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Clinical analysis of first-ever acute ischemic stroke involving the territory of paramedian mesencephalic arteries

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Abstract: To determine one-year clinical outcome of patients with first-ever acute ischemic stroke involving the territory of paramedian mesencephalic arteries (PMAS), we conducted a prospective study evaluating the cognitive functions of 28 patients with PMAS. Neuropsychological tests were performed during the first month of stroke onset and at the 12^{th} month of follow-up. There were 12 women and 16 men. Mean age of onset for women and men was 70 years and 65 years, respectively. Progressing strokes occurred in 62% of patients and 96% developed a full-blown picture of the clinical triad of akinetic mutism, hypersomnolence, and bilateral blepharoptosis and ophthalmoparesis. Involuntary movements occurred in 6, and focal myoclonus in 4 patients. The top four associated risk factors were hypertension (68%), hyperlipidemia (57%), diabetes mellitus (46%), and atrial fibrillation (36%). Unilateral midbrain infarctions occurred in 12 patients and bilateral lesions in 16. Thalamic infarctions were unilateral in 10 and bilateral in 13 cases. Three of the 28 (11%) patients died of recurrent cerebral infarctions within 1 year of the onset of PMAS. The recurrent infarctions involved the basilar artery territory in two cases and the carotid system in another. One patient died of acute myocardial infarction. Of the 24 patients who had survived the stroke by 1 year, 20 (71%) developed dementia. We conclude that first-ever ischemic stroke with PMAS is not a benign syndrome. Most patients developed dementia by 1 year after the stroke.

Keywords: Akinetic mutism, cerebral infarction, dementia, hypersomnolence, paramedian mesencephalic artery, midbrain, ophthalmoplegia, ptosis

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1 Introduction

Top of the basilar artery syndrome [1] (TBAS) has two different clinical forms, namely, posterior cerebral artery syndrome (PCAS), and mesencephalic artery syndrome (MAS) [2] or paramedian mesencephalic artery syndrome (PMAS). PCAS is more common than PMAS. However, PCAS and PMAS may occur concurrently, and therefore TBAS is an appropriate term to describe the overlap syndrome. Before the era of magnetic resonance imaging (MRI), PMAS [2, 3] had frequently been overlooked due to its rarity [2–10] or a poor sensitivity of computed tomography (CT) in showing up small infarcts in the midbrain. The diagnosis depends on the clinical presentation of the triads of akinetic mutism, hypersomnolence, and third nerve palsy, and autopsy findings showing an occlusion of one or more of the posterior thalamoperforating arteries of Percheron [2–5, 7–9]. We herein present the clinical and radiological features of 28 patients with PMAS, and analyze the 1-year clinical outcome.

2 Statistical methods and Experimental Procedures

Among 164 patients with first-ever acute ischemic strokes involving the posterior circulation, the vertebrobasilar artery systems, twenty-eight (17%) patients fulfilled the clinical and radiological criteria of the paramedian mesencephalic artery syndrome (PMAS). The clinical criteria for diagnosis of PMAS were the presence of two of the three cardinal features, hypersomnolence or drowsiness, akinetic mutism, and bilateral oculomotor nerve palsy [2–6]. The radiological criterion for diagnosis of PMAS was the radiological evidence of an acute infarction in the territory of the paramedian mesencephalic arteries, either an isolated unilateral paramedian midbrain infarction, or a bilateral midbrain infarction with or without the involvement of the medial thalamus on one side or both sides. To avoid confusion of the extent of the structures involved caused by PMAS, patients with a past history of strokes and previous supratentorial or infratentorial cerebral infarctions (VB system) were excluded. Nine patients with old thalamic infarcts, two with old occipital infarcts, and one with previous cerebellar infarct were excluded. Only those with first-ever acute stroke in the territory of the paramedian mesencephalic arteries were included in this study. Brain CT and MRI were performed in all patients within 5 days of onset of the symptoms. Magnetic resonance angiogram (MRA; 1.5 T) and diffusion weighted images (DWI) were carried out in only six patients of the latest hospitalizations, and electrophysiological studies in nine patients. MRA showed mild degree of segmental stenosis of the basilar artery in one patient, and concomitant segmental stenosis of uni- or bi-lateral M1 or PCA or both in 3 patients. Conventional angiogram was not performed.

The demographic characteristics, the initial symptoms and signs, the associated risk factors, and 1-year clinical outcome were analyzed. Cognitive functions were assessed using the Mini Mental State Examination (MMSE) [11] and Modified Mental Test (MMT) [12] at 1-month and 1-year after stroke onset. Evaluation on the cognitive function at the hyperacute stage of stroke was not possible because of the hypersomnolence and aki-

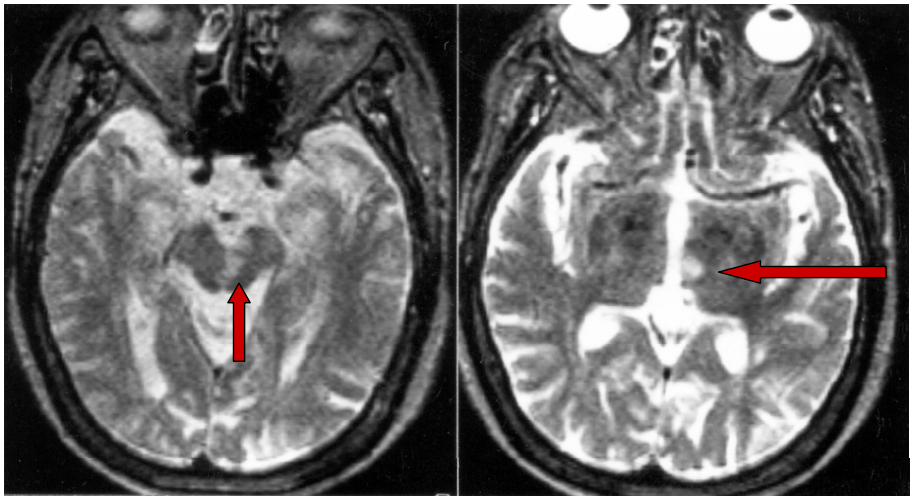
netic mutism. Patients with MMSE scores $\leq$25 and MMT score of $\leq$ 55/33 [12] were generally considered as having dementia. All patients had received oral administration of either aspirin or warfarin (for those with atrial fibrillation) for secondary stroke prevention. Treatments for the underlying diseases such as hypertension, diabetes mellitus, hyperlipidemia, and hyperuricemia continued during the studying period.

3 Results

For the 12 women and 16 men, age at onset of stroke ranged from 49 to 86 years. The mean age for women and men was 70 and 65 years, respectively. The initial symptoms and signs at onset of PMAS, and the associated risk factors were shown in Table 1. Progression of the symptoms and signs occurred in 62% of cases, and 96% of patients eventually developed a full-blown picture of the clinical triad of PMAS, with akinetic mutism, hypersomnolence, and bilateral blepharoptosis and ophthalmoparesis. The severity of akinetic mutism, hypokinesia, and hypersomnolence varied from patient to patient in the first week after onset. Acute bilateral blepharoptosis and ophthalmoparesis may be complete or incomplete, symmetrical or asymmetrical. Involuntary movements occurred in six out of 28 (21%) patients, and focal myoclonus was the most common (4 patients). Brain MRI showed unilateral midbrain infarcts in 12 patients (Fig. 1), and bilateral lesion in 16 patients (Fig. 2). Thalamic infarctions occurred in 23 patients, with unilateral involvement (Fig. 1) in 10 patients and bilateral involvement (Fig. 2) in 13 patients. The locations and laterality of the cerebral infarctions were shown in Table 2. Patients with MMSE scores $\leq$25 and MMT $\leq$ 55/33 were considered as having dementia [12]. Nine of 10 patients with atrial fibrillation were placed on warfarin therapy (INR ranged from 1.5 to 3.0). Fifteen were under 100mg of daily aspirin, and four patients were placed on either ticlopidine or clopidogrel because of intolerance to warfarin or aspirin. The 1-year clinical outcome was shown in Table 1.

4 Discussion

By definition, mesencephalic arteries are penetrating arteries arising from the proximal 3 mm to 4 mm of each posterior cerebral artery (PCA), the very proximal part of PCAs situated between the bifurcation of the basilar artery and the ostium of the posterior communicating artery. They are also called basilar communicating arteries, and thalamoperforating arteries of Percheron [2, 3, 8, 9]. Blood supply to the mesencephalon comes from the paramedian mesencephalic perforators and the circumflex arteries. There are 3 groups of small branches of mesencephalic arteries: (1) the anterior paramedian thalamo-subthalamic arteries; (2) the posterior paramedian arteries; and (3) the superior paramedian mesencephalic arteries. The polar arteries, the thalamogeniculate arteries, and the posteromedial choroidal and posterolateral choroidal arteries are not branches of the mesencephalic arteries [9]. There are many variations of the mesencephalic arteries. The paramedian and circumflex branches of the mesencephalic arteries provide



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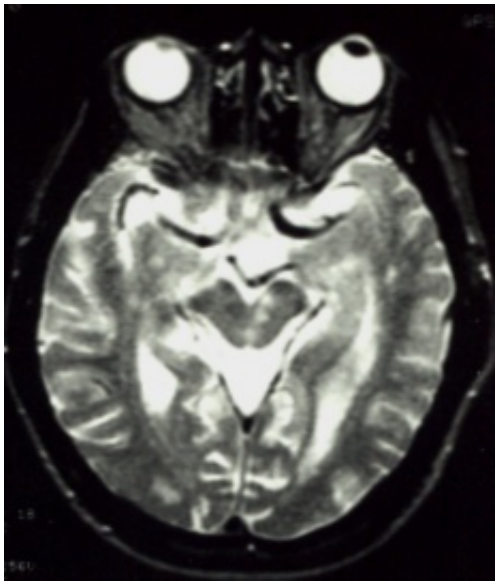

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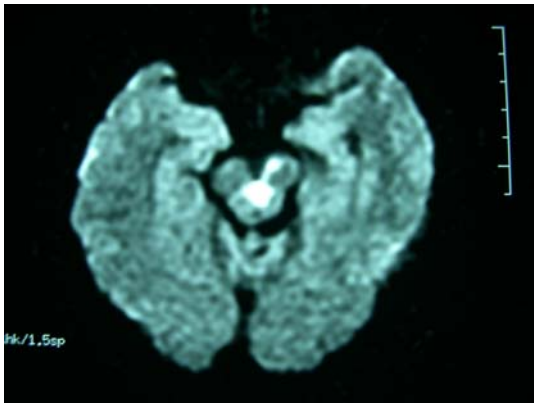

c)

Fig. 1 Magnetic resonance images show unilateral acute infarctions of the paramedian midbrain and medial thalamus in a patient with paramedian mesencephalic artery syndrome (T2-weighted image) (A). T2WI (B) and Diffusion weighted image (DWI) (C) of another case shows an infarction involving the paramedian midbrain and left cerebral peduncle.

blood supply to both sides of the paramedian midbrain, and parts of the medial thalami and subthalami. Therefore, a single episode of stroke with occlusion of these arteries may cause bilateral small infarctions in the midbrain and medial thalami, with clinical constellations of the symptom-triad of hypersomnolence, akinetic mutism, and bilateral drooping eyes (bilateral third cranial nerve palsy, nuclear type). In this study, PMAS constituted about 16% of all ischemic strokes involving the posterior circulation (28 out of 176 patients, including 164 with first-ever stroke and 12 with previous ischemic strokes

Table 1 Frequency of symptoms and signs at onset, associated risk factors, and one-year outcome of 28 patients with paramedian mesencephalic artery syndrome (PMAS).

	Number of patients	Frequency (%)
Symptoms and signs at onset:		
Akinetic mutism	22	79
Hypersomnolence	15	54
Double vision/ophthalmoparesis	14	50
Bilateral blepharoptosis	12	43
Vertigo	10	36
Unsteady gait	9	32
Weakness of limbs	9	32
Dysarthria	6	21
Involuntary movements*	6	21
Drop attacks	5	18
Numbness of limbs/face	2	7
Occipital headache	1	4
Associated risk factors:		
Hypertension	19	68
Hyperlipidemia	16	57
Diabetes mellitus	13	46
Atrial fibrillation (AF)	10	36
Hyperuricemia	9	32
Smoking	9	32
Non-AF cardiac arrhythmia and PFO**	6	21
Hyperfibrinogenemia ($\geq$400mg/dL)	4	14
Elevated hematocrit ($\geq$50%)	3	11
Anticardiolipin antibodies	1	4
Syphilis	1	4
Elevated serum homocysteine level***	1 (1 out of 13)	8
One-year outcome:		
Died (caused by: 2 BAO, 1 CAD, 1 AMI)#	4	14
Survived: with dementia 20 (71%), with residual ophthalmoparesis but no dementia 4 (4%)	24	86

* Myoclonus in 4 patients, athetosis in 1, and unilateral limb dystonia in another. **PFO, patent foramen ovale.
** Only 13 patients had blood levels of homocysteine; 1 of the 13 had elevated serum levels of homocysteine.
# BAO, basilar artery occlusion; CAD, carotid artery disease; AMI, acute myocardial infarction.

of the posterior circulation). This figure reflects that PMAS is not rare.

An elegant study on 71 patients with acute isolated thalamic infarctions covering a 13-year period, showed that 30% of cases had involvement of the thalami outside the classical territories (variant types), and 13% involved the anteromedian territory, and 6% the central territory [13]. The former has been accrued to cardiac embolism, whereas the

Table 2 Laterality of neuroimaging results for 28 patients with paramedian mesencephalic artery syndrome.

Brain structure Involved	Number of patients with Unilateral lesion	Bilateral lesions
Midbrain	12	16
Thalamus (medial)	10	13

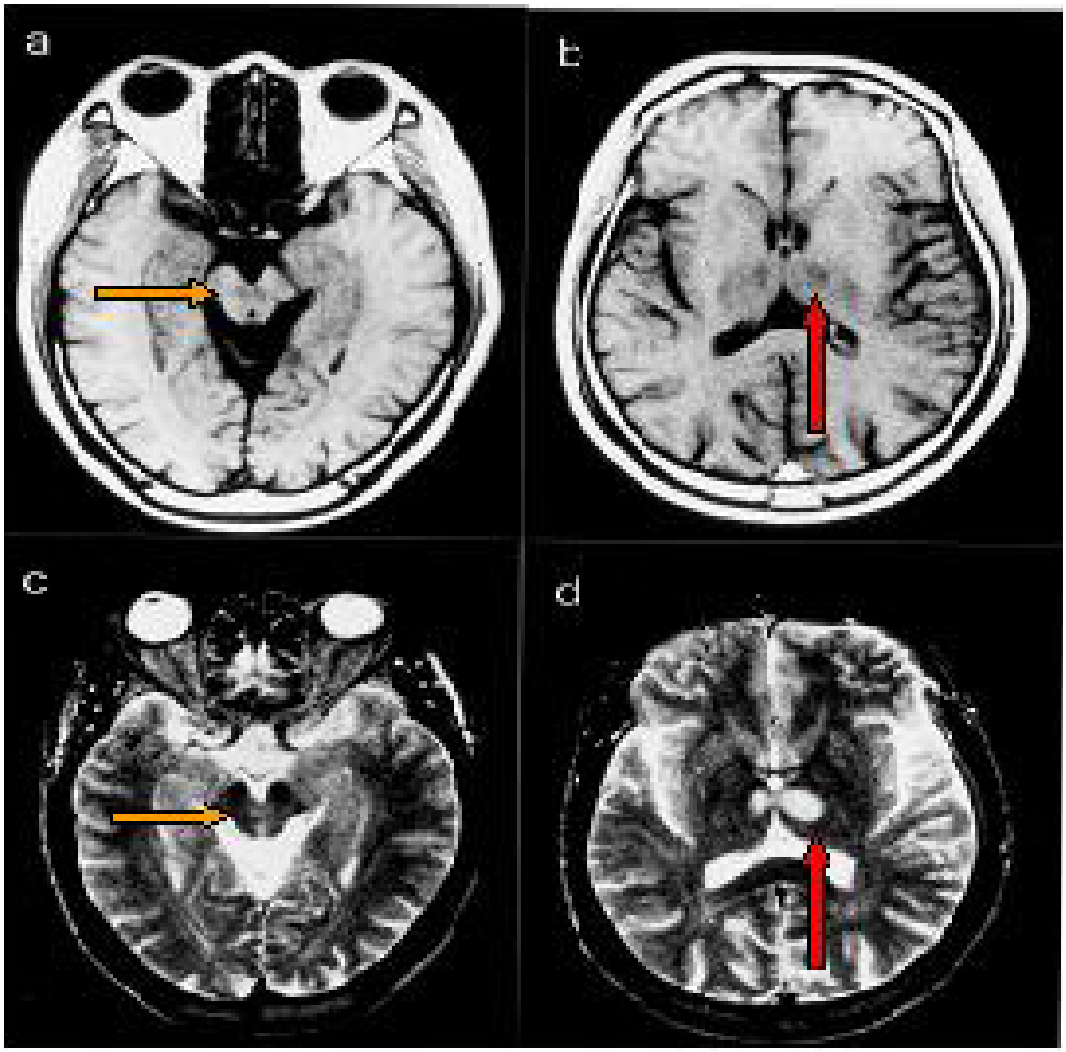

Fig. 2 Magnetic resonance images show acute bilateral infarctions of the paramedian midbrain and medial thalamus in a patient with paramedian mesencephalic artery syndrome (A, B: T1-weighted images; C, D: T2-weighted images).

latter was mostly due to microangiopathy. Regardless of whether the etiology was embolic (cardiac embolism or artery-to-artery embolism) or microangiopathic or thrombosis, both variants manifested with certain degree of either a cognitive impairment or some other neuropsychological deficit. Due to lack of autopsy data on our patients, we did not know the actual proportion of the etiological subcategories of our PMAS cases whether they

were caused by a cardiogenic brain embolism, an atherothrombosis, an artery-to-artery embolism, a microangiopathy or simply a cryptogenic infarction. Analysis on the risk factors revealed that hypertension (68%), hyperlipidemia (57%), and diabetes mellitus (46%) were the top 3 underlying diseases associated with PMAS. Atrial fibrillation occurred in only approximately one-third of our patients. This figure was in agreement with the previous report [13] that isolated paramedian thalamic infarct variant constituted 35% of all thalamic infarcts, and it was mostly caused by a cardiogenic embolism [14]. How frequent has this isolated thalamic stroke variant eventually hit on the midbrain is not clear. But, we speculate that there is certain proportion of overlapping between the isolated paramedian thalamic infarct and PMAS.

Different from the isolated inferolateral territory and the posterior thalamic infarcts, the anterior and paramedian variants frequently manifested with some behavior alterations, neuropsychological changes, and dementia [14]. The present study showed that 3 of the 28 (11%) PMAS patients died of recurrent cerebral infarctions within 1 year of first-ever stroke onset. The fatal recurrent infarctions involved the basilar artery territory in 2 cases, and the carotid system in another. One patient died of acute myocardial infarction. Of the 24 patients who had survived the stroke by 1 year, 20 (71%) developed dementia. Although the pathogenesis of dementia may be multifactorial, we agree with the hypothesis by Carrera and Bogousslavsky that a disconnection of the thalamocortical projections has occurred in patients with PMAS and medial thalamic lesions. Another plausible explanation is a disrupted mammillothalamic tract that resemble Wernicke-Korsakoff syndrome. Further pathological study might be needed.

Before the era of MRI and MRA in early 1980, Fisher has commented [15] that brain CT might not sensitive enough to detect a small infarction in the midbrain. Hence, PMAS could have been under-diagnosed in the past. Recognition of the unique clinical features, good MRI resolution for images of the brainstem structure, diffusion weighted-image (DWI) and apparent diffusion coefficient (ADC) map has improved the clinical and radiological diagnosis of PMAS. Lesions with an increased signal on DWI and a decreased signal on the ADC map are characteristics of the hyperacute or acute infarctions of PMAS (Fig. 1). Previous report has shown that typical radiological findings of PMAS would be a symmetrical bilateral paramedian thalamic and mesencephalic infarctions [16]. However, the present study shows that the infarctions can be asymmetrical and unilateral. This depends on the three different types of normal variations of the mesencephalic arteries. Type 1 variation is characterized by the ostia of the mesencephalic arteries arising from bilateral P1 segments of PCAs. Type 2 variant shows a common trunk of the mesencephalic arteries arising from one side of the P1 segment. In type-3-variation, an arcade of the perforating branches bridges the P1 segments of both PCAs. Asymmetrical bilateral or unilateral infarctions are most likely caused by occlusion of mesencephalic arteries with type 1 variation. Occlusion of the orifices of these arteries is often more severe on one side than the other, and therefore results in the formation of asymmetric paramedian mesencephalic and medial thalamic infarcts.

When an isolated small infarction involves the mesencephalic dorsal tegmental area,

the oculomotor nuclear complex and medial longitudinal fasciculus, a transient convergence retractory nystagmus ensues [6]. A dilatation of the third ventricle may occur [17, 18]. A pathological study had shown that it was due to squeezing and stenosis of the aqueduct of Sylvius [18]. When ataxia, hypokinesia, and thalamic dementia/amnesia are accompanying this phenomenon, we call it bilateral "Nothnagel syndrome" [17]. So far, we did not observe this unique syndrome, or sign of convergence retractory nystagmus among 28 of our patients with PMAS.

A recent case report on the complex abnormality of the eye movement called the "vertical one-and-a-half syndrome" in a 36-year-old man with sudden double vision and gait imbalance has been accrued to the involvement of the intralaminar nuclei of bilateral thalami, the pretectal and rostromedial tegmental region of the mesencephalon. Occlusion of the thalamoperforant and the superior paramedian mesencephalic arteries originating from a common branch of the communicant basilar artery was thought to be the cause [19]. Rarely, bilateral thalamic infarcts and mesencephalic lesions may also be caused by thrombosis of the internal cerebral veins rather than the mesencephalic arteries [20]. The presence of a hyperdense sign of the cerebral sinuses or cerebral veins and filling defects in the cerebral venous sinuses in a contrast-enhanced CT are distinctive features [20].

As all other stroke syndromes, the pathogenesis and etiologies of PMAS are diverse. Pathological studies have shown that atherosclerosis [3, 21] or embolism [1, 6] may be 2 common causes. A dislodged embolus following percutaneous transluminal coronary artery angioplasty may occlude the mesencephalic arteries by chance [6]. However, a dissecting microscopic examination of the brain of a patient died of an ischemic stroke with midbrain ptosis showed that the mesencephalic penetrating arteries were patent [7]. This provided the evidence that the exact cause (thrombosis or microemboli) of some mesencephalic infarction cannot be determined, and it was called a "cryptogenic" infarction. Furthermore, in some circumstances, paramedian thalamic infarcts of PMAS overlap with so-called "atypical" thalamic lacunar syndromes [22]. Hence, we would like to extend the etiological classification of PMAS in the subcategory of: (1) the cardioembolic cause, (2) an artery-to-artery embolism, (3) an atherothrombosis, (4) a microangiopathy with a lacunar syndrome, (5) an undetermined or cryptogenic cause, or (6) an unusual rare etiology.

Conventional cerebral angiogram is an invasive technique not frequently performed in patients with PMAS. MRA studies of a single case report on a patient with chronic akinetic mutism after mesencephalic-diencephalic infarction showed a thombostenosis of the distal basilar artery [23]. Two weeks after the onset of symptoms and the initiation of heparin therapy, continuous clinical deterioration occurred and a follow-up MRI showed additional pontine infarction. A conventional cerebral angiogram demonstrated a segmental narrowing of the mid-basilar artery and no filling of the distal basilar artery [23]. This is actually a case of basilar artery trunk-vessel disease that manifests initially as PMAS. Our present study also supports this contention that PMAS is not always benign. Two out of the 28 patients of PMAS died of basilar occlusion within 1 year of follow-up. If a conventional cerebral angiogram cannot be performed in every patient with PMAS,

we suggest that at least MRA has to be done in every case of PMAS looking at the possibility of concomitant basilar artery trunk-vessel stenosis.

In conclusion, paramedian mesencephalic artery syndrome is not uncommon. The clinical outcome is not benign. A total of 14% of patients died within 1 year because of recurrent strokes involving the large cerebral arteries, or an acute myocardial infarction, even though they have been placed under aspirin therapy. Stenosis or occlusion of the basilar artery or the carotid systems may co-exist in patients with PMAS. Among those who had survived the stroke of PMAS for 1 year, more than 80% of cases developed dementia.

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