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Spontaneous Cervical Epidural Hematoma Treated with rt-PA: A Pitfall in Stroke Practice

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Abstract

Although hemorrhagic complications may arise with thrombolytic therapy using recombinant tissue plasminogen activator (rt-PA), deterioration following administration of rt-PA for hemorrhagic disease is an iatrogenic complication. Caution has recently been raised regarding aortic dissection. A case of cervical epidural hematoma treated with rt-PA is reported herein. The patient was an 87-year-old woman with a history of hemodialysis, brainstem infarction, and stenosis of bilateral internal carotid arteries treated with ticlopidine. She was transferred to our hospital with severe occipital and neck pain. Diffusion-weighted imaging revealed patchy signal hyperintensity in the left cerebellar hemisphere. Right hemiparesis appeared 2 h later, but repeat magnetic resonance imaging (MRI) revealed no new lesions. Administration of rt-PA was performed under a diagnosis of hyper-acute cerebral infarction. Irregular hemodialysis was initiated for pulmonary edema. Complete tetraplegia appeared after hemodialysis, 10 h after rt-PA administration. Repeat MRI revealed cervical epidural hematoma, and hematoma removal was performed. After 10 days, hemiparesis recovered to manual muscle testing (MMT) 2 in the left extremities but remained at MMT0 in the right extremities. Cervical epidural hematoma is a rare complication in stroke practice. Although rt-PA should be administered as soon as possible, since "time is brain," spending a few minutes on spinal MRI is preferable to prevent iatrogenic deterioration. For atypical cases of cerebral infarction, the possibility of cervical epidural hematoma should be considered.

Keywords: rt-PA, spontaneous spinal epidural hematoma, thrombolytic therapy

Introduction

Recombinant tissue plasminogen activator (rt-PA) was approved for acute-phase treatment of cerebral infarction in Japan in 2005, and this treatment has become common practice. The initial time limit of 3 h was extended to 4.5 h in 2012, as recommended by the 3rd edition of the Intravenous Thrombolysis (rt-PA) Therapy Appropriate Treatment guidelines (3rd edition guidelines).[1)] Cases meeting the indications have increased since then. A dramatic improvement of cerebral infarction is expected, but fatal complications can arise. As a result, regulations have been implemented for the use of rt-PA by hospitals and physicians. Since 2018, mandatory learning has changed from a lecture course to e-learning.[1)]

Administration of rt-PA for hemorrhagic disease is contraindicated because rt-PA resolves thrombus. Some cases have been reported in which patients with ischemic stroke were administered rt-PA, overlooking that the stroke was due to dissecting aortic aneurysm. An alert for dissecting aortic aneurysm was provided in the 3rd edition guidelines. Although spontaneous spinal epidural hematoma (SSEH) is a hemorrhagic disease and thus contraindicated for rt-PA, some cases are occasionally administered rt-PA.

We present herein a case of cervical SSEH treated with rt-PA under a diagnosis of super-acute cerebral infarction, in which tetraparesis developed and emergent hematoma removal was performed. The background of such oversights and a proposal for future treatment are discussed.

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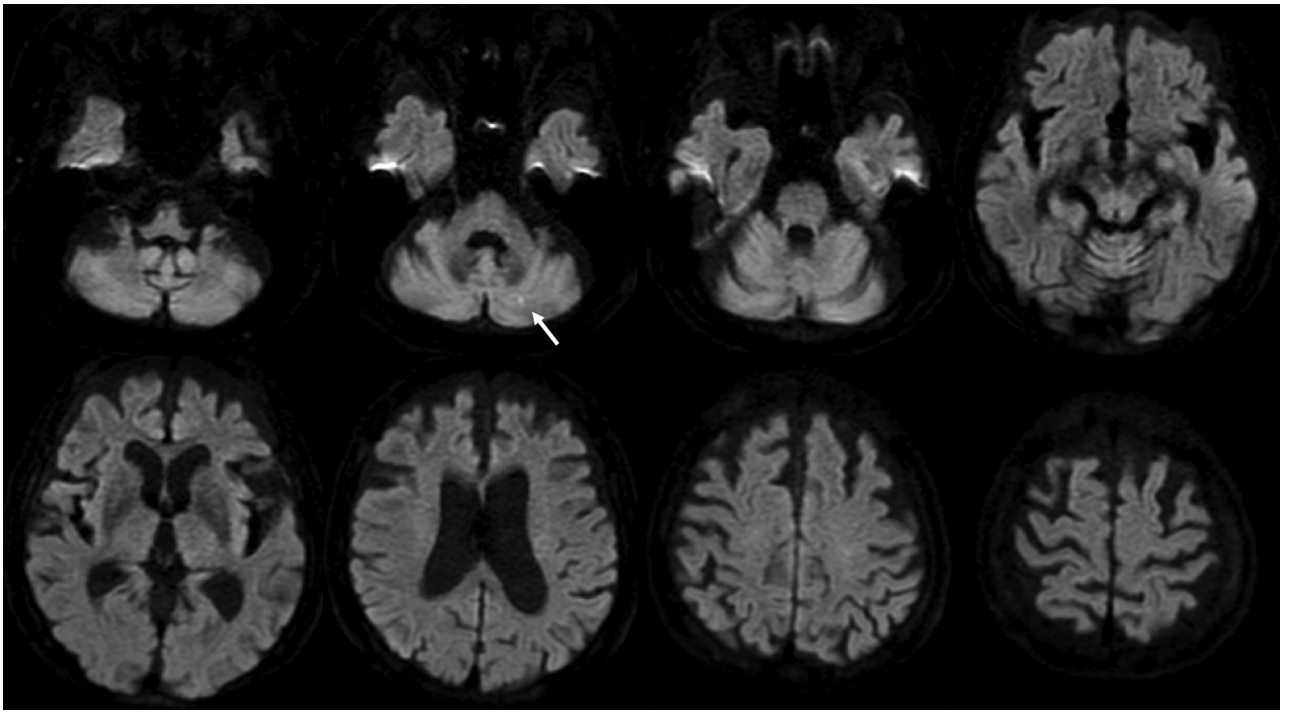

Fig. 1 MRI-DWI taken immediately after arrival. Patchy high signals are seen in the left cerebellar hemisphere (arrow). DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging.

Case Presentation

Patient: An 87-year-old woman.
Chief complaint: Neck pain.
Past history: #1 An 11-year history of hemodialysis for chronic renal failure due to diabetes mellitus or hypertensive nephropathy. #2 Administration of the antiplatelet agent ticlopidine for past brainstem infarction, and stenosis of bilateral internal carotid arteries. #3 Dementia.
Present illness: She developed neck pain and was transported to the emergency department at 3 am, 1 h after onset. Physical examination on arrival showed the following: blood pressure, 225/113 mmHg; heart rate, 88 beats/min; respiratory rate, 18 breaths/min; and SpO_2, 94%. She showed no paresis. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) taken just after arrival revealed patchy signal hyperintensities in the left cerebellar hemisphere on diffusion-weighted imaging (DWI) and intracranial carotid stenosis in the right C3 and left C2 portions (Fig. 1). Vertebral artery dissection was ruled out as the cause of the neck pain (Fig. 2). Two hours after arrival, right-side hemiparesis (upper extremities, manual muscle testing [MMT] 1; lower extremities, MMT2) and sensory disturbance developed. However, at this time she did not complain of neck pain and showed no facial paresis, but dysarthria seemed present. Repeated MRI and MRA revealed only the lesion previously described, with no new lesions (Fig. 3). The diagnosis was hyperacute-phase cerebral infarction before the appearance of signal hyperintensity on DWI. Aortic dissection was excluded by chest X-ray and computed tomography (CT). Under this diagnosis, rt-PA was administered. The timing of rt-PA administration was 1 h 45 min after confirmation of symptom appearance, and 1 h 10 min after the second MRI.
In-hospital course: Lung edema was diagnosed on chest X-ray and CT, which were conducted before administration of rt-PA. Additional hemodialysis was performed during the daytime. Nafamostat mesilate, instead of heparin, was used for hemodialysis after the administration of rt-PA. In the evening of the day after hemodialysis, the patient exhibited complete tetraplegia. Cervical MRI was taken for the first time, and revealed hematoma in the dorsal epidural space at the C2-Th2 level, lateralized to the right side (Fig. 4). Cervical SSEH was finally diagnosed. The chest CT taken before the administration of rt-PA was reviewed, and a high-density lesion suggestive of hematoma was recognized in the spinal canal (Fig. 5). The patient was re-diagnosed with SSEH. Emergent hematoma removal was performed with C3-Th1 laminectomy. The hematoma

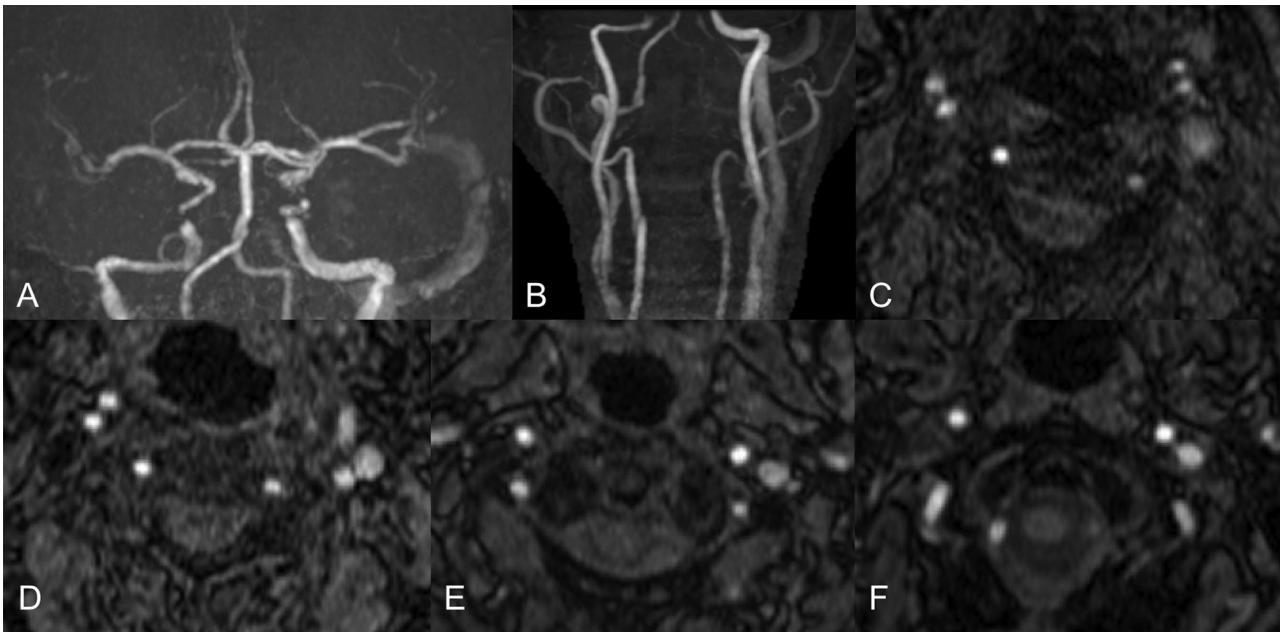

Fig. 2 MRA taken simultaneously with DWI (Fig. 1). (A) Intracranial MRA. Carotid stenosis is seen in the right C3 and left C2 portion. (B) Neck MRA. (C–F) MRA original images are at the V4 portion, V3 portion, V2 portion at the level of the C3 vertebral body, and V2 portion at the level of the C4 vertebral body, respectively. Dissection of VA is ruled out. MRA: magnetic resonance angiography, MRI: magnetic resonance imaging, VA: vertebral artery.

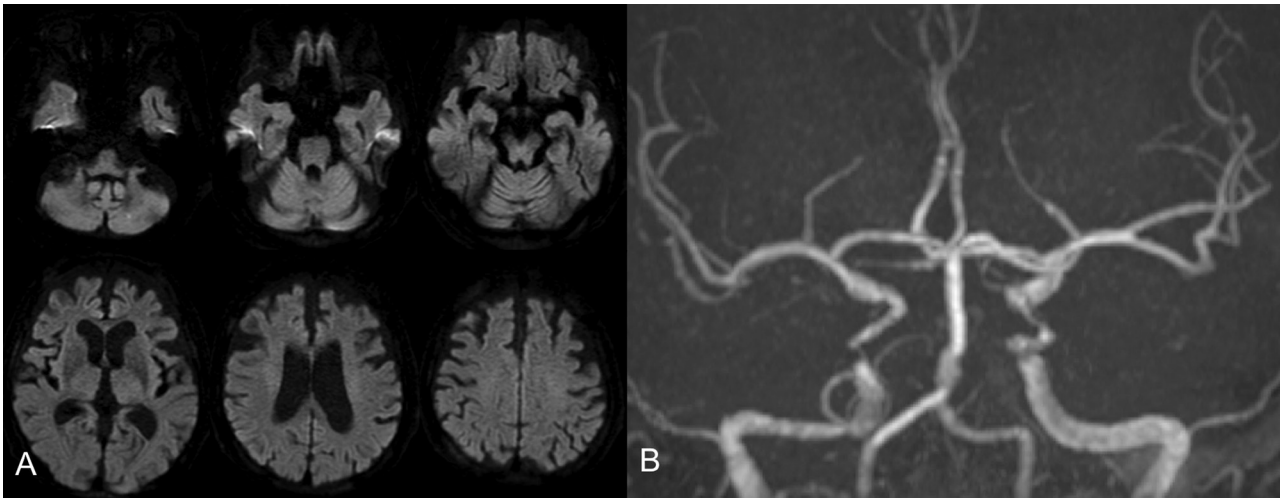

Fig. 3 Repeated MRI and MRA, taken at the time hemiparesis developed. (A) DWI; (B) Intracranial MRA. The finding is the same as in Fig. 1, and no new lesion is evident. DWI: diffusion-weighted imaging, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging.

was lateralized to the right side. Bleeding occurred from the epidural venous plexus; however, no abnormal vessels or origin of bleeding was found. Left hemiparesis improved to MMT2, but remained at MMT0 in the right extremities, postoperatively. She was transferred to a rehabilitation hospital on postoperative day 11.

Discussion

Timing of rt-PA therapy

In the 3rd edition guidelines, the recommendation is to start treatment as soon as possible (within 1 h of arrival at the latest), since the odds of a good outcome increase with less treatment delay;

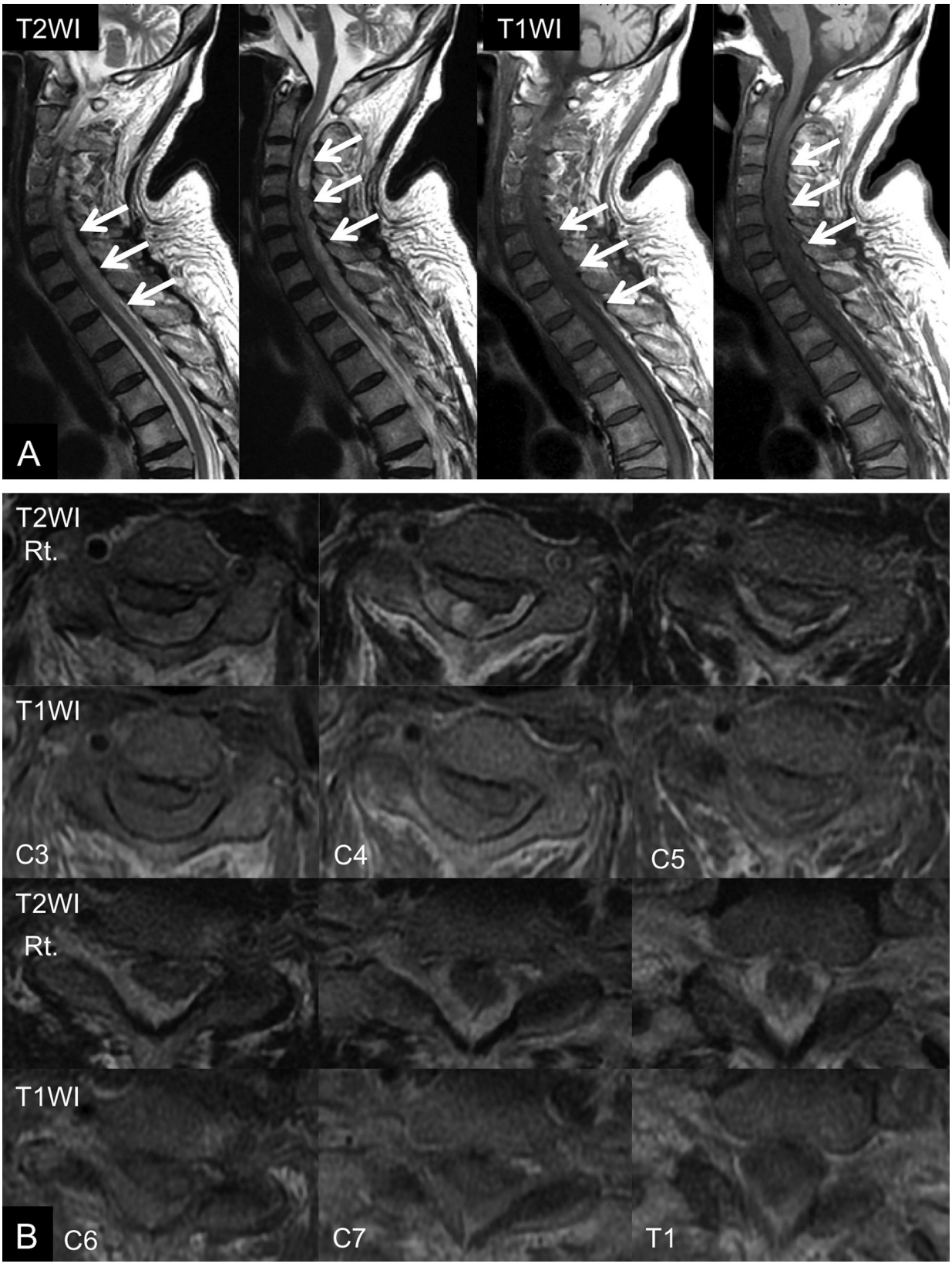

Fig. 4 Cervical MRI at the time of deterioration to tetraplegia. (A) Sagittal view. A lesion appearing hyperintense on T2-weighted imaging and isointense on T1-weighted imaging is apparent in the posterior epidural space (arrow). (B) Axial view. MRI: magnetic resonance imaging.

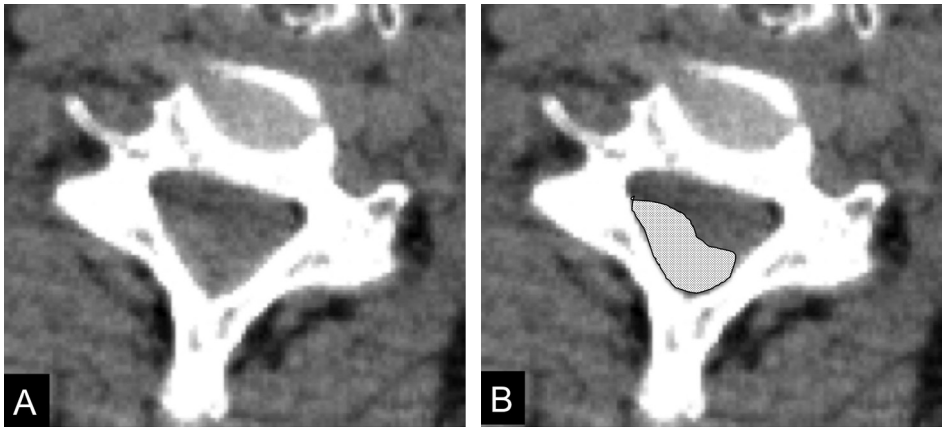

Fig. 5 Plain CT taken before administration of rt-PA, after the development of hemiparesis. (A) Axial section at the C6 level. (B) Same image, indicating the position of the hyperdense area, representing epidural hematoma, by a dotted area. The hematoma is lateralized to the right side. CT: computed tomography, rt-PA: recombinant tissue plasminogen activator.

therefore, minimal diagnostic imaging avoids wasting time.[1)]

A study by Emberson et al., cited in the 3rd edition guidelines, compared three groups with alteplase injection within 3 h, within 3–4.5 h, or over 4.5 h, and concluded that the odds ratio for a good outcome ratio was highest in the early treatment group, at 1.75, 1.26, and 1.15, respectively.[2)] However, careful reading of this manuscript showed that the actual ratios of good outcome were 32.9%, 35.3%, and 32.6%, respectively, in the three groups, showing no statistical differences. The odds ratio for a good outcome was derived from the low percentages of good outcomes in the early phase for the control group, at 23.1%, 30.1%, and 30.6%, respectively.

In the 3rd edition guidelines, although "epidural hematoma" was not included as a contraindication in the checklist, "coexistence of hemorrhagic disease (intracranial, intestine, urinary tract, retroperitoneum, or hemoptysis)" was. Considering the significance of consequences of hematoma expansion, SSEH should be included as a "coexistence of hemorrhagic disease." The 3rd edition guidelines also recommend exclusion of diseases other than stroke, and accurate elicitation of medical history, neurological examination, and emergency examinations focusing on stroke mimic. SSEH is a stroke mimic and is considered likely to deteriorate with rt-PA therapy. Thus, exclusion of SSEH is not a time-wasting issue, but rather a mandatory process. In many situations, additional cervical MRI or CT can be performed while preparing the drug and explaining and acquiring consent from the patient's family. If there is any suspicion about the diagnosis of cerebral infarction, cervical spine imaging should be performed.

Etiology and epidemiology of SSEH

The source of SSEH is mainly the epidural venous plexus. The etiology of SSEH has been reported as coagulopathy associated with anticoagulant drugs or pathologies, arterial and/or venous malformation, pregnancy, or hypertension; however, no particular etiology was identified in around half of the cases.[3)] One case of cervical epidural hematoma was identified after chiropractic spinal manipulation.[4)] SSEH is considered a rare disease, with a reported frequency of 0.1/100000 population/year. However, the reference source in past manuscripts was a 1996 report by Holtås et al.,[5)] before MRI entered common use. Although the frequency of SSEH has not been reported, it may be higher than reported, from our experience and personal communications.

The symptoms of SSEH include neck pain, motor paresis, sensory disturbance, urinary disturbance, and Horner's syndrome. Neck pain is characteristic of this disease, and radiating pain from the posterior neck to the shoulder is typical.[6)] Cervical hematoma is inclined to cause tetraparesis. However, many cases develop hemiparesis, since the origin of bleeding is the venous plexus and the hematoma is typically lateralized. Hara et al. reported 16 cases of cervical SSEH, of which 10 developed hemiparesis, two showed no paresis, and only four developed typical tetraparesis.[6)] Almost all of the cases with hemiparesis were stroke. Therefore, if no or incongruous findings are identified on DWI, hyperacute cerebral infarction should not be assumed, and active exclusion of cervical SSEH is warranted.

Table 1 List of patients who had been administered or nearly administered rt-PA

Case	Age/sex	Side of Hx	Neck pain	Motor disturbance	Sensory disturbance	Additional symptoms	Remarks
Hara N (Case 6) [6]	68/M	lt.>rt.	+	rt. hemiparesis	rt. U/E	Hornel's syndrome	
Okada E [7]	49/F	lt.	–	lt. hemiparesis	NC	–	
Liou KC (Case1) [8]	60/F	NC	+	rt. hemiparesis	NC	–	*1
Liou KC (Case2) [8]	58/F	NC	+	rt. hemiparesis	NC	–	*2
Son S [9]	63/M	lt.	+	lt. hemiparesis	lt. U/E & both L/E	LOC, mild dysarthria	
Schmidley JW (Case1)[10]	96/F	lt.	+	lt. hemiparesis	–	lt. facial palsy	*3
Schmidley JW (Case2)[10]	81/F	rt.	+	rt. hemiparesis	lt. T2 level	–	*4
Yurter A [11]	69/F	lt.	NC	lt. hemiparesis	NC	NC	
Morimoto T [12]	71/M	lt.	+	lt. hemiparesis	NC	NC	
Asamoto [13]	65/F	lt.	+	rt. hemiparesis	NC	NC	*5
Nakayama [14]	77/F	lt.>rt.	–	rt. hemiparesis	–	rt. facial palsy, mild dysarthria	
Lee CH [15]	66/F	lt.	+	lt. hemiparesis	–	–	
Present case	87/F	rt.>lt.	+ → –	rt. hemiparesis	rt. U/E&L/E	Mild dysarthria	

Many patients had neck pain. The motor symptoms of onset were hemiparesis, not tetraparesis which was thought as typical as cervical hematoma. Remarks: *1 Injection was considered but not performed due to deterioration to tetraparesis. *2 Injection was considered but not performed due to disappearance of rt. hemiparesis and development of lt. hemiparesis. *3 Injection was not administered because of advanced age and uncertainty regarding time of onset. *4 Injection was not administered because of uncertainty regarding time of onset. *5 Injection was planned but stopped by another neurosurgeon. F: female, Hx: hematoma, L/E: lower extremities, LOC: loss of consciousness, lt.: left, M: male, NC: not clarified, rt.: right, U/E: upper extremities.

Thrombolysis and antithrombotic therapy for SSEH

As mentioned above, early symptoms of cervical SSEH and stroke are sometimes similar. Some reports have described cases that had been administered or nearly administered rt-PA (Table 1).[6–15] In addition, cases involving urokinase,[16] heparin,[17,18] ozagrel sodium,[18] and argatroban hydrate[18] have been described.

In the 3rd edition guidelines, treatment is recommended to be "as fast as possible (at the latest, within 1 hour)." This unrealistic time limit in many institutions may cause SSEH to be misdiagnosed. We propose that safety should take precedence over quickness.

Another contributing factor may be the situation in Japan, in that neurosurgeons provide initial care for non-surgical patients. Compared with neurosurgeons in other countries, many neurosurgeons in Japan are entirely focused on brain surgery, and do not receive sufficient opportunities to learn about the spine and spinal cord surgeries.[13] The physician who decided to administer rt-PA was a board-certified neurosurgeon with enough clinical experience. However, even certified neurosurgeons could overlook SSEH, if they do not treat spinal disease in daily practice.

Some objections may be raised that justify overlooking SSEH. Some may argue that rare and "not-in-specialty" diseases cannot be ruled out under rushed circumstances. However, SSEH is in fact a stroke mimic bleeding disease, thus representing a direct contraindication for rt-PA as described in the 3rd edition guidelines. The Japan Neurosurgical Society (JNS) considers neurosurgeons as general practitioners for the nervous system, providing acute therapy, and preventing diseases of the brain and spinal cord.[19] Under this definition, spinal disorder falls under the area of expertise of neurosurgeons. Furthermore, alerts have been issued in several previous papers.[8–14,16–18] If a legal dispute arises, the doctors who administered rt-PA for SSEH could be blamed and may have to pay compensation. If a cerebral infarction that explains the symptoms cannot be found on imaging examinations, SSEH should be considered among the differential diagnoses.

Conclusions

Early symptoms of SSEH resemble those of early-phase stroke. SSEH is not a particularly rare disease, as some papers have described thrombolysis therapy for SSEH under a diagnosis of cerebral infarction.

If there is any doubt regarding the diagnosis of cerebral infarction, cervical imaging should be considered mandatory.

Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare. The corresponding author, as certifying instructor of the Neurospinal Society of Japan (NSJ) and a neurosurgical specialist of the JNS, has declared a conflict of interest (COI) for the JNS.

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