Case Report: Vertebro-vertebral arteriovenous fistula showing symptoms mimicking ALS: Diagnostic imaging supports accurate differentiation between ALS and mimicking conditions [version 3; peer review: 1 approved with reservations, 1 not approved]

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Abstract
We report a rare case of a vertebro-vertebral arteriovenous fistula (VAVF) manifesting as amyotrophic lateral sclerosis (ALS). A 76-year-old female patient presented with progressive weakness, muscle atrophy, fasciculation, and preserved deep tendon reflexes in the right upper limb. Electrophysiological testing showed lower motor neuron dysfunction. The patient was suspected to have ALS, but cervical magnetic resonance imaging (MRI) revealed enlarged blood vessels in the spinal canal, which compressed the cervical spinal cord and nerve roots. Angiography showed a shunt from the right vertebral artery to the right intervertebral vein and the vertebral venous plexus; therefore, the patient was diagnosed with VAVF. Transarterial embolization was performed to obliterate the shunt, and weakness in the patient's right upper limb subsequently improved. It is worth considering VAVF as a differential diagnosis of ALS-like diseases.
Introduction
Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease that affects upper motor neurons (UMNs) and lower motor neurons (LMNs), causing muscle weakness and atrophy and, eventually, death.1 Published criteria for diagnosing ALS include the assessment of clinical or electrophysiological signs of UMN and LMN dysfunction, as well as the exclusion of ALS-mimicking diseases.2

Vertebro-vertebral arteriovenous fistula (VVAVF) is a rare vascular malformation defined as a direct shunt from the vertebral artery (VA) to the surrounding venous plexus.3 Although the most frequent symptom of this disorder is bruit, some patients present with neurological symptoms such as muscle weakness, numbness, and pain.3,4 VVAVF diagnosis is made via magnetic resonance angiography (MRA), computed tomography angiography (CTA) and/or digital subtraction angiography.5 In many cases, subsequent endovascular or surgical treatment results in symptom improvement.3,5

Here we describe a case of a patient with VVAVF presenting symptoms mimicking ALS.

Case report
A 76-year-old unemployed Japanese woman presented to our hospital with a complaint of weakness in the right upper limb that had developed progressively over a period of more than eight months. The patient had a history of schizophrenia with onset at the age of 19, which included seizures and insomnia, and she was treated with oral medications of clorazepam (20 mg three times a day every day), quetiapine (320 mg four times a day every day), sertraline (25 mg once a day every day), levetiracetam (500 mg twice a day every day), brotizolam (0.25 mg once a day every day), and suvorexant (15 mg once a day every day). She had no history of trauma or surgery other than a history of a fracture of the left upper arm at the age of 68. She had no findings that would suggest connective tissue diseases (e.g., tissue fragility, hyperextensibility of skin or joints, neurofibroma, elevated inflammatory markers, or collagen disease-related auto-antibodies). Her mother suffered from a mental illness of unknown details, and there is no other apparent family history.

Neurological examination revealed moderate muscle atrophy and weakness (they reflected LMN dysfunction) in the right upper limbs with preserved reflexes (it reflected UMN dysfunction), and fasciculation in the right first dorsal interosseous muscle (it reflected LMN dysfunction).

Electromyography showed active and chronic denervation in the right biceps brachii and first dorsal interosseous muscle. Nerve-conduction studies showed repeated F-waves and decreased F-wave persistence in the bilateral median and ulnar nerves. Sensory nerve conduction studies revealed a mild decrease of the amplitude in bilateral ulnar nerves, which were otherwise normal. These results suggested the presence of LMN dysfunction in the cervical region. Therefore, the patient appeared to meet the criteria for “possible ALS” according to the revised El Escorial criteria.6

However, cervical magnetic resonance imaging (MRI) demonstrated a dilated internal vertebral venous plexus in the right side of the spinal canal from the C1 to C6/7 levels (Figure 1A); this imaging showed compression of the spinal cord and spinal nerve roots at the same level, most severely at the C6/7 level (Figure 1B). Axial T2-weighted imaging showed high signal intensity around the right anterior horn (AH) at that level (Figure 1B). MRA and CTA revealed an arteriovenous fistula from the right VA to the right vertebral vein at the C6/7 level and showed dilation of the right intervertebral vein and the vertebral venous plexus (Figure 1C-E). After reviewing the imaging findings, a careful review of the physical examination revealed bruit in the right neck, and a slight tingling sensation in the radial side of the right forearm. Somatosensory evoked potentials revealed a decrease in the amplitude of N9 in the right upper extremity, which could be the effect of the compression of the spinal nerve roots at C1 to C6/7 level by dilated blood vessels. Right vertebral angiography revealed right VVAVF with reflux to the anterior internal vertebral venous plexus via the right intervertebral vein (Figure 2A and B). Left vertebral angiography showed retrograde filling of the right VA distal to the arteriovenous fistula and running into the draining vein (Figure 2C), but the patient had no symptoms suggestive of vertebral-basilar ischemia (e.g., vertigo, dizziness, loss of vision, nausea, vomiting, and dysarthria). Reflux into the anterior and posterior spinal arteries was not apparent.
Figure 1. Magnetic resonance imaging and computed tomography angiography. (A) Sagittal T2-weighted imaging of the cervical spine showed the dilated internal vertebral venous plexus in the right side of the spinal canal from the C1 to C6/7 levels (arrowheads). (B) (the cross-section image of A at the yellow line) Axial T2-weighted imaging of the cervical spine showed the dilated right intervertebral vein (asterisk) at the C6/7 level compressing the spinal cord, and high signal intensity around the right AH at the same level. (C) Three-dimensional reconstruction of contrast-enhanced computed tomography revealed a dilated intervertebral vein and anterior internal vertebral venous plexus (blue, arrowheads). Arteriovenous fistula at the C7 level (purple) was also shown. The red blood vessels represent the anterior and posterior spinal arteries. (D) Oblique view of maximum-intensity projection cervical MRA showed a dilated right intervertebral vein and anterior internal vertebral venous plexus. The yellow line indicates the cross-sectional position of (E). (E) Axial image of time-of-flight cervical MRA showed an arteriovenous fistula at the C7 level (arrow). AH, anterior horn; MRA, magnetic resonance angiography.

Figure 2. Preprocedural angiography. (A, B) Right vertebral angiography revealed the right vertebro-vertebral arteriovenous fistula with reflux to the anterior internal vertebral venous plexus via the right intervertebral vein. (C) Left vertebral angiography showed retrograde filling of the right vertebral artery distal to the arteriovenous fistula and running into the draining vein (arrowheads).
Transarterial embolization of the fistula was performed using coil and n-butyl cyanoacrylate with no adverse events. There were no significant problems with intervention adherence and tolerability. Postprocedural angiography demonstrated a significant reduction of the shunt blood flow (Figure 3A and B). Three months after treatment, a follow-up angiography was performed and revealed complete disappearance of the shunt blood flow (Figure 3C). The presenting weakness in the patient’s right upper proximal limb slightly improved although muscle atrophy remained. Furthermore, no new neurological abnormalities have occurred.

**Discussion**

VVAVF is a rare vascular malformation, and, to our knowledge, a total of 293 cases have been reported from 1990 to 2018, of which 280 cases were well-documented. Of these 280 cases and the present case, 136 cases (49%) were spontaneous, 76 (27%) were traumatic, and 68 (24%) were iatrogenic. The male/female ratios of spontaneous, traumatic, and iatrogenic VVAVF were 1:2, 2:1 and 1:1, respectively. Although the etiology of VVAVF was not identified in the present case, spontaneous VVAVF would be associated with connective tissue disorders including Ehlers-Danlos syndrome, neurofibromatosis type 1, and fibromuscular dysplasia. Among the variety of presenting symptoms and clinical observations in VVAVF, bruit is the most common clinical manifestation. Other frequently observed symptoms include weakness and numbness, pain, and headache. On fewer occasions, tinnitus, subarachnoid hemorrhage, and congestive heart failure have also been reported. Radiculopathy has been rarely reported as a manifestation of VVAVF.

Symptoms in the present case were likely caused by compression of the spinal cord and the ventral nerve root, as the patient’s symptoms were localized to the right upper limb without sensory involvement and partially improved following shunt-vessel embolization. The dilated blood vessels compressed the spinal cord from the C1 to C7 levels—most severely at the C6/7 level—and a high signal intensity around the right AH at that level was revealed via T2-weighted imaging, whereas no signal change was observed in the spinal cord at other affected levels. This suggests that the AH cells at the C6/7 level were more severely affected than in the other regions, leading to the patient’s partial posttreatment improvement. Furthermore, it is likely that the AH and the ventral nerve root were selectively damaged by spinal-cord compression, resulting in ALS-like symptoms brought on by damage to the affected UMN and LMN cells.

In the present case, the patient’s initial presenting symptoms were progressive UMN and LMN signs in the right upper limb, which are classified by current diagnostic criteria as possible ALS. According to criteria for diagnosis of ALS—including revised El Escorial, Awaji, and recently proposed Gold Coast criteria—the clinical or electrophysiological signs of UMN and LMN dysfunction, and exclusion of other possible diagnoses, are necessary for accurate ALS diagnosis.
Certain medical conditions that can be described as “ALS mimics” show motor neuron dysfunctions similar to those of ALS. ALS mimics tend to present atypical initial symptoms, namely the absence of LMN signs via electromyography and the absence of isolated UMN or LMN signs in the physical examination. Other atypical signs suggesting ALS mimics include patient age younger than 50 years, slow or no progression of symptoms, and involvement of sensory symptoms. A recent retrospective study conducted at an ALS clinic in Argentina found that 11.7% of patients with motor neuron disease symptomatology were later diagnosed as having ALS mimics. Furthermore, even after being diagnosed as ALS, fully 3.9–9.7% of cases later turned out to be ALS mimics. The alternative diagnoses of those patients include spinal cord pathology, hereditary spastic paraparesis, neuropathy, inclusion body myositis, multiple sclerosis, and paraneoplastic syndrome. Accurate diagnosis of ALS mimics—even following an initial incorrect diagnosis of ALS—can lead to improved treatment options and higher quality of life.

Vascular malformations including epidural AVF, dural AVF, and perimedullary AVF may present symptoms mimicking ALS and may lead to spinal-cord compression that can be treated by endovascular or surgical treatment. To our knowledge, this is the first case report of VVAVF with symptoms mimicking ALS.

When diagnosing a patient with an ALS-like clinical presentation, it is critical to consider all the other possible diagnoses. More precisely, diagnostic imaging such as computerized tomography (CT), CTA, MRI, and/or MRA should be performed to differentiate from alternative diagnoses, including VVAVF.

Conclusions

We report a case of VVAVF presenting motor neuron symptoms mimicking ALS. VVAVF is treatable and is worth considering as a differential diagnosis despite its clinical rarity, and diagnostic imaging should be performed when a patient presents with motor neuron dysfunctions resembling those of ALS.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Acknowledgements

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References


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Corrado Angelini

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This is a possible treatable cause of mimicking ALS syndrome, the case might be susceptible to surgical treatment, so recognition of this entity is important. In this case description timing of muscle atrophy recovery is not described. Was sensory deficit investigated by sensory nerve conduction, SSEP (Somatosensory Evoked Potentials), or neurophysiology? In some motor neuron disease cases, there might be an abnormality of sensory function also in ALS (Facco E.et al.1989), however different from the described case, a differential statement might be useful.

References

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
No

Is the case presented with sufficient detail to be useful for other practitioners?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuromuscular Disorders.
I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Oct 2022

Ryuhei Harada, Tohoku University Graduate School of Medicine, Sendai, Japan

Dear Dr. Corrado Angelini,

Thank you very much for the thoughtful and constructive feedback. We are thankful for the time and energy you expended. Our responses to your comments are as follow:

> "This is a possible treatable cause of mimicking ALS syndrome, the case might be susceptible to surgical treatment, so recognition of this entity is important."

**Response:** Thank you very much for your comment. We agree that it is important to recognize the other treatable diseases when diagnosing a patient with an ALS-like clinical presentation.

**Q1:** "In this case description timing of muscle atrophy recovery is not described."

**A1:** Thank you for this suggestion. Muscle atrophy of the patient's right upper proximal limb remained after treatment, but weakness slightly improved. We have reflected this comment in lines 76-77 from the top of the “Case report” section.

**Q2:** "Was sensory deficit investigated by sensory nerve conduction, SSEP (Somatosensory Evoked Potentials), or neurophysiology? In some motor neuron disease cases, there might be an abnormality of sensory function also in ALS (Facco E.et al.1989), however different from the described case, a differential statement might be useful."

**A2:** Thank you for raising this point, and for the reference. Sensory nerve conduction studies revealed a mild decrease of the amplitude in bilateral ulnar nerves (8 μV for the left ulnar nerve, 11 μV for the right ulnar nerve), which were otherwise normal. Right upper extremity SSEP revealed a decrease in the amplitude of N9, which could be the effect of the compression of the spinal nerve roots at C1 to C6/7 level by dilated blood vessels, while central conduction time was normal. Left upper extremity and bilateral lower extremities SSEPs showed no abnormalities. We have reflected this comment in lines 18-20 and 32-34 from the top of the “Case report” section.

Again, thank you for allowing us to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions persuade you to accept our submission.
The authors report a case of VVAVF (Vertebro-vertebral arteriovenous fistula) with ALS-like symptoms. The present case is a typical case of VVAVF and the authors suggest that novelty exists only because ALS was required for differential diagnosis.

When there are few abnormal findings in imaging studies, it may be challenging to differentiate the case from ALS. On the other hand, in the present case, the abnormalities are evident in imaging studies, and it is questionable whether ALS should be listed as a differential diagnosis. In the setting of progressive paralysis and muscle atrophy in the upper extremities, imaging studies of cervical spine lesions are often performed before suspecting ALS.

- The presence or absence of trauma or findings suspicious of connective tissue disorder should be noted.
- The presence or absence of bruit or findings suspicious of radiculopathy, such as pain and numbness, should be noted.
- The authors should state whether the findings described in the case report are upper or lower motor neuron dysfunction.
- The CTA shows red coiling vessels suggesting intradural reflux of shunt flow. Is there reflux on angiography? Intradural reflux may cause progressive congestive myelopathy. How about the presence of myelopathy on MR imaging and clinical examination?
- Right vertebral angiography shows the steal phenomenon, but is there any symptom of stealing, such as vertebra-basilar ischemia?
On treatment, the coil mass appears to protrude into the VA; if the coil protrudes into the VA, there is a risk of thrombosis and stroke. It would be better to reconstruct the VA with a stent or occlude the VA completely.

What do the authors believe is causing the hyperintensity signal in the anterior horn at the C6/7 level, spinal cord compression, or myelopathy due to intradural reflux of abnormal shunt flow?

The authors state that the damaged anterior horn leads to partial posttreatment improvement, but I think the mass effect of the coil is the cause of the limitation of the symptom improvement.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: "dural arteriovenous fistula", "spinal arteriovenous fistula", "neuroendovascular therapy"

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 29 Jul 2022

Ryuhei Harada, Tohoku University Graduate School of Medicine, Sendai, Japan

Dear Dr. Hiramatsu,

Thank you very much for the thoughtful and constructive feedback. We are thankful for the time and energy you expended. Our responses to your comments are as follow:

Q1: "The authors report a case of VAVF (Vertebro-vertebral arteriovenous fistula) with ALS-like
symptoms. The present case is a typical case of VVAVF and the authors suggest that novelty exists only because ALS was required for differential diagnosis. When there are few abnormal findings in imaging studies, it may be challenging to differentiate the case from ALS. On the other hand, in the present case, the abnormalities are evident in imaging studies, and it is questionable whether ALS should be listed as a differential diagnosis. In the setting of progressive paralysis and muscle atrophy in the upper extremities, imaging studies of cervical spine lesions are often performed before suspecting ALS.

A1: Thank you for raising an important point. We agree that the diagnosis of VVAVF was clear from the imaging findings. However, in the progressive course, upper motor neuron signs and lower motor neuron signs were observed, especially muscle atrophy, weakness, and fasciculation, and the clinical findings were mimicking ALS. On the other hand, VVAVF is rare, and the present patient had no past medical history that may be involved in the development of VVAVF (more detailed description in Q2). From this point of view, we considered it to be an instructive case.

Q2: "The presence or absence of trauma or findings suspicious of connective tissue disorder should be noted."

A2: Thank you for this suggestion. The patient had no history of trauma other than a history of a fracture of the left upper arm at the age of 68. The patient had no findings suggesting connective tissue diseases (e.g., tissue fragility, hyperextensibility of skin or joints, neurofibroma, elevated inflammatory markers, or collagen disease-related autoantibodies). We have reflected this comment by lines 8-11 from the top of the “Case report” section.

Q3: "The presence or absence of bruit or findings suspicious of radiculopathy, such as pain and numbness, should be noted."

A3: Thank you for this suggestion. After reviewing the imaging findings, a careful review of the physical examination revealed a bruit in the right neck and a slight tingling sensation in the radial side of the right forearm. Symptoms of pain were not present. We have reflected this comment by lines 29-31 from the top of the “Case report” section.

Q4: "The authors should state whether the findings described in the case report are upper or lower motor neuron dysfunction."

A4: Thank you for this suggestion. Preserved reflexes in the right upper extremity with muscle atrophy reflect upper motor neuron dysfunction. Muscle atrophy and fasciculation in the right upper extremity reflect lower motor neuron dysfunction. We have reflected this comment by lines 13-15 from the top of the “Case report” section.

Q5: "The CTA shows red coiling vessels suggesting intradural reflux of shunt flow. Is there reflux on angiography? Intradural reflux may cause progressive congestive myelopathy. How about the presence of myelopathy on MR imaging and clinical examination?"
A5: Thank you for providing these discussions. The red coiling vessels of figure 1C represent anterior and posterior spinal arteries. Angiography did not reveal reflux into them, and their involvement in the arteriovenous shunt was not apparent. We have not observed clinical or imaging findings suggestive of congestive myelopathy. We have reflected this comment by figure legend 1C and lines 36-37 from the top of the “Case report” section.

Q6: “Right vertebral angiography shows the steal phenomenon, but is there any symptom of stealing, such as vertebra-basilar ischemia?”

A6: Thank you for this suggestion. The patient had no symptoms suggestive of vertebra-basilar ischemia (e.g., vertigo, dizziness, loss of vision, nausea, vomiting, and dysarthria). We have reflected this comment by lines 34-36 from the top of the “Case report” section.

Q7: “On treatment, the coil mass appears to protrude into the VA; if the coil protrudes into the VA, there is a risk of thrombosis and stroke. It would be better to reconstruct the VA with a stent or occlude the VA completely.”

A7: Thank you for the important advice. Follow-up angiography after 3 months of treatment showed residual protrusion of the coil mass into the VA, although the blood flow in the VA main trunk was maintained. Therefore, we agree that careful follow-up is needed.

Q8: “What do the authors believe is causing the hyperintensity signal in the anterior horn at the C6/7 level, spinal cord compression, or myelopathy due to intradural reflux of abnormal shunt flow?”

A8: Thank you for this suggestion. You have raised an important question. We consider the hyperintensity signal in the anterior horn at the C6/7 level to be caused primarily by spinal cord compression by dilated blood vessels. The level of intramedullary hyperintensity signal coincidences with the site of the most intense spinal cord compression. It is a finding that supports the mechanism of spinal cord compression. On the other hand, the intramedullary lesion appears too localized to be considered congestive myelopathy. As noted above, there is also no apparent reflux of the anterior and posterior spinal arteries, nor is there apparent regurgitation in the spinal canal. Please see lines 13-23 from the top of the “Discussion” section.

Q9: “The authors state that the damaged anterior horn leads to partial posttreatment improvement, but I think the mass effect of the coil is the cause of the limitation of the symptom improvement.”

A9: Thank you for providing these insights. Indeed, I agree with the point that the mass effect of the coils may offset the improvement.
in spinal cord compression due to the reduction of dilated vessels. However, we have observed improvement in clinical symptoms and imaging findings of spinal cord compression after endovascular treatment.

Again, thank you for giving us the opportunity to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions persuade you to accept our submission.

Sincerely,
Ryuhei Harada
Department of Neurology, Tohoku University Graduate School of Medicine

Competing Interests: No competing interests were disclosed.