Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET

Hiroshi Yamauchi, Hidenao Fukuyama, Yasuhiro Nagahama, Hidehiko Nabatame, Kazuo Nakamura, Yasumasu Yamamoto, Yoshiharu Yonekura, Junji Konishi, Jun Kimura

Abstract

Objectives—In major cerebral arterial occlusive diseases, patients with inadequate blood supply relative to metabolic demand (misery perfusion) may be at increased risk for cerebral ischaemia. This study investigated whether patients showing misery perfusion on PET have a high risk of recurrent ischaemic stroke.

Methods—The relation between the regional haemodynamic status of cerebral circulation and the subsequent risk of recurrent stroke was prospectively evaluated in 40 patients with symptomatic internal carotid or middle cerebral arterial occlusive diseases who underwent PET. Patients were divided into two haemodynamic categories according to the mean hemispheric value of oxygen extraction fraction in the hemisphere supplied by the artery with symptomatic disease: patients with normal oxygen extraction fraction and those with increased oxygen extraction fraction (misery perfusion). All patients were followed up for at least 12 months.

Results—The one year incidence of ipsilateral ischaemic strokes for patients with normal oxygen extraction fraction and those with increased oxygen extraction fraction were two of 33 and four of seven patients respectively. A significantly higher incidence of ipsilateral strokes was found in patients with increased oxygen extraction fraction (Fisher's exact test; P = 0.005). In patients with increased oxygen extraction fraction, three of four strokes were watershed infarctions and the location of the infarction corresponded with the area of increased oxygen extraction fraction.

Conclusion—These findings contradict conclusions of a previous study and suggest that patients with major cerebral arterial occlusive diseases and misery perfusion have a high risk for recurrent ischaemic stroke.

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Keywords: cerebrovascular disease; computed tomography; haemodynamics; stroke risk

In patients with major cerebral arterial occlusive disease, an inadequate blood supply relative to metabolic demand (misery perfusion) may increase the risk of cerebral ischaemia, suggesting that identification and optimal treatment of patients with misery perfusion could help prevent stroke. However, it remains unclear whether patients with misery perfusion on PET have a high risk of ischaemic stroke, especially strokes of haemodynamic origin. Although case reports and retrospective studies have indicated that bypass surgery relieved patients with misery perfusion from abnormal haemodynamics and recurrent ischaemic attacks, few studies have systematically investigated the relation between cerebral haemodynamics determined by PET and the subsequent risk of stroke. A previous longitudinal study did not find a relation between abnormal cerebral haemodynamics and the subsequent occurrence of stroke, but the data of the study were limited and not conclusive because of the few patients studied. To further investigate whether patients with misery perfusion have a high risk of recurrent ischaemic stroke, we prospectively followed up 40 patients with severe symptoms who had already undergone treatment with symptomatic major cerebral arterial occlusive disease who underwent PET.

Methods

PATIENTS

We followed up 40 patients with symptomatic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease who were under medical treatment. All subjects were prospectively selected from 52 patients with symptomatic ICA or MCA occlusive disease in whom regional cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO₂), oxygen extraction fraction (OEF), and cerebral blood volume (CBV) were measured using PET at our university hospital between 1985 and 1994. They were consecutive patients who had been referred to the department of neurology from related hospitals for pathophysiological study of major cerebral arterial occlusive diseases using PET. Thus they were not consecutive patients in the related hospitals. Inclusion criteria for the PET studies were as follows: (1) angiographically documented occlusion or stenosis (> 70% diameter reduction) of the ICA or MCA; (2) transient ischaemic attacks or minor stroke with mild disability in the arterial distribution distal to the lesion. Exclusion criteria for the follow up study were patients who were scheduled for vascular reconstruction surgery. Seven underwent superficial temporal artery—MCA anastomosis between 1985 and March 1988. During this period, indications

Department of Neurology
H Yamauchi
J Kimura
Y Nagahama

Department of Brain Pathophysiology
H Fukuyama

Department of Radiology and Nuclear Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan
Y Yonekura
J Konishi

Department of Neurology, Shiga Medical Center for Adult Diseases, Shiga, Japan
H Nabatame
K Nakamura

Department of Neurology, Kyoto Second Red Cross Hospital, Kyoto, Japan
Y Yamamoto

Japan Foundation for Aging and Health, Tokyo, Japan
H Yamauchi

Correspondence to: Dr H Fukuyama, Department of Brain Pathophysiology, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606, Japan
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Table 1  Characteristics of patients at entry

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>Normal</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>40</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
<td>41-80</td>
<td>41-80</td>
<td>47-74</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 30</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Female 10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Amputation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hemispheric TIA</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Minor stroke</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Most recent symptom:</td>
<td>30-90 Days before PET</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>4-12 Months</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Other medical illness:</td>
<td>Hypertension</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Prior MI</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Angiography:*</td>
<td>MCA stenosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>MCA occlusion</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis(intracranial)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>ICA stenosis(extracranial)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ICA occlusion</td>
<td>29</td>
<td>25</td>
</tr>
</tbody>
</table>

*Most severe angiographic lesion in MCA or ICA ipsilateral to symptoms.
TIA = transient ischaemic attack; MI = myocardial infarction; ICA = internal carotid artery; MCA = middle cerebral artery.

for this surgery were controversial, and these seven patients underwent the surgery after providing informed consent as part of a study to evaluate the haemodynamic and metabolic effects of this surgery, irrespective of cerebral haemodynamics. After March 1988, all patients except those with extracranial ICA stenosis were medically treated. Five patients with unilateral extracranial ICA stenosis underwent carotid endarterectomy between 1988 and 1994, irrespective of cerebral haemodynamics.

The subjects included 30 men and 10 women aged 41 to 80 (mean: 62 (SD) 8 years; table 1). Six patients had had transient ischaemic attacks and 34 had had minor stroke. The intervals between the most recent ischaemic event and PET studies ranged from one to 55 (mean 8 (SD) 11 months.

Recurrent symptoms before PET after angiographic demonstration of ICA or MCA disease were identified in only one patient who had intracranial ICA stenosis and experienced orthostatic transient ischaemic attacks despite antiplatelet treatment (patient 1 in table 2). In all patients, CT disclosed only minor abnormalities in the MCA territory or watershed areas of the hemisphere with major arterial disease. Only one patient also had symptoms related to posterior cerebral artery distribution and CT also disclosed a low density area in the posterior cerebral artery territory ipsilateral to major arterial disease. Conventional angiography at the time of the first stroke disclosed unilateral ICA occlusion in 23 patients, unilateral extracranial ICA stenosis (70 and 90%) in two, unilateral intracranial ICA stenosis (80, 90, 95, and 95%) in four, unilateral MCA occlusion in two, unilateral MCA stenosis (90%) in one, ICA occlusion with contralateral extracranial ICA stenosis (50 and 80%) in two, ICA occlusion with contralateral intracranial ICA stenosis (65 and 70%) in two, MCA occlusion with contralateral extracranial ICA stenosis (60%) in one, and bilateral ICA occlusions in three patients. In eight patients with bilateral disease, the symptomatic vascular lesion was unilateral. Of five patients with ICA or MCA occlusion and contralateral ICA stenosis, the lesion involved ICA or MCA occlusion in four patients and intracranial ICA stenosis in one patient. The vertebrobasilar system was angiographically normal in all but two patients. All but two (with extracranial ICA stenosis) patients fulfilled radiological entry criteria for the Extracranial-Intracranial Bypass Trial (stenosis or occlusion of the trunk or major branches before the bifurcation or trifurcation of the MCA; stenosis of the ICA at or above the C2 vertebral body; or occlusion of the ICA), and 17 of 40 patients met the clinical criteria (transient ischaemic attack or stroke within three months before entry).

All patients were treated with antiplatelet therapy (aspirin or ticlopidine HCl), but the treatment of risk factors and use of other drugs were left to individual clinical judgement. All patients were examined at one month intervals after PET studies. At each visit, an interim history was obtained and a neurological examination was performed. End points were defined as the occurrence of stroke or death. In patients with recurrent stroke, MRI or CT was obtained and compared with initial studies to confirm the occurrence of recurrent stroke. Stroke in the previously symptomatic arterial territory without evidence of primary intracranial haemorrhage was classified as an ipsilateral ischaemic stroke.

POSITRON EMISSION TOMOGRAPHY
Regional CBF, CMRO2, OEF, and CBV were measured with PET at the beginning of the observation period. In 24 patients studied between 1985 and 1989, PET was performed.
with a Positologica III PET scanner and the remaining examinations between 1990 and 1994 were carried out with a PCT3600W, both manufactured by Hitachi Medical Co., Japan. Technical data regarding these two scanners are described elsewhere. Each device has four and seven rings and can obtain seven and 15 tomographic slices in a single scanning process. The best spatial resolution is 7.6 and 6.5 mm at full width half maximum at the centre of the scanning field, and the axial resolution is 12 and 7 mm at the centre. Before the study, a 186 germanium–18 gallium transmission scan was performed for 20 minutes to allow attenuation correction. Cerebral blood flow was determined while the subject continuously inhaled 18 O2 through a mask. Measurements of CMRO2 and OEF were obtained during continuous inhalation of 18 O2. Data were collected for five minutes. A single breath of 18 O2 was used to measure CBV. We calculated CBF, CMRO2, and OEF by the steady state method, and CMRO2 and OEF were corrected by CBV. The ratio CBF/CBV was calculated pixel by pixel as an indicator of cerebral perfusion reserve. All subjects and their relatives gave informed consent to the PET study.

We analysed three (Positologica III) or six (PCT3600W) tomographic planes located 43 to 82 mm above and parallel to the orbitomeatal line, which corresponded to the levels from the basal ganglia and thalamus to the centrum semiovale. The region of interest was placed on the CBF images and CT-PET imaging coregistration was not used. Each image was examined by placing a total of 18–20 circular regions of interest 10 mm in diameter over the cerebral cortex. According to the atlas developed by Kretschmann and Weinrich,21 the regions of interest in all images included the distribution of the anterior cerebral artery (ACA), the MCA, and the posterior cerebral artery, as well as the watershed areas between the ACA and MCA (anterior watershed) and MCA and PCA (posterior watershed). In five patients with infarction in the cerebral cortex, the regions of interest corresponding to the infarcted area were excluded from analysis, by comparing PET images with CT or MRI. The mean hemispheric value was calculated as the average of the MCA, anterior watershed, and posterior watershed regions of interest, and was weighted by region size.

The haemodynamic state of cerebral circulation in the hemisphere ipsilateral to symptomatic ICA or MCA lesion was determined based on the value of OEF. Using PET, we studied 10 normal subjects, eight men and two women aged 35 to 78 (mean 52 (SD 3) years. In five subjects (four men and one woman), PET was performed with a Positologica III PET scanner and the remaining five examinations were carried out with a PCT3600W. Although no significant differences were found in age or mean hemispheric CBF, CMRO2, OEF, CBV, or CBF/CBV values between these two populations (Student’s t test), PET data obtained by the camera with higher spatial resolution had a tendency to provide higher PET values. The normal values in 20 hemispheres ranged from 36.1 to 51.7 (mean 42.6 (SD 5.1)% for OEF. No significant difference among the individual regions of interest (MCA, anterior watershed, and posterior watershed) existed in this subgroup of normal subjects (analysis of variance with post hoc Scheffe’s F test). Absolute hemispheric values beyond the upper 95% confidence intervals defined in normal subjects (above 53.3%)
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Table 2 continued

<table>
<thead>
<tr>
<th>Collaterals</th>
<th>Oxygen extraction fraction</th>
<th>Recurrent ischaemic stroke</th>
<th>Interval after PET (months)</th>
<th>Related conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Side, type, and location of infarct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal</td>
<td>Increased</td>
<td>Ipsilateral, cortico-subcortical MCA-PCA watershed</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ophthalmic leptomeningeal</td>
<td>Increased</td>
<td>Ipsilateral, lacune in internal capsule</td>
<td>1</td>
<td>Unknown (poor control of DM)</td>
</tr>
<tr>
<td>A com ophthalmic</td>
<td>Increased</td>
<td>Ipsilateral, subcortical ACA-MCA watershed</td>
<td>2</td>
<td>Unknown (poor control of DM)</td>
</tr>
<tr>
<td>A com</td>
<td>Increased</td>
<td>Ipsilateral, subcortical ACA-MCA watershed</td>
<td>11</td>
<td>Unknown</td>
</tr>
<tr>
<td>Leptomeningeal</td>
<td>Increased</td>
<td>Contralateral, striato-capsular infarct</td>
<td>11</td>
<td>Suspect dehydration due to fever (pyelonephritis)</td>
</tr>
<tr>
<td>P com</td>
<td>Normal</td>
<td>Ipsilateral, subcortical ACA-MCA watershed</td>
<td>2</td>
<td>Excessive drop in blood pressure (108/64), anaemia</td>
</tr>
<tr>
<td>Leptomeningeal</td>
<td>Normal</td>
<td>Ipsilateral, cortico-subcortical ACA-MCA watershed</td>
<td>2</td>
<td>Suspect dehydration after hiking</td>
</tr>
<tr>
<td>A com</td>
<td>Normal</td>
<td>Deep MCA watershed</td>
<td>30</td>
<td>Excessive drop in blood pressure (130/50), dehydration (PCV 51-4%), Progression of the L ICA stenosis (90%)</td>
</tr>
<tr>
<td>A com</td>
<td>Normal</td>
<td>Ipsilateral, small frontoparietal immediately-subcortical infarcts</td>
<td>57</td>
<td>Contralateral intracranial ICA Stenosis (90%) with ulceration</td>
</tr>
</tbody>
</table>

were considered abnormal. The 40 patients were divided into two haemodynamic categories according to the OEF data: patients with normal OEF and those with increased OEF (misery perfusion).

STATISTICAL ANALYSIS
We compared the incidence of recurrent stroke in patients with normal OEF and that of those with increased OEF using Fisher's exact test; Significance was established at $P < 0.05$.

Figure 2  PET images of cerebral blood flow (CBF; first column) and oxygen extraction fraction (OEF; second column) before recurrence and T2 weighted MRI images (third column) after recurrence in three patients with increased OEF and ipsilateral recurrent stroke (watershed infarction) within the first year of follow up. Arrows indicate the site of recurrent stroke and corresponding areas on PET images. PET images of patient 1 were resliced for the coregistration to MRI. Numbers correspond to the patient numbers in table 2.
Figure 3 PET of cerebral blood flow (CBF; first column) and oxygen extraction fraction (OEF; second column) and the ratio of cerebral blood flow to cerebral blood volume (CBF/CBV; third column) before recurrence and T2 weighted MRI images (fourth column) after recurrence in two patients with normal OEF and ipsilateral recurrent stroke (watershed infarction) within the first year of follow up. Arrows indicate the site of recurrent stroke. Numbers correspond to the patient numbers in table 2.

Results
No patient showed a significant change in PaCO₂ during PET. Based on PET measurements in the hemisphere supplied by the symptomatic ICA or MCA (in the “ipsilateral” hemisphere), 33 patients had normal OEF values and seven had increased OEF values (miser perfusion; table 1). Patients with increased OEF also had decreased CBF and CBF/CBV values (fig 1). The OEF values of the asymptomatic (“contralateral”) hemispheres were normal in all 33 patients with normal ipsilateral OEF, whereas they were normal in four and increased in three in seven patients with increased ipsilateral OEF.

Seven (six ipsilateral and one contralateral) ischaemic strokes occurred during the first two months after entering the study. Of patients with normal OEF values, two developed ipsilateral stroke. These two patients had a somewhat low CBF/CBV value (fig 1, bottom). Of patients with increased OEF values, four developed ipsilateral stroke and one had stroke in the contralateral hemisphere with increased OEF. Because no deaths occurred within the first year, all 40 patients were at risk for 12 months. The one year incidence of stroke in patients with increased OEF was five of seven for all strokes and four of seven for ipsilateral ischaemic strokes. The one year incidence of stroke for patients with normal OEF was two of 33 for all strokes and ipsilateral ischaemic strokes. The incidence of ipsilateral ischaemic strokes in patients with increased OEF and normal OEF was 57.1% and 6.0% respectively (Fisher’s exact test; P = 0.005). A significant difference was found between patients with ipsilateral stroke and those without in the value of OEF (mean 51.6 (SD 5.2) v 45.5 (SD 6.0%), Mann-Whitney U test; P < 0.05) or CBF/CBV (7.0 (SD 2.3) v 9.4 (SD 2.0)/min, P < 0.05).

All patients with recurrent stroke had minor stroke at entry. Minor stroke may carry a greater risk of recurrent stroke than transient ischaemic attacks. When 34 patients with minor stroke were analysed, the incidence of ipsilateral ischaemic strokes in patients with increased OEF and normal OEF was four of seven (57.1%) and two of 27 (7.2%), respectively (Fisher’s exact test; P = 0.0096). In our patients, the intervals between the most recent ischaemic event and PET studies varied (one to 55 months). When data from 33 patients with transient ischaemic attack or stroke within one year before entry were analysed, the results were three of five (60%) and two of 28 (7.1%), respectively (Fisher’s exact test; P = 0.0165).

Although five of six patients with ipsilateral recurrent stroke had hypertension or diabetes,
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Evidence of abnormal cerebral haemodynamics from PET implies a vulnerability to reduction in cerebral perfusion pressure and a tendency to develop cerebral infarction due to haemodynamic factors. No study has, however, shown a high incidence of haemodynamic infarction in patients with major cerebral arterial occlusive diseases and abnormal cerebral haemodynamics. In our study, five of six ipsilateral recurrent strokes during the first year of follow up were watershed infarctions. The location of three strokes in patients with increased OEF corresponded to the area of increased OEF. Although no apparent associated conditions were identified in these strokes in patients with increased OEF, two strokes in patients with normal OEF (but somewhat low CBF/CBV) were related to conditions leading to deterioration in haemodynamic state; a reduction in systemic blood pressure or haemoconcentration due to dehydration. These findings suggest that patients with major cerebral arterial occlusive disease have a tendency to develop haemodynamic infarctions with (in patients with normal OEF) or without (in patients with increased OEF) apparent additional causes of haemodynamic disturbance. In one study, watershed infarctions accounted for 72% of delayed strokes in patients with ICA occlusion. Associated conditions suggesting haemodynamic mechanisms included raised packed cell volume, severe heart disease with episodes of decreased output and syncope, and severe disease of the contralateral ICA. Appropriate treatment of the causes of systemic haemodynamic disturbance may be crucial in the management of patients with major cerebral arterial occlusive disease, especially patients with increased OEF. In patients with major cerebral arterial occlusive disease, individual treatment strategies according to the haemodynamic state of each patient may be needed, including consideration of the degree of hypertension control and the optimal packed cell volume. In our patients with follow up stroke, optimal treatment and good compliance might have prevented haemodynamic strokes.

Few studies have systematically investigated the relation between cerebral haemodynamics determined by PET and the subsequent risk of stroke. A longitudinal study by Powers et al did not show a relation between abnormal cerebral haemodynamics (abnormal CBV/CBF ratio defined as outside normal range) and the subsequent occurrence of stroke. If patients with haemodynamic abnormality ranging from mild to severe, such as those with an abnormal CBV/CBF ratio, were considered as a group, they did not show a high risk for early stroke. A small subgroup of patients with increased OEF, however, could have an increased risk of developing a stroke, because both their study and ours included small patient samples and patient selection could have biased the outcome causing different results. The incidence of ipsilateral stroke within the first year in their study (one of 30) was apparently lower than that in our sample.
Bypass within formed PET underwent patients more cerebral haemodynamics may include more patients with poor collateral development than were included in the comparable group in the study by Powers et al, leading to the higher risk for ischaemic stroke seen in our study. Moreover, two of five patients with intracranial ICA stenosis showed increased OEF and developed ipsilateral ischaemic strokes in our study, whereas a patient with intracranial ICA stenosis and normal haemodynamics was the only one to develop ipsilateral stroke in their study. Patients with symptomatic intracranial ICA stenosis are reported to have a high risk of stroke. The difference in haemodynamic state between these patients might have affected the results. Also, our study included more patients with minor strokes than the study by Powers et al; and all patients with recurrence initially had minor strokes. Lastly, differences in medical treatment and patient compliance would affect the results. Irrespective of these differences, the combination of these two PET studies shows that ipsilateral strokes within the first year occurred in four of 12 patients with increased OEF, and three of 58 patients with normal OEF. There is still a significant relation between the incidence of ipsilateral recurrent strokes and increased OEF (Fisher's exact test; P = 0.0139).

Recent studies of larger samples of patients using SPECT and intravenous injection of acetazolamide or transcranial Doppler sonography and CO2 inhalation have disclosed that a small subgroup of patients with highly impaired cerebrovascular reactivity at entry had an increased risk of developing a stroke during the follow-up period. A close relation has been shown between impaired cerebrovascular reactivity measured by both stimuli and increased OEF, supporting the finding that patients with increased OEF have a high risk of stroke. Other findings suggesting misery perfusion include (a) very low CBF/CBV ratio, poor collateral circulation through leptomeningeal anastomoses, decreased CBF without contralateral cerebellar hyperperfusion.

In conclusion, in our small, selected patient sample, patients with major cerebral arterial occlusive diseases and increased OEF (misery perfusion) showed a high risk of recurrent ipsilateral ischaemic strokes. Thus identification and optimal treatment of patients with this problem may be essential in preventing recurrent stroke. Firstly, the control and elimination of risk factors are desirable, but excessive falls in blood pressure must be avoided. Secondly, the causes of systemic haemodynamic disturbance such as dehydration and heart failure must be treated appropriately. Thirdly, besides antplatelet treatment, specific medical treatments including haemodilution and specific drugs may be beneficial. Lastly, patients not responding to current medical treatment might be indicated for vascular reconstructive surgery. We must seek the optimal medical treatment for patients with major cerebral arterial occlusive disease based on the haemodynamic state of each patient.

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NEUROLOGICAL STAMP

Louis Charles Alfred de Musset (1810-57)

After a brilliant scholastic career at the Lycée Henri IV, Musset, French poet, novelist, and playwright, briefly considered law and medicine as a career. He dabbled in painting before finally turning to literature. Musset contracted syphilis as a young man, which led to his early death. The syphilis caused an aortic aneurysm and aortic insufficiency. He developed a rhythmic movement of his head synchronous with his heartbeat. This phenomenon became eponymically known as Musset’s sign and was first described by A Delpech. Philatelically he was honoured as a great poet but is of medical interest because of Musset’s sign. He was honoured by his native country, France, in 1951. The stamp shown here is one produced by Romania in 1960 (Stanley Gibbons 2763, Scott 1343). Two colleagues Anton Chekov and Robert Koch are portrayed in the same series.

L F HAAS