Using low-dose tissue plasminogen activator through external ventricular drain and Cerebrolysin for the treatment of severe intraventricular hemorrhage: A case report

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Abstract
Acute obstructive hydrocephalus is a complication of intraventricular hemorrhage, which requires a combination of medical and surgical treatments. We report a clinical case of intraventricular hemorrhage extension secondary to a ruptured arteriovenous malformation, successfully treated with a combination of methods: endovascular embolization of arteriovenous malformation, external ventricular drainage, intraventricular fibrinolysis with low-dose recombinant tissue plasminogen activator, and medical treatment with the neurotrophic drug Cerebrolysin in combination with neurorehabilitation.

Keywords
External ventricular drain, Cerebrolysin, intraventricular hemorrhage, neurology

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Introduction
Patients with intraventricular hemorrhage (IVH) due to a ruptured arteriovenous malformation (AVM) with acute obstructive hydrocephalus are at high risk of mortality and poor functional outcome.\(^1\) Treatment is difficult and requires a clinical strategy that combines medical, surgical, and endovascular methods.\(^2\) The high volume of blood in the third and fourth ventricles may cause hydrocephalus; however, insertion of an external ventricular drainage (EVD) is ineffective due to the blood clots formed in the ventricles.\(^3\) Intraventricular fibrinolysis via the EVD is known to facilitate the removal of blood from the ventricles and has a good safety profile.\(^4\) A large amount of blood in the ventricles may damage neurons and the blood–brain barrier, leading to acute hydrocephalus and increased intracranial pressure.\(^5\) Pharmacological treatment was applied to treat cerebral edema, and the neurotrophic agent Cerebrolysin was used as an add-on therapy to minimize neuronal damage and to stimulate neurorecovery.\(^6\) Rehabilitation measures followed the recommendations of the AVANT (Austrian Vietnamese Advancement Neurorehabilitation Treatment) program,\(^7\) with essential exercises to help stroke patients regain independence. We report a case of a patient with acute obstructive hydrocephalus after IVH due to rupture of an AVM, who was successfully treated with the above strategy.

Case report
A 18-year-old woman with normal medical history suddenly collapsed and was admitted to the emergency department 5 hours after symptom onset. On examination, the patient was found to be in a comatose status, Glasgow Coma Scale (GCS) 7\(^8\) (Table 1), left pupil dilated to 3 mm, right pupil dilated to 2 mm, both pupils non-reactive, with paralysis of all extremities, blood pressure of 140/80 mmHg, pulse rate of 80 bpm, and mild fever of 38°C.

Initial non-contrast computed tomography (CT) scan showed all four ventricles full of blood, the lateral ventricles enlarged, suggestive of obstructive hydrocephalus, and a Graeb score of 12 points (Figure 1(a) and (b)). A CT angiogram done shortly thereafter confirmed an AVM located beside the left lateral ventricle (Figure 1(c) and (d)).

A digital subtraction angiography showed a Spetzler–Martin Grade 3 AVM. The feeding vessels were the branches of the anterior cerebral artery. The size of the nidus was...
2 \times 2 \text{ cm} \text{ and it drained into the vein of the superior sagittal sinus}. \text{ Endovascular embolization is most commonly used to reduce the size of the AVM in preparation for surgery; thus, a microcatheter was placed via AVM feeding arteries close to the nidus, and then the embolic agent Onyx was infused in the nidus. As a result, the AVM was fully embolized. The patient was immediately taken to the operating room and an EVD was placed, intravenous Cerebrolysin 20 mL and mannitol were administered, and the patient’s blood pressure was kept below 140/90, mmHg. The postoperative clinical status of the patient did not improve and a cast was formed in the ventricular system. Ventriculostomy was adequately positioned but demonstrated a poor waveform, and cerebrospinal fluid (CSF) output was judged to be slow at 3 mL/h (Figure 2(a)).

| Table 1. NIHSS, GCS, and mRS scores over time. |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Baseline | Day 15 | Day 30 | Day 40 | Day 60 | Day 90 |
| NIHSS | 30 | 20 | 22 | 12 | 2 | 1 |
| GCS | 7 | 9 | 8 | 15 | 15 | 15 |
| mRS | – | 5 | 5 | 4 | 2 | 1 |

NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; mRS: modified Rankin Scale.

The possible risk of re-hemorrhage and subsequent death was discussed with the family, but the decision to give intraventricular thrombolytics due to the high rate of mortality associated with the patient’s condition was made. Specifically, the large volume of blood in all four ventricles, the obstructive hydrocephalus, and the poor clinical status worsened the prognosis. We administered 1 , mg of recombinant tissue plasminogen activator (rt-PA) through the EVD and then flushed the EVD with 3 mL of normal saline. After administrating the rt-PA, the ventriculostomy was clamped and the intracranial pressure was monitored closely. After 1 h, the ventriculostomy was opened and allowed to drain at a height of 10, cm above the patient’s ear. Rt-PA was given every 8 h, for a total of seven doses (Figure 2(b)–(d)).

The patient received intensive care and the previously described treatment. Cerebrolysin was administered intravenously at a daily dose of 20 mL for 14 days. A tracheostomy for prolonged ventilation was carried out after 12 days. The patient was also enrolled in a rehabilitation program following the AVANT recommendations.

**Post-bleed day (PBD) 15:** The patient’s neurological functions improved (GCS 9, Table 1), she could move both extremities by herself and breathe without mechanical ventilation, and the left pupil dilation decreased to 2 , mm and the right pupil dilation to 1.5 , mm.

Figure 1. (a, b) Non-contrast CT scan and (c, d) AVM located in the left lateral ventricle.

Figure 2. (a) Before treatment; (b) after 5 doses of rt-PA; (c) after 7 doses of rt-PA; and (d) after removal of the drain.
PBD 30: The patient developed increased confusion and lethargy, the GCS decreased to 7–8 (Table 1), and the patient was put on mechanical ventilation again. A CT scan of the head showed an acute hydrocephalus (Figure 3(a) and (b)). It was evident that the patient required permanent CSF shunting; consequently, we decided to establish a ventriculo-peritoneal shunt (Figure 3(c) and (d)). Cerebrolysin 20 mL was administered intravenously daily for another 10, days, from day 31 to day 40. Participation in the AVANT rehabilitation program was interrupted.

PBD 40: The patient’s consciousness improved moderately, and she recovered partial motor function with muscle strength of 3/5. She could breathe without mechanical ventilation. The patient continued with the AVANT rehabilitation program.

PBD 60: The patient’s mRS (modified Rankin Scale)\(^9\) was 2 (Table 1); she showed good recovery in terms of communication and was able to take care of her daily needs without assistance, although she remained unable to resume all her previous activities.

PBD 90: The patient continued improving in motor and speech functions. NIHSS (National Institutes of Health Stroke Scale)\(^10\) assessment showed a score of 0 and the mRS a score of 1 (Table 1). Figure 4 shows that the excess fluid had been drained, and the brain had stabilized.

Discussion

The prognosis for patients with IVH is very poor, with high rates of disability and mortality, in the presence of any IVH up to 50%\(^11\). This high mortality rate is proportional to the amount of ventricular hemorrhage and increases when the third and fourth ventricles are involved\(^12,13\). In observational studies, the mortality rate after intracranial hemorrhage from AVM rupture ranges from 12% to 66.7%\(^14,15\).

The successful treatment of this case is attributable to a combination of medical, surgical, endovascular, and pharmacological methods. Endovascular embolization of the AVM prior to surgery helped reduce the risk of hemorrhagic complications due to the use of rt-PA. This was followed by the placement of an EVD and administration of rt-PA to remove the blood clot and drain the ventricles. After seven doses of rt-PA, most of the blood was drained from the ventricles, but the patient’s clinical status did not improve due to aresorptive hydrocephalus and complications.
Aiming to reduce complications and to stimulate functional recovery, we decided to apply Cerebrolysin. Previous research has shown a positive effect on neurorecovery after various types of brain lesions such as ischemic stroke and brain trauma. In addition, the patient received essential neurorehabilitation exercises in accordance with the recommendations of the AVANT program.

Although only little improvement could be seen in the acute phase after seven doses of rt-PA, this case finally resulted in a very positive and unexpected outcome after applying the AVANT neurorehabilitation program in combination with intravenous Cerebrolysin treatment. The patient was discharged after 54 days and continued to recover with excellent results. By day 90, the patient had an mRS of 1, could walk by herself, showed good speech recovery, and had no signs of local paralysis. The patient was able to carry out daily activities without assistance, such as walking, communicating, and eating.

**Conclusion**

The combination of medical, surgical, and endovascular methods with pharmacological treatment and a structured rehabilitation program to support neurorecovery was a successful and safe therapeutic strategy, which should therefore encourage further research in the development of a comprehensive treatment strategy for patients with IVH and hydrocephalus.

**Declaration of conflicting interests**

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**Ethical approval**

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**Informed consent**

The authors confirm that the patient had the capacity to provide written informed consent for their anonymized information to be published in this article.

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