による脳塞栓予防が推奨される[47]．ただし，男性においては抗リン脂質抗体陽性の頻度は極めて少ない[45]．男女とも全身性エリテマトーデス合併例での脳梗塞症例において，原疾患の活動性が高ければステロイド薬が推奨される[47]．

高ホモシステイン血症は，虚血性心疾患と脳梗塞の発症リスクになる[46]．葉酸，ビタミンB_6/B_{12}による治療により，凝固能，血管内皮障害，炎症マーカーなどの改善が再現性よく確認できず，心筋梗塞等のリスクを有する症例に対する治療効果はないことが報告されたことから，今後この治療の脳卒中予防効果を再度前向きに研究する必要性がある[49]．

経口避妊薬による脳静脈洞血栓症はまれではないが，メタ解析では脳卒中発症を増加させない[50]．閉経後ホルモン補充療法は，脳卒中を増加させる危惧があるので推奨されない[51]．

10 炎　症

感染症では動脈硬化部位が易血栓性に傾くので，脳梗塞発症のリスクとなりうる．気道や尿路感染症が脳卒中に先行することが示されている[52]．また，*Chlamydia pneumoniae*(肺炎クラミジア)，*Helicobacter pylori*(ヘリコバクター・ピロリ)，cytomegalovirus(サイトメガロウイルス)，*Mycoplasma pneumoniae*(マイコプラズマ・ニューモニエ)，*Hemophilus influenzae*(インフルエンザ菌)等の感染症は動脈硬化と相関している[53]．それゆえ，インフルエンザ等の気道や全身感染症は，脳梗塞再発予防の観点から予防接種等による方策をとるべきである．また，高齢脳卒中患者における肺炎予防として，肺炎球菌ワクチンの接種，誤嚥対策としてとろみをつけた水分や食事摂取とACE阻害薬，アマンタジン，シロスタゾール，カプサイシン等の投与を考慮する．

動脈硬化は慢性の血管内皮の炎症状態と考えられ，高感度C反応性蛋白(C-reactive protein；CRP)がその有用な指標となる[54]．つまり，CRPは不安定プラーク，症候性内頸動脈狭窄症の症例では上昇し，脳梗塞の予測因子となりうる．しかし，高C反応性蛋白血症における脳卒中発症予防として，抗炎症作用のあるHMG-CoA還元酵素阻害薬やカルシウム拮抗薬，ARB投与が考慮されるが，その脳卒中再発予防効果は不明である．

11 遺伝子

先天性血栓性素因(アンチトロンビンIII欠損症，プロテインC欠損症，プロテインS欠損症，プラスミノゲン異常症および欠乏症，日本人にはないがLeiden因子変異)では，脳梗塞の家族歴が明らかになることがある．一般に脳静脈洞血栓症が多いが，脳血栓・塞栓症もありうる．抗凝固療法を考慮してもよいが，一次予防としての科学的根拠はない．高ホモシステイン血症はmethylene-tetrahydrofolate reductase(*MTHFR*)遺伝子の点変異による．抗リン脂質抗体症候群，動脈解離，もやもや病，線維筋異形成の10～20%は遺伝性素因をもつ．動脈解離やもやもや病は，虚血性のみならず出血性脳卒中を発症しやすいので，抗血栓療法の投与はその利点とリスクを天秤にかけて慎重に行うべきである．

また，アイスランドの遺伝子多型の検討では，ホスホジエステラーゼ4Dや5-lipoxygenase activating protein遺伝子と脳梗塞との関連が示された[55, 56]．

Recklinghausen神経線維症，Marfan症候群，cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy(CADASIL)，Fabry病は，出血性または虚血性脳卒中を発症しやすいが，抗血栓療法による一次予防の有用性は不明である．また，CADASILに対する片頭痛抑制作用を有するアセタゾラミド投与[57]，Fabry病に対する遺伝子組み換えαガラクトシダーゼA補充療法[58]による脳梗塞発症予防等の長期効果も不明である．

12 内臓肥満

メタボリックシンドロームの診断基準の必須項目が内臓脂肪過多であり，日本内科学会によると腹囲が男性85 cm，女性90 cm以上である．①中性脂肪150 mg/dL以上かつ，またはHDLコレステロール40 mg/dL以下，②血圧130/85 mmHgいずれか以上，③空腹時血糖110 mg/dL以上の2項目以上で診断基準を満たす．

内臓肥満単独では脳卒中発症のリスクとなりうるか否か現在議論中であるが，脳卒中症例における再発予防のための肥満に対するダイエットは，インスリン抵抗性，高中性脂肪血症等脂質異常症，高血圧に対してよい影響をきたし，推奨するべきである[59]．現時点では内臓肥満と高血圧，脂質異常症，糖尿病は互いに交絡因子であるので単独の治療に有用性を示すことは容易ではないが，腹囲が脳卒中発症リスクに有用な指標であり女性80 cm男性88～90 cm程度まで減少させるダイエット単独が脳卒中発症予防に有効であると日本の疫学調査から示唆されている[60, 61]．

(大槻俊輔 / 松本昌泰)

脳血管障害

Stroke

大槻俊輔/松本昌泰

脳卒中超急性期における高血圧は，画像による虚血性または出血性病変の診断の後，初めて治療すべきか否かを決定することができる．

概　念

脳血管障害は多様な病態生理を有しており，実地臨床では脳卒中発症機序の迅速な解明が急性期治療と再発予防に直結している．

脳は全身の需要エネルギーのうち20％を消費し，自らエネルギーの備蓄を有せず，血液が運搬する糖と酸素によってのみ機能が維持されている．脳血管の血流が血栓や塞栓子により途絶すると，すぐに供給不全のため脳の活動が障害される．脳血流が30％以下になると機能障害が発生し，10～20％に至ると血流再開が短時間で得られなければ，脳実質に不可逆的壊死すなわち梗塞に至る．すでに梗塞に陥った虚血中心部の周辺には，脳血流の低下が持続すれば今後梗塞に至る生存部位があり，虚血性ペナンブラと呼ぶ．神経細胞死に至るまでにできるだけ早く血栓を溶解して局所脳血流を改善させ，ペナンブラ領域を救い，脳機能改善を目指すのが基本治療理念である．この脳梗塞急性期では，脳循環の自動調節能は障害されており(**図1**)，降圧を行うと局所脳血流量も低下し梗塞巣は拡大するので，原則的には高血圧状態が生じていても降圧療法は百害あって一利なしである．

一方，脳出血は脳血管の破綻により生じ，血腫が脳神経組織を圧迫し，意識障害や麻痺を生じる．高血圧性と非高血圧性に大別されるが，前者は長年の高血圧により穿通枝のリポヒアリン変性・フィブリノイド壊死と微小動脈瘤の破綻により発症する．後者は脳血管奇形，感染性動脈瘤，アミロイドアンギオパチーなどによる血管破綻により，高血圧性と比較して若年者に多い．脳出血は発症24時間，とくに6時間以内に血腫が拡大し，症状進行と機能予後不良に直結する．脳梗塞とは逆に，高度の血圧上昇が血腫拡大および症状進行に相関するため，すみやかな降圧療法導入が基本治療となっている．

以上から，虚血性および出血性脳卒中はbrain attackと呼ばれ，一刻を争う(Time is brain)疾患である．必ずCTやMRIにより早期診断を行い，それぞれ超急性期再灌流療法または降圧療法のプロトコールが選択される．

発症機序と診断(図2)

1．血行力学的梗塞

脳主幹動脈に高度狭窄があるもしくは完全閉塞しており，側副血行路により遠位側が灌流され安静時脳血流量は低下している．しかし，頭蓋内血管が限界まで拡張することにより血流を代償維持している状態に対し，完全閉塞・血圧の低下や脱水により代償機構が破綻し，灌流終末領域に脳梗塞が発生する．脳CTおよびMRIでは，いわゆる分水嶺(中大脳動脈と前大脳動脈，または後大脳動脈の灌流境界)に梗塞巣が生じる．脳血流SPECT検査で，灌流領域の安静時脳血流量が正常値の80％以下，血管拡張作用のあるアセタゾラミドを負荷し，血流増加が10％以下にとどまるかむしろ減少する(脳内盗血症候群)所見を認める．ポジトロンCTでは，同部位の局所脳血流量の低下と酸素摂取率の上昇が観察される．

2．アテローム血栓性脳梗塞

高血圧，高脂血症，糖尿病，喫煙等の動脈硬化の危険因子に加齢という時間的負荷が加わり，血管内中膜にプラーク・粥腫が形成される．粥腫による狭窄部での血栓形成，狭窄・閉塞部から血栓の遠位塞栓，高度狭窄・閉塞部位の遠位に低灌流の機序が，単独もしくは合併して脳梗塞を発症する．脳血管の評価を頸部超音波やMRA，脳血管造影で有意狭窄(50％以上の管腔狭窄)を評価する．近年，破綻し血栓形成しやすい不安定プラークは頸部超音波やMRIで診断可能となり，経頭蓋超音波ドプ

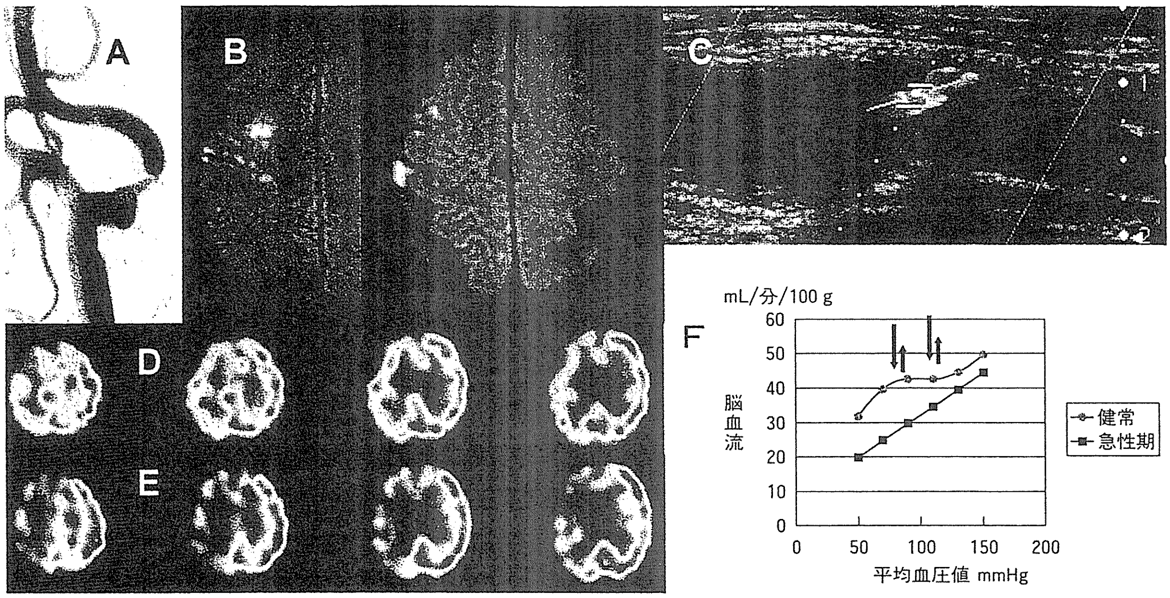

図 1　脳梗塞急性期における脳血流自動調節能の消失

脳血管造影(A)，頸動脈超音波(C)により右内頸動脈始起部高度狭窄による中大脳動脈領域の梗塞(artery-to-artery embolism)の症例(MRI 画像 B)である．脳血流検査では中大脳動脈領域の安静時血流が約 10 %低下しており(D)，ダイアモックス負荷により血流増加が認められず(E)，低灌流状態かつ血管予備能の低下が想定される．F では脳血流の自動調節能(autoregulation)を示す．健常者では平均血圧が 60～150 mmHg までは脳血流は一定になるように血管の拡張収縮調整が行われているが，脳虚血症状や脳梗塞発症時には血管麻痺(vasoparalysis)のため拡張しきっており，血圧の低下に比例して脳血流が低下する．つまり，脳梗塞急性期では生体反応として血圧が上昇しているが，虚血脳では降圧すればするほど，局所脳血流は低下し梗塞巣が進展する．

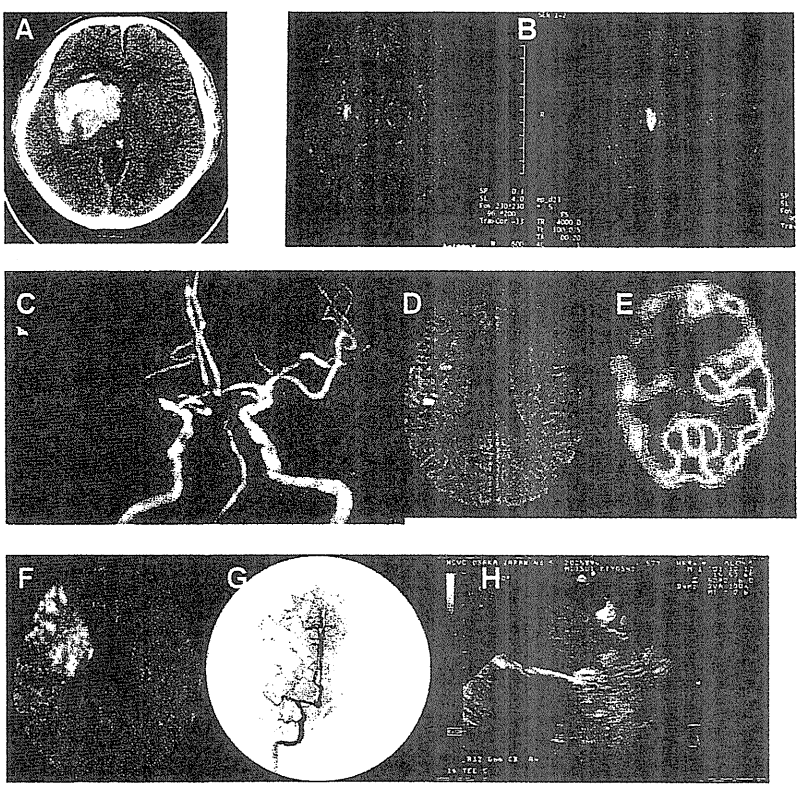

図 2　病系分類別特徴的画像所見

A：高血圧性脳内出血(被殻)CT 画像，B：ラクナ梗塞の MRI(基底核に 1 cm 大の梗塞)，C～E：アテローム血栓性脳梗塞，MRA(右中大脳動脈高度狭窄：C)，MRI(前頭葉梗塞巣：D)，脳血流 SPECT(右中大脳動脈領域の血流低下：E)を示す．F～H：心原性脳塞栓症，右前頭葉の皮質を含んだ急性梗塞(F)，中大脳動脈の塞栓性途絶(G)，経食道心エコーによる左心耳内血栓(H)を示す．

略　語

CT : computed tomography

MRI : magnetic resonance imaging

SPECT : single photon emission computed tomography

MRA : magnetic resonance angiography

関連事項

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ラ法による狭窄部からの塞栓子(microembolic signal)の検出やモニターが治療効果の評価に有益である．

3．ラクナ梗塞

ラクナ梗塞は，穿通枝動脈支配に一致した直径 15 mm 以下の梗塞のことである．ラクナ梗塞の発症機序は複数の病態を含む．3〜7 mm の小さなラクナは直径 200 μm 以下の穿通枝のリポヒアリン変性閉塞により生じる．頭蓋内主幹動脈病変がなく，頸動脈や大動脈弓，心臓に明らかな塞栓源がなく，画像上放線冠や半卵円中心，視床，基底核，橋に直径 15 mm 以下の脳主幹動脈から連続していない小病変であれば，症候的，画像的，病態生理的にもラクナ梗塞と確定する．

4．心原性脳塞栓症

側副血行路の発達を待たず急速な梗塞巣の形成をきたし，再灌流に伴い出血性変化や高度の脳浮腫，脳ヘルニアの形成に至り，また 1 日当たり約 0.5〜1 %の急性期再発が発症 2 週間以内に生じることから最も死亡率が高く，機能予後も不良である．非弁膜症性心房細動，僧帽弁狭窄，心筋梗塞後心室瘤，機械弁，心筋症における心内血栓，卵円孔開存が原因となり，経食道心臓エコーやホルター心電図が診断に有効である．

5．高血圧性脳内出血

CT により高吸収域を，被殻・視床・小脳・橋・皮質下に認める．高血圧の既往がない皮質下および被殻出血には血管異常が合併することがあるので，MRA/MRI や脳血管造影が必要となることもある．

脳梗塞の急性期治療

1．基本治療

脳卒中専門医師，看護師，理学療法士のチームにより急性期脳卒中専門病棟(stroke care unit；SCU/stroke unit；SU)への入院が推奨される．頭部挙上を禁じベッド上安静を指示し，脱水予防と血液粘度を低下させるため持続輸液を行い，脳灌流圧の維持を行う．急性期は交感神経系が亢進し高血圧状態を示すが，脳血流の自動調節能が障害されているので降圧療法は原則禁忌である．症状動揺がなければ，順次頭部挙上を評価後許可する．意識障害のため経口摂取が困難な場合経管栄養を開始，意識レベルが良好であれば，嚥下機能の評価後，誤嚥に注意を払い経口摂取を行う．発熱や高血糖の是正も必須である．

2．超急性期血栓溶解療法

発症 3 時間以内に治療が開始できる超急性期すべての脳梗塞に対しては **t-PA**(tissue plasminogen activator，アルテプラーゼ)の適応となる．投与基準を満たし，CT 上早期虚血徴候(early CT sign：レンズ核構造の不鮮明化，島皮質の消失，皮髄境界の不鮮明化)陰性であれば t-PA 0.6 mg/kg を静脈投与する．t-PA による早期再灌流療法は，症候が軽快し軽微な後遺症で社会復帰できる割合が 27 %から 37 %へと増す．高度の高血圧の合併，重症例や昏睡症例，高齢者において頭蓋内出血による症状悪化や死亡の危険が増加する．また，発症 6 時間以内の中大脳動脈への塞栓症に対してウロキナーゼによる動脈内血栓溶解療法の有用性も示され，発症 3 時間から 6 時間以内の脳梗塞に適応となると考える．

3．抗血栓療法

t-PA 適応症例以外は，抗血小板療法としてアスピリン(100〜200 mg/日)の早期投与が推奨される．アテローム血栓性脳梗塞には抗血小板作用も有する抗トロンビン薬アルガトロバンの併用，ラクナ梗

塞には血管拡張作用も有するトロンボキサン合成酵素阻害薬オザグレルナトリウムが投与される．心原性脳塞栓症では軽症や分枝閉塞でない限り24時間待機し，出血性変化が軽度であれば，ヘパリン・ワルファリンによる抗凝固療法が導入される．また，t-PA投与後24時間以内は抗血栓療法を待機する．

4．脳保護薬等

活性酸素消去薬(フリーラジカル・スカベンジャー)エダラボンが脳保護薬として，脳浮腫に対して浸透圧利尿薬10％グリセリンが併用される．血行力学的脳梗塞に対し，血液灌流量の増加かつ粘稠度改善のため低分子デキストランが追加される．

5．降圧療法

脳梗塞急性期には収縮期血圧220 mmHg以上，拡張期血圧120 mmHg以上でない限り，あるいは平均血圧130 mmHg以上の高度の高血圧を示さない限り，積極的な降圧を行うべきではない．しかし，大動脈解離，急性心筋梗塞，急性心不全や腎不全等生命にかかわる高度の高血圧が合併するときには慎重な降圧が例外的に行われる．t-PA投与症例では投与後24時間は180/105 mmHg以上のときに限り，塩酸ニカルジピンやジルチアゼムによる降圧を神経学的所見を評価しながら行う．

高血圧性脳内出血の超急性期治療

1．基本治療

安静と呼吸循環管理が基本である．消化管出血の予防のためのH_2受容体拮抗薬やプロトンポンプ阻害薬が投与される．脳浮腫による脳ヘルニアや意識障害を認めた場合，グリセロールが投与される．

2．降圧療法

高血圧性脳内出血超急性期の降圧目標については，収縮期180 mmHg以上，拡張期105 mmHg以上，または平均血圧130 mmHg以上のいずれかが20分以上持続すれば治療開始すべきである．降圧目標は前値の80％，130～150/70～90 mmHgになるように，静脈投与薬剤(ニカルジピン，ジルチアゼム，ニトログリセリン)が投与される．これらは止血が完了していない症例や頭蓋内圧の亢進の症例では禁忌とされているが，血腫拡大や脳浮腫進展の危険に細心の注意を払って処方しているのが現状である．

3．手術適応

被殻出血では推定血腫量が30 mL，皮質下出血50 mL以上でかつ中等度以上の意識障害が出現，小脳出血では直径3 cm以上で意識障害が発現する例が開頭血腫除去術や内視鏡的血腫吸引術が救命目的で適応となる．橋，視床出血は閉塞性水頭症によるヘルニアに対して救命目的で脳室ドレナージが適応になるときがある．

用語解説――――t-PA

組織プラスミノーゲンアクチベータ．血栓に親和性の高いプラスミンを活性化させ，血栓を溶解させる．半減期が短く，脳梗塞後の出血性変化の悪化を最小限にとどめるアルテプラーゼが使用可能である．

関連事項

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脳血管疾患合併時の薬物療法(急性期) ▶▶ 286頁

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Ⅱ．トピックス 各論

Treatable dementia（治療可能な認知症）を見逃さないために

大槻俊輔[*1]　宮地隆史[*2]　松本昌泰[*3]

Abstract 認知症は，早期発見し適切な対応をすれば急激な進行を防ぎ遅らせることができる．一部の認知症は手術や内服療法により劇的に治療可能である．家族がおかしいと思ったらぜひとも専門医を受診することを勧める．早期発見のための問診や診察所見，補助検査についてまとめる．

Key words 正常圧水頭症（normal pressure hydrocephalus），慢性硬膜下血腫（chronic subdural hematoma），甲状腺機能低下症（hypothyroidism），ビタミン欠乏症（vitamin deficiency），脳腫瘍（brain tumor）

認知症は単なる老化現象ではなく，脳の障害により高次機能が低下する病気の総称である．物忘れが続いて，日常生活や社会生活に支障をきたす状態である．例えば，食べた朝ごはんのおかずを忘れるくらいではなく，朝ごはんを食べたこと自体を忘れるような状態である．

認知症では必ず現れる症状があり，物忘れなどの記憶障害や判断能力の低下，様々な物事の実行機能の障害，失語や失認などで，これらを中核症状という．この症状に精神的な不安や混乱，環境など様々な要因が加わることにより起きる暴言，暴力，徘徊といった行動障害を行動心理症状または周辺症状という．本人は周りを困らせてやろうなどの気持ちはなく，不安でどうしていいかわからない状況でこのような症状が出る．周りの人が少し大きな声やきつい表現で注意してもその理由が理解できないので，大きな恐怖や不安となって伝わり，興奮したり暴れたりするといわれている．

しかし，早期に発見して原因となる要因を改善し，良い対応をすると症状を改善させることができる．悪いところを指摘するより良いところを褒めることにより，つまり周囲が良い対応をすることは，すべての認知症の進行を遅らせたり，一時的にも改善させる可能性がある．

それでは，認知症の診断にはどうすればよいであろうか？　本人および同居している家族から問診，それから診察を行う．次に認知機能検査として改定長谷川式簡易知能評価スケールなどを選択して，総合的に臨床診断を行う．これに血液検査や多くの施設で検査可能な頭部X線CT（コンピューター断層撮影）や全国で3,000以上の施設に導入されているMRI（磁気共鳴画像），全国で約900施設に設置されている脳血流SPECT（単一光子放出コンピューター断層撮影）検査により，診断を正確にする（表1，図1）．

これらの画像検査により，早期治療につながり，患者の病状の進行を少しでも遅らせることができる．CTでは脳梗塞や脳出血の既往が確認できる．MRIでは，脳の局所的な萎縮，例えばアルツハイマー病における海馬の萎縮，水頭症における脳室

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