Pathologic Reappraisal of Wallenberg Syndrome: A Pathologic Distribution Study and Analysis of Literature

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ABSTRACT

Background   Wallenberg syndrome was first reported by Adolf Wallenberg as arising due to the obstruction of the posterior inferior cerebellar artery (PICA), which caused an infarct in the lateral medulla oblongata (MO).
Methods   This study was carried out on brain tissue from 2 patients with typical Wallenberg syndrome and 10 autopsy cases without central nervous system disturbances.
Results   Patient 1 exhibited the 3 major neurological symptoms of right crossed sensory disturbance, right cerebellar ataxia and bulbar palsy. There was the pathological obstruction of the right vertebral artery (VA). Regarding the histopathlogical distribution, the infarct extended on the right side to the lateral spinothalamic tract, nucleus of the spinal tract of the trigeminal nerve, spinal tract of the trigeminal nerve, inferior cerebellar peduncle, spinocerebellar tract and nucleus ambiguous. Moreover, a clear infarct in the left lateral MO was pathologically identified, but pathological obstruction of the left PICA or left VA could not be found. The left cerebellar ataxia and bulbar palsy were observed among these 3 major symptoms. Patient 2 showed the 3 major symptoms of right crossed sensory disturbance, right cerebellar ataxia and bulbar palsy. A pathological luminal occlusion was identified in the right PICA. Regarding the histopathological lesion, the infarct disturbed on the right side the lateral spinothalamic tract, nucleus of the spinal tract of the trigeminal nerve, spinal tract of the trigeminal nerve, spinocerebellar tract, inferior cerebellar peduncle and nucleus ambiguus.
Conclusion   Based on our investigation of pathological lesions using our 2 autopsies, we suggest calling the cases that satisfy the following 3 criteria "definite pathologic Wallenberg syndrome": i) identifiable pathological obstruction of the PICA or VA; ii) infarction in the lateral MO based on PICA or VA obstruction; and iii) a 1-to-1 correspondence between clinical symptoms and neuropathological lesions.

Wallenberg syndrome was first mentioned in a report by Adolf Wallenberg in 1895 on only the clinical symptoms of an alive case of lateral medulla oblongata (MO) infarct. He performed a pathological analysis on this same autopsy case in 1901, reporting a detailed pathological lesion. In this autopsy report, Adolf Wallenberg verified that the disease is caused by the obstruction of the posterior inferior cerebellar artery (PICA).[1] After 1901, this disease was called Wallenberg syndrome. However, there have been few reports on autopsy cases with Wallenberg syndrome. Hata et al. reported 3 of their own surviving cases of Wallenberg syndrome from Japan. They also analyzed 153 cases from the Japanese literature, including the 3 cases they experienced, of which only 16 cases were autopsies.[2] To date, literature studies have reported that in addition to PICA, the vertebral artery (VA) can also serve as the blocked blood vessel responsible for Wallenberg syndrome.[3–6] Adolf Wallenberg originally described the typical 3 major symptoms that are characteristic of Wallenberg syndrome: i) crossed sensory disturbance or alternative hemianesthesia (disturbance of thermal and pain sensibility on one side of the face as well as on the opposite side of the body except the face), ii) cerebellar ataxia and iii) bulbar palsy. These typical 3 major symptoms have been considered the core clinical symptoms of Wallenberg syndrome. As more case reports were accumulated, the cases without facial sensory disturbance have come to be considered Wallenberg syndrome. Currently, even cases devoid of 1 symptom out of the typical 3 major symptoms are considered as Wallenberg syndrome, showing that the definition of the disease has widened. This wider interpretation is thought to come from individual variations in the vascular supply regions of the MO, which lead to a wide variety of symptoms in Wallenberg syndrome

patients.[2] In this study, we report 2 autopsy cases with typical Wallenberg syndrome. Based on these 2 autopsies, we reappraised Wallenberg syndrome from a pathological standpoint through an analysis of the past 24 autopsy reports from the literature.

MATERIALS AND METHODS
Subjects and histopathology

This study was carried out on brain tissue from 2 patients with Wallenberg syndrome. The brain was fixed in 10% buffered formalin. The brain stem and cerebellum were removed from the cerebrum at the midbrain level. Routine control sectioning of the cerebrum was performed. The brain was cut starting from the level of the mammillary body of the base aspect of the cerebrum. The brain stem was cut transversely along the long axis resulting in sections parallel to the midbrain, pons and MO. The thickness of these section slices was about 5 mm thick. The cut was continuous and severed the 5-mm thick sections completely. The specimens of the brain tissue including MO were embedded in paraffin, and cut into 6-μm thick sections. The sections were stained by the following routine methods: hematoxylin and eosin (HE) and HE-luxol fast blue (HE-LFB) double stains as well as Klüver-Barrera (KB) stain. In addition, special histochemical stains were performed on the sections with Holzer, Bodian and modified Hirano-Bielschowsky stains. Five-millimeter thick slices of the major arteries of the brain including the circle of Willis were also embedded in paraffin, and cut into 5-μm thick sections: the sections were stained by HE, HE-LFB and elastica van Gieson (ELVG) stains. Histologically, normal MO from 10 individuals without central nervous system disturbances (ages: 50–85 years) severed as normal controls. The protocols of this study were approved by the Ethics Committee of Tottori University (No. 2261: 2013).

Immunohistochemical analysis

Representative paraffin sections were used for an immunohistochemical assay. An IgG1 mouse monoclonal antibody to purified glial fibrillary acidic protein (GFAP) (high performance, ready-to-use; BioGenex, San Ramon, CA) was used as a primary antibody. Sections were deparaffinized, and endogenous peroxidase activity was quenched for 30 min with 0.3% H_2O_2. Sections were then washed in PBS, pH 7.4. Normal serum homologous with the secondary antibody was used as blocking reagents. Sections were incubated with the primary an-

| No.	Anatomical region
1	Hypoglossal N.
2	Sublingual N. (Roller)
3	Dorsal vagal N.
4	Hypoglossal intrafascicular N.
5	Dorsal central medullary N.
6	Dorsal paragigantocellular N.
7	Medial vestibular N. (Schwalbe)
8	N. of solitary tract
9	N. ambiguus
10	Lateral paragigantocellular N.
11	Lateral or accessory cuneate N. (von Monakow)
12	N. of spinal tract of trigeminal nerve
13	Medial longitudinal fascicle
14	Medial lemniscus
15	Solitary tract
16	Spinal tract of trigeminal nerve
17	Internal arcuate fibers
18	Inferior cerebellar peduncle
19	Lateral spinothalamic tract
20	Spinocerebellar tract
21	Sympathetic descending tract
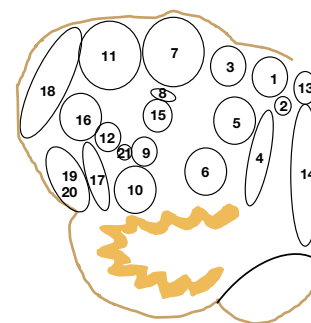
Fig. 1. Schematic diagram of nerve nuclei and tracts in MO. MO, medulla oblongata; N, nucleus.

tibody for 18 h at 4 ℃. Bound antibody was visualized by the avidin-biotin-immunoperoxidase complex (ABC) method using the appropriate Vectastain ABC kit (Vector Laboratories, Burlingame, CA) and 3,3′-diaminobenzidine tetrahydrochloride (Dako, Glostrup, Denmark) as the final chromogen.

Analysis about the correlation between the clinical symptoms and pathologic legions

A diagram of the neuroanatomical locations of nerve nuclei and tracts was created from the MO sections from 10 normal controls using a light microscope (Olympus BX-50 F4, Tokyo, Japan) (Fig. 1) with digital camera (Olympus D12). Then, the locations of infarcts were identified in the MO sections from the 2 Wallenberg syndrome autopsies and were recorded on the MO diagram, using a light microscope with digital camera. We analyzed the relationship between clinical symptoms and areas damaged by the infarcts.

RESULTS
Patient 1
Clinical history

The patient was male and 59 years old at death. At age 56, he experienced a brain-stem and cerebellar infarct. The neurological symptoms were right crossed sensory disturbance (simultaneous disturbance of thermal and pain sensibility on the right face as well as on the left side of the body except the face), right cerebellar ataxia, bulbar palsy, right Horner's syndrome and vertigo. An infarct in the right lateral MO was suspected and then he was clinically diagnosed with Wallenberg syndrome. At age 58, he was hospitalized due to left cerebellar ataxia and the exacerbation of both bulbar palsy and vertigo. At age 59, he developed aspiration pneumonia due to severe

Fig. 2. Macroscopic findings of the MO in Patient 1. An old and cavitated infarct can be seen on the right side. On the other hand, a recent infarct with a softened lesion on the left side in this formalin-fixed wet tissue is not clear. Bar = 5 mm. MO, medulla oblongata.

Fig. 3. Macroscopic findings of the major arteries of the brain in Patient 1. With respect to the left-right difference in thickness in VA, the right VA (double arrowheads and double small arrows) is much thinner than the left VA. The lumen of the right VA is obstructed 3 mm (double arrowheads) down toward the heart side from the PICA bifurcation (large arrow with asterisk). In addition, the right VA exhibits a dysplasia called "a VA-PICA variation": the diameter of the right VA down toward the heart side (double arrowheads) before the right PICA bifurcation is about twice the diameter of the right VA after the right PICA bifurcation (double small arrows) until the BA. The right PICA has almost the same diameter as the right VA (double small arrows) after the bifurcation until the BA. The diameter of the right VA (double small arrows) becomes thinner from the right PICA bifurcation (large arrow with asterisk) to the BA. Marked atherosclerosis can be observed in the left VA. No thrombi or other pathological findings of occlusion are evident in the left VA or left PICA. In order to remove the vertebrobasilar arterial structure without damaging from the cerebrum, both posterior communication arteries that make up the circle of Willis are severed on purpose. The photographic left is corresponding to the right side of Patient 1, because of the observation from the cerebral base. Bar = 2 cm. BA, basilar artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery.

Fig. 4. Klüver-Barrera (KB) staining of the MO in Patient 1. A cavitary lesion originated from an old infarct can be seen in the right lateral medulla oblongata. A recent infarct exhibiting decreased stainability is also evident on the left side. Bar = 5 mm. MO; medulla oblongata.

dysphagia based on bulbar palsy, and died of respiratory failure.

Macroscopic findings

The brain weighed 1,220 g after fixation. The macroscopic distribution of the MO included an old and cavitated infarct on the right side (Fig. 2). A recent infarct with a softened lesion on the left side was observed (Fig. 2). An old infarct was also observed on the right cerebellar hemisphere. A macroscopic analysis of the major arteries
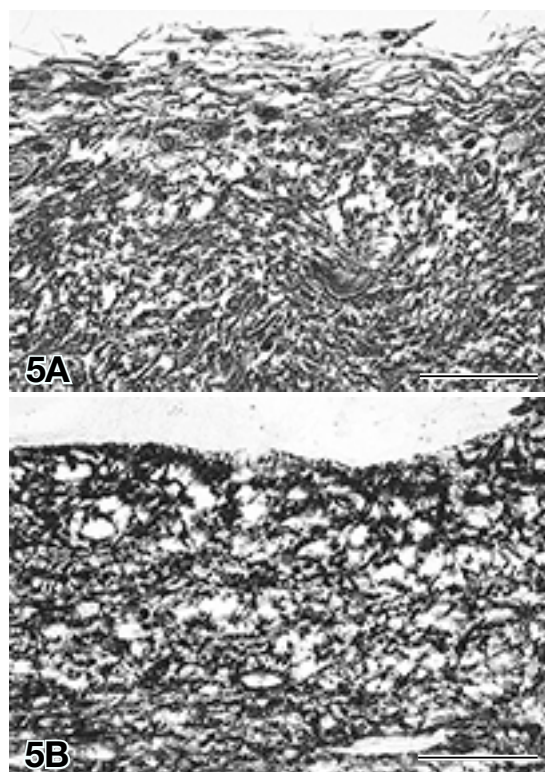

Fig. 5. Pathological findings of the old infarct in the right lateral MO in Patient 1.
  A: Histopathological finding of an old infarct with fibrillary gliosis observed around the cavitation (HE staining). Bar = 50 μm.
  B: GFAP-positive fibrillary gliosis around the cavitation (GFAP immunostaining). Bar = 50 μm.
GFAP, glial fibrillary acidic protein; HE, hematoxylin and eosin; MO, medulla oblongata.

of the brain showed that the right VA was much thinner than the left VA. The lumen of the right VA was obstructed 3 mm toward the heart side from the right PICA bifurcation. Additionally, the right VA exhibited a dysplasia called "a VA-PICA variation" (Fig. 3): the diameter of the right VA on the heart side before the right PICA bifurcation was about twice the diameter of the right VA after the right PICA bifurcation until the basilar artery (BA). The right PICA maintained the same diameter as the right VA after the bifurcation until the BA. The right VA diameter became thinner after the right PICA bifurcation until the BA. Severe atherosclerosis was observed in the left VA. There were no significant thrombi in the left VA or left PICA.

Histological findings

In HE, HE-LFB and KB stainings, a cavitary lesion was observed in the right lateral MO due to an old infarct (Fig. 4). As for pathohistological findings, fibrillary glio-

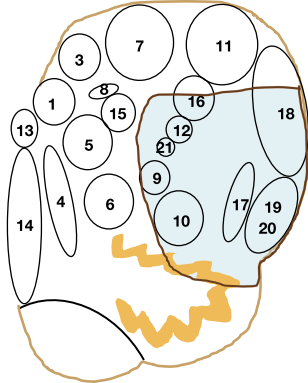| Clinical sign	Pathological legion	
Crossed sensory disturbance	N. of spinal tract of trigeminal nerve	12
	Spinal tract of trigeminal nerve	16
	Lateral spinothalamic tract	19
Cerebellar ataxia	Inferior cerebellar peduncle	18
	Spinocerebellar tract	20
Dysphagia	N. Ambiguus	9
Horner's syndrome	Sympathetic discending tract	21

Fig. 6. Diagram of the relationship between clinical symptoms and the pathological distribution impaired by the old infarct in the right lateral MO in Patient 1. The nucleus of the spinal tract of the trigeminal nerve (No. 12), spinal tract of the trigeminal nerve (No. 16), lateral spinothalamic tract (No. 19), inferior cerebellar peduncle (No. 18), spinocerebellar tract (No. 20), nucleus ambiguus (No. 9) and sympathetic descending tract (No. 21) are impaired. There is also partial impairement of the inferior olivary nucleus. The clinical symptom of right crossed sensory disturbance is considered to be due to the infarct in the nucleus of the spinal tract of the trigeminal nerve (No. 12), and spinal tract of the trigeminal nerve (No. 16), the lateral spinothalamic tract (No. 19). Right cerebella ataxia is considered to be due to the infarct in the inferior cerebellar peduncle (No. 18) and spinocerebellar tract (No. 20). Dysphagia is considered to be due to disturbance of the nucleus ambiguus (No. 9). The symptom of right Horner's syndrome is considered to be caused by disturbance of the sympathetic descending tract (No. 21). MO, medulla oblongata; N, nucleus.

sis was observed around the cavitation and there were astrocytic demarcation areas surrounding the cavitation (Fig. 5A). There were few reactive astrocytes and foamy macrophages. Astrocytic demarcation area positive for GFAP were observed around the cavitation in GFAP immunostaining (Fig. 5B). The histopathological distribution of the old lesion on the right side extended to nucleus of the spinal tract of the trigeminal nerve (No. 12 in Fig. 6), spinal tract of the trigeminal nerve (No. 16
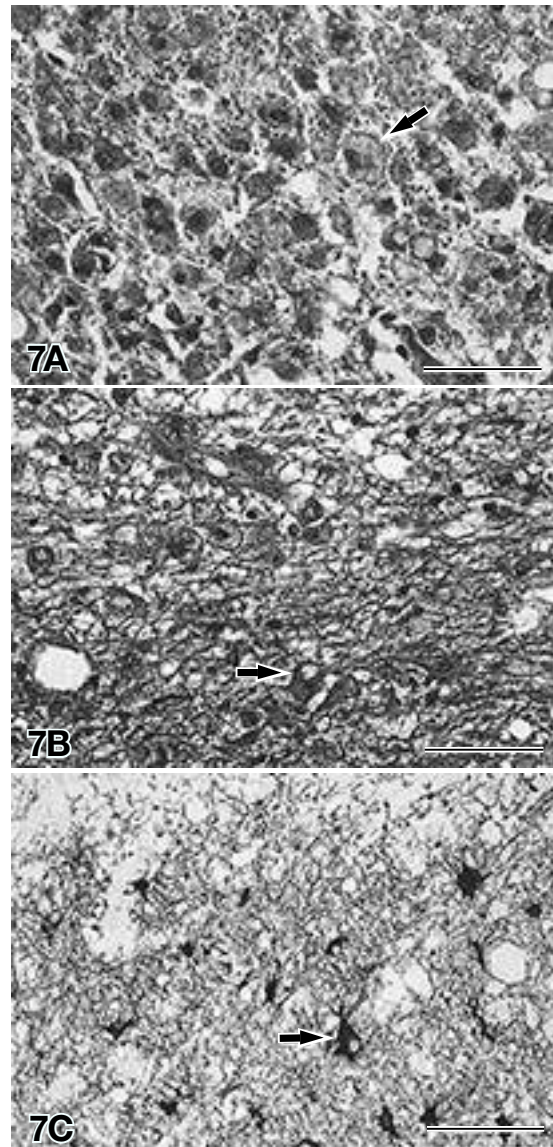

Fig. 7. Pathological findings of the recent infarct in the left MO in Patient 1.
  A: A large number of foamy macrophages (arrow) are observed (HE-LFB double staining). Bar = 50 μm.
  B: Reactive astrocytes (arrow) around the recent infarct are also seen (HE-LFB staining). Bar = 50 μm.
  C: Reactive astrocytes (arrow) around the recent infarct are strongly positive for GFAP (GFAP immunostaining). Bar = 100 μm.
GFAP, glial fibrillary acidic protein; HE, hematoxylin and eosin; LFB, luxol fast blue; MO, medulla oblongata.

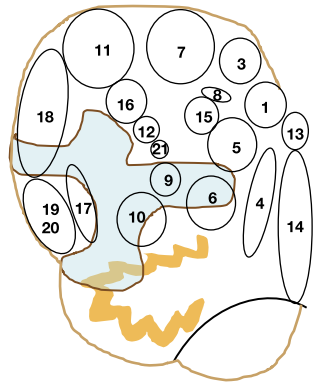| Clinical sign	Pathological legion	
Cerebellar ataxia	Inferior cerebellar peduncle	18
Dysphagia	N. Ambiguus	9

Fig. 8. Diagram of the relationship between clinical symptoms and the pathological distribution disturbed by the recent infarct in the left lateral MO in Patient 1. There is disturbance of the inferior cerebellar peduncle (No. 18) and nucleus ambiguus (No. 9). Left cerebellar ataxia is due to disturbance to the inferior cerebellar peduncle (No. 18). An exacerbation of dysphagia is observed due to disturbance to the left nucleus ambiguus (No. 9). MO, medulla oblongata; N, nucleus.

in Fig. 6), the lateral spinothalamic tract (No.19 in Fig. 6), inferior cerebellar penduncle (No. 18 in Fig. 6), spino-cerebellar tract (No. 20 in Fig. 6), nucleus ambiguus (No. 9 in Fig. 6) and sympathetic descending tract (No. 21 in Fig. 6).

An accumulation of a large number of foamy macrophages was observed in the recent infarct that exhibited a softening lesion on the left side (Fig. 7A). Reactive astrocytes were also observed around the left recent infarct lesion (Fig. 7B). These reactive astrocytes were strongly positive for GFAP (Fig. 7C). The distribution of the recent infarct on the left extended to the inferior cerebellar penduncle (No. 18 in Fig. 8) and nucleus ambiguus (No. 9 in Fig. 8). Neither the left or right infarct lesion extended to the dorsal vagal nucleus, solitary tract, nucleus of the solitary tract, hypoglossal nucleus, medial longitudinal fascicle, medial lemniscus or pyramid of MO.

A histopathological analysis of the major arteries of the brain showed an organized thrombus blocking the lumen of the right VA (Fig. 9A). With respect to the right VA, there was severe degeneration of the tunica media: the smooth muscle cells in the tunica media had almost disappeared, having been replaced with fibroblasts and collagen fibers. Severe fibrous hypertrophy of the vascular intima was also observed, with the infiltration of some foamy macrophages (Fig. 9B). An increase in ELVG-positive elastic fibers was observed in the vascular intima (Fig. 9C). The normal wavy corrugation in the internal elastic lamina disappeared (Fig. 9C). Although severe atherosclerosis was observed in the left VA and
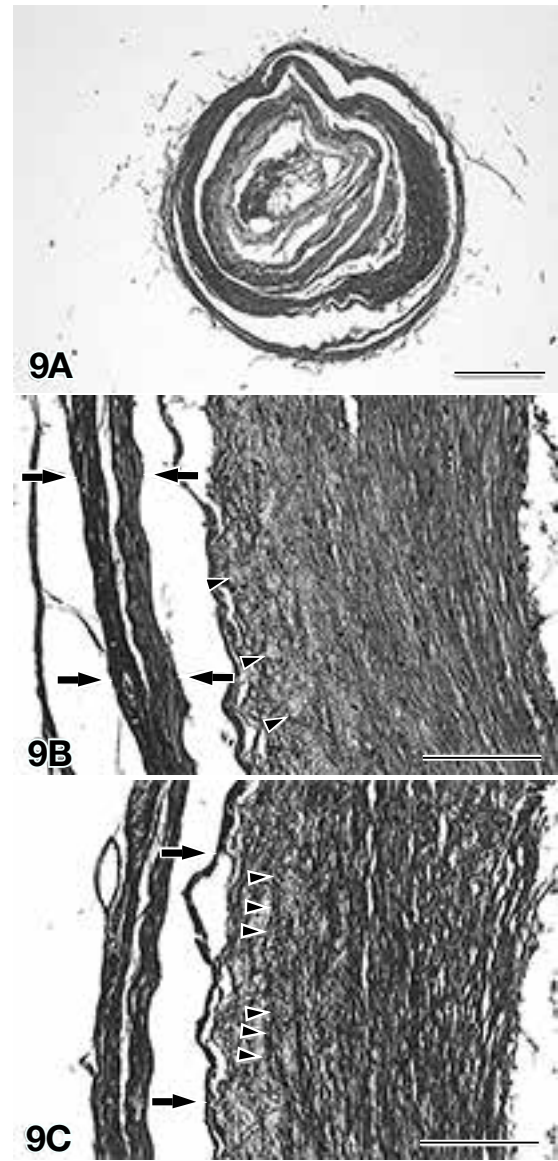

Fig. 9. Histopathological findings of the right VA in Patient 1.
 A: A thrombus accompanied by organization is blocking the lumen (ELVG staining). Bar = 500 μm.
 B: Severe degeneration of the tunica media can be seen (arrows). Histologically, the smooth muscle cells in the tunica media almost disappear, having been replaced with fibroblasts and collagen fibers. Severe fibrous hypertrophy of the vascular intima is also observed, with the infiltration of some foamy macrophages (arrowheads) (HE-LFB staining). Bar = 100 μm.
 C: An increase in ELVG-positive elastic fibers is observed in the vascular intima (arrowheads). The normal wavy corrugation disappears in the internal elastic lamina (arrows) (ELVG staining). Bar = 100 μm.
ELVG, elastica van Gieson; HE, hematoxylin and eosin; LFB, luxol fast blue; VA, vertebral artery.

left PICA, obstruction was not observed in the left VA or left PICA.

Results of analysis about the correlation between the clinical symptoms and pathologic legions

Right crossed sensory disturbance (simultaneous disturbances of thermal and pain sensibility on the right head as well as on the rest of the left body except the head) was observed at the 1st attack. The responsibility lesion corresponding to this right crossed sensory disturbance was considered to be the right infarct in the nucleus of the spinal tract of the trigeminal nerve (No. 12 in Fig. 6), spinal tract of the trigeminal nerve (No. 16 in Fig. 6) and lateral spinothalamic tract (No.19 in Fig. 6). Right cerebellar ataxia was considered to be the disturbances of the right inferior cerebellar penduncle (No. 18 in Fig. 6) and spinocerebellar tract (No. 20 in Fig. 6). The symptoms of dysphagia were considered to be due to disturbance of the nucleus ambiguus (No. 9 in Fig. 6), and the symptoms of right Horner's syndrome were considered to be due to disturbance of the right sympathetic descending tract (No. 21 in Fig. 6). Left cerebellar ataxia was observed at the 2nd attack. This was thought to have arisen from disturbance of the left inferior cerebellar penduncle (No. 18 in Fig. 8). An exacerbation of dysphagia was also observed at the 2nd attack. This dysphagia symptom had already occurred with the 1st attack due to disturbance of the right nucleus ambiguus (No. 9 in Fig. 6), and this 1st attack dysphagia was thought to have continued until the 2nd infarct. In the patient with this 1st attack dysphagia, the 2nd infarct lesion disturbed the left nucleus ambiguus (No. 9 in Fig. 8), which made the dysphagia worse: i.e., an exacerbation of dysphagia was observed after the 2nd attack.

Patient 2
Clinical history

The patient was male and 79 years old at the time of death. At age 74, he was diagnosed with chronic heart failure. At age 79, he was hospitalized after the appearance of vertigo, vomiting and headache. His neurological symptoms were right crossed sensory disturbance, right cerebellar ataxia, bulbar palsy and right Horner's syndrome. An infarct in the right lateral MO was suspected from the only clinical symptoms, and thus he was given a clinical diagnosis of Wallenberg syndrome. Aspiration pneumonia occurred on day 2 of the illness. On day 4 of the illness, he was put on a ventilator after the respiratory arrest, but his heart rate decreased. He died on the 10th day of the illness due to heart failure.

Macroscopic findings

The brain weighed 1,300 g after fixation. The macroscopic distribution of the lesion was a fresh infarct accompanied by severe edema in the right lateral MO (Fig. 10). The right cerebellar hemisphere also exhibited a fresh infarct with severe edema. A macroscopic analysis of the major arteries of the brain revealed occlusion of the lumen of the right PICA about 3 mm distal from its bifurcation with the right VA (Fig. 11).

Fig. 10. Macroscopic findings of the MO in Patient 2. A fresh infarct is seen in the right lateral MO. Since the acute infarct region of the right MO becomes very fragile, the upper part of the infarct region is artificially destroyed on the occasion of brain cutting. Bar = 5 mm. MO, medulla oblongata.
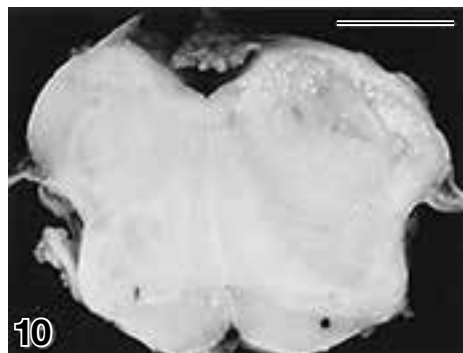
Fig. 11. Macroscopic findings of the major arteries of the brain in Patient 2. The right PICA is obstructed about 3 mm distal from the right bifurcation (double arrowheads). The photographic left is corresponding to the right side of Patient 2, because of the observation from the cerebral base. Bar = 2 cm. PICA, posterior inferior cerebellar artery.
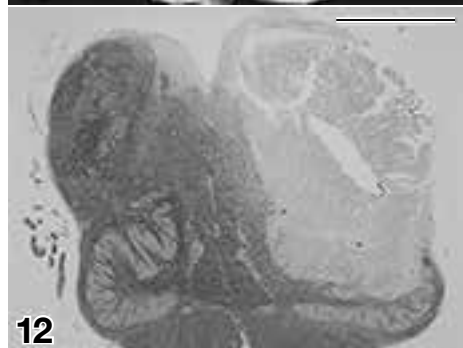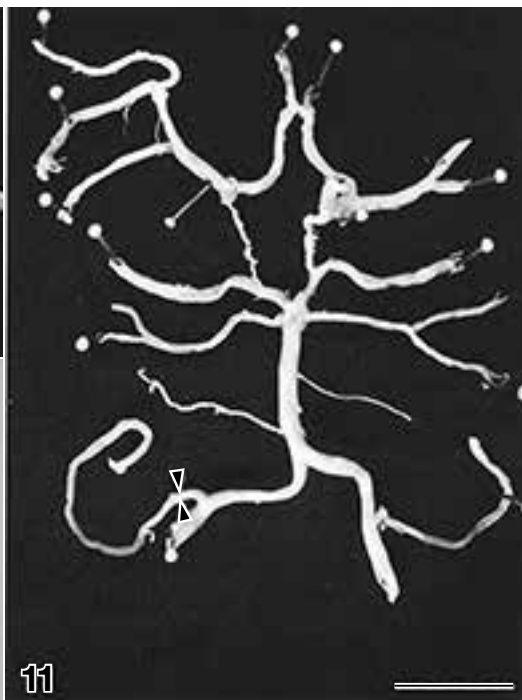
Fig. 12. KB staining of the MO in Patient 2. A fresh infarct is observed in the right lateral MO. A strong decrease in stainability can be seen. Bar = 5 mm. KB, Klüver-Barrera; MO, medulla oblongata.

Histological findings

In HE, HE-LFB and KB staining, a fresh acute infarct was observed in the right lateral MO and exhibited a strong decrease in stainability (Fig. 12). Macrophages or reactive astrocytes were not observed in the area of infarction (Fig. 13A). Neurons in the infarct area were identified as "red neurons" by HE staining: the typical neuropathological finding of these red neurons is called "Spielmeyer's acute ischemic change" (Fig. 13B). These

red neurons showing Spielmeyer's acute ischemic change were not stained with KB staining. Severe edematous tissue change was observed in neuropils around the acute infarct. There was no structure positive for GFAP in and around the acute infarct area in GFAP immunostaining (Fig. 13C). This acute infarct lesion extended to disturb the nucleus of the spinal tract of the trigeminal nerve (No. 12 in Fig. 14), spinal tract of the trigeminal nerve (No.16 in Fig. 14), the lateral spinothalamic tract (No. 19 in Fig. 14), inferior cerebellar penduncle (No. 18 in Fig. 14), spinocerebellar tract (No. 20 in Fig. 14), nucleus ambiguus (No. 9 in Fig. 14), sympathetic descending tract (No. 21 in Fig. 14), medial vestibular nucleus (No. 7 in Fig. 14), nucleus of the spinal tract of the trigeminal nerve (No.
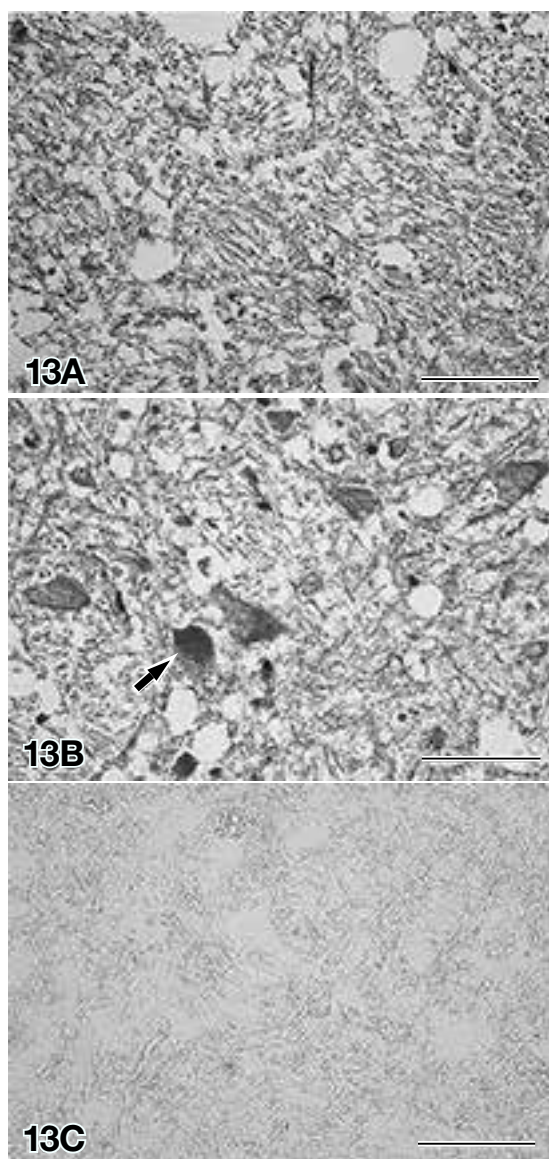

Fig. 13. Pathological findings of the fresh infarct in the right lateral MO in Patient 2.

  A: Histopathological finding of a fresh infarct. Macrophages or reactive astrocytes are not observed (HE staining). Bar = 50 µm.
  B: A red neuron showing Spielmeyer's acute ischemic change (arrow) can be observed (HE staining). Bar = 50 µm.
  C: There is no structure positive for GFAP (GFAP immunostaining). Bar = 50 µm.
HE, hematoxylin and eosin; GFAP, glial fibrillary acidic protein; MO, medulla oblongata.

| Clinical sign	Pathological legion	
Crossed sensory disturbance	N. of spinal tract of trigeminal nerve	12
	Spinal tract of trigeminal nerve	16
	Lateral spinothalamic tract	19
Cerebellar ataxia	Inferior cerebellar peduncle	18
	Spinocerebellar tract	20
Dysphagia	N. Ambiguus	9
Horner's syndrome	Sympathetic discending tract	21
Vertigo	Medial vestibular N.	7
Headache	N. of spinal tract of trigeminal nerve	12
	Spinal tract of trigeminal nerve	16
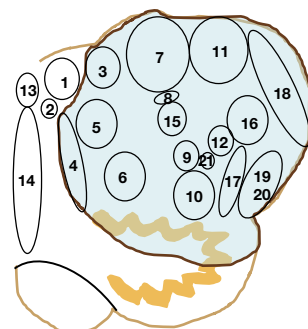
Fig. 14. Diagram of the relationship between clinical symptoms and the pathological distribution disturbed by the acute infarct in the right lateral MO in Patient 2. There is disturbance of the nucleus of the spinal tract of the trigeminal nerve (No. 12), spinal tract of the trigeminal nerve (No. 16), lateral spinothalamic tract (No. 19), inferior cerebellar peduncle (No. 18), spinocerebellar tract (No. 20), nucleus ambiguus (No. 9), sympathetic descending tract (No. 21), medial vertebular nucleus (No. 7), nucleus of the spinal tract of the trigeminal nerve (No. 12) and spinal tract of the trigeminal nerve (No. 16). There is also disturbance of the dorsal vagal nucleus (No. 3) and inferior olivary nucleus. The clinical symptom of right crossed sensory disturbance is based on an infarct in the nucleus of the spinal tract of the trigeminal nerve (No. 12), spinal tract of the trigeminal nerve (No. 16) and lateral spinothalamic tract (No. 19). Right cerebellar ataxia is due to disturbance of the inferior cerebellar peduncle (No. 18) and spinocerebellar tract (No. 20). Dysphagia is due to disturbance of the nucleus ambiguus (No. 9). The symptom of right Horner's syndrome is due to disturbance of the sympathetic descending tract (No. 21). Vertigo is thought to be due to disturbance of the medial vestibular nucleus (No. 7). Headache is thought to be due to disturbance of the nucleus of the spinal tract of the trigeminal nerve (No. 12) and spinal tract of the trigeminal nerve (No. 16). MO, medulla oblongata; N, nucleus.

12 in Fig. 14) and spinal tract of the trigeminal nerve (No. 16 in Fig. 14). Portions of the dorsal vagal nucleus (No. 3 in Fig. 14) and inferior olivary nucleus were also disturbed (Fig. 14). However, no significant pathological change was identified in the hypoglossal nucleus, medial longitudinal fascicle, medial lemniscus or pyramid of MO.
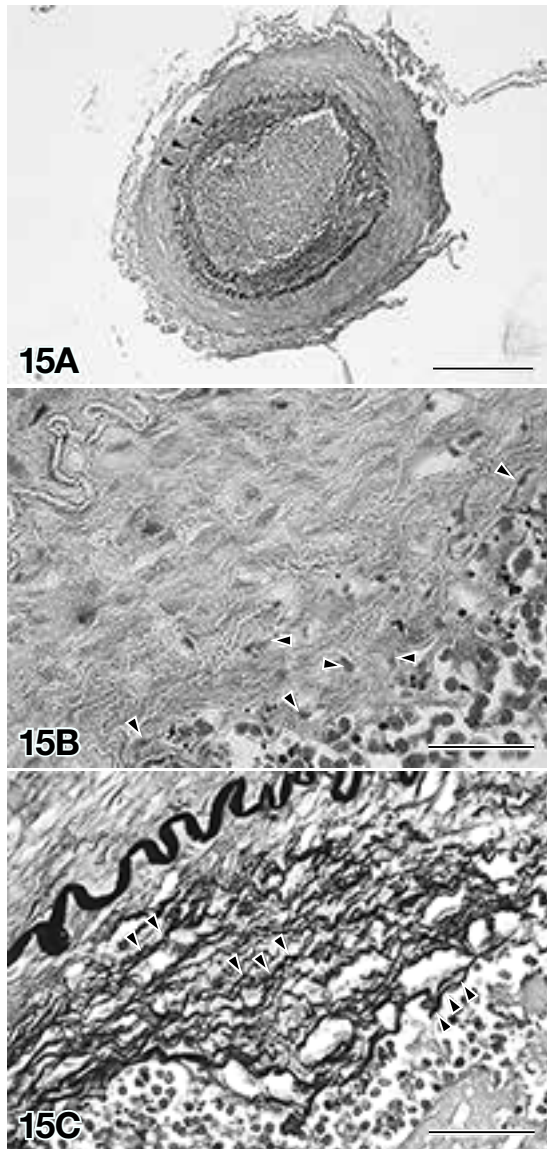

Fig. 15. Histopathological findings of the right PICA in Patient 2.

A: The lumen of the right PICA is occluded by fresh erythrocytes. Partial stretching of the internal elastic lamina is observed (arrowheads) (ELVG staining). Bar = 300 μm.

B: Vascular endothelial cells almost disappear from the vascular intima, and fibroblasts is observed from the vascular intima toward the thrombus (arrowheads). Thickening of the vascular intima is also seen (HE staining). Bar = 30 μm.

C: There is an increase in the ELVG-positive elastic fibers within the vascular intima (ELVG staining). Bar = 30 μm.

ELVG, elastica van Gieson; HE, hematoxylin and eosin; PICA, posterior inferior cerebellar artery.

A pathological analysis of the major arteries of the brain showed occlusion of the lumen of the right PICA by fresh erythrocytes (Fig. 15A). Vascular endothelial cells had almost disappeared from the vascular intima, and fibroblasts were observed from the vascular intima toward the thrombus (Fig. 15B). Namely, these tissue findings showed the organization of the thrombus started from the side of the vascular intima. Thickening of the vascular intima was also observed. In ELVG staining, there was an increase in the ELVG-positive elastic fibers within the vascular intima (Fig. 15C). Foamy macrophages were also observed within the vascular intima. Partial stretching of the internal elastic lamina was observed (Fig. 15A). Decreased smooth muscle cells as well as increased fibroblasts and collagen fibers were observed in the tunica media. Occlusion were not observed in the right VA.

Results of analysis about the correlation between the pathologic legions and clinical symptoms

Right crossed sensory disturbance was considered to be due to the infarct in the nucleus of the spinal tract of the trigeminal nerve (No. 12 in Fig. 14), spinal tract of the trigeminal nerve (No. 16 in Fig. 14) and lateral spinothalamic tract (No. 19 in Fig. 14). Right cerebellar ataxia was considered to be due to the infarct in the inferior cerebellar peduncle (No. 18 in Fig. 14) and spinocerebellar tract (No. 20 in Fig. 14). Dysphagia was considered to be due to disturbance of the nucleus ambiguus (No. 9 in Fig. 14). The symptoms of right Horner's syndrome were considered to be due to disturbance of the sympathetic descending tract (No. 21 in Fig. 14). Vertigo was thought to be due to disturbance of the medial vestibular nucleus (No. 7 in Fig. 14). Headache was thought to be due to disturbance of the nucleus of the spinal tract of the trigeminal nerve (No. 12 in Fig. 14) and spinal tract of the trigeminal nerve (No. 16 in Fig. 14).

DISCUSSION

In this study, we analyzed 2 autopsy cases with typical Wallenberg syndrome. In the 1st case, occlusion of the right VA was confirmed by pathological analyses. In the 2nd case, occlusion of the right PICA was pathologically confirmed. In a search of the literature from 1933 to 2013, we could only find 24 autopsy case reports of Wallenberg syndrome in Japan (Table 1). A literature analysis of overseas reports from 1946 to 2013 using PubMed resulted in only 4 autopsies of Wallenberg syndrome.[7–10] Of 2,200 autopsy cases performed at our Neuropathology Division, only 2 cases (0.09%) had a pathologically definite diagnosis of Wallenberg syndrome. As shown in the report by Hata et al.,[2] Wallenberg syndrome has

a good prognosis. The authors suggest the following hypothesis: even when there is dysphagia due to the disturbed nucleus ambiguus, only the dyspnea based on Wallenberg syndrome is not considered to be the direct cause of death. The main reason is that there could be compensation from the nucleus ambiguous on the normal side and the non-disturbed hypoglossal nuclei on the both sides. Further, recent advancements in MRI and other neuroradiological imaging examinations have made it possible to identify vessel occlusion and infarct in the lateral MO, while Wallenberg syndrome patients are still alive. Good prognosis and easy-to-diagnose neuroradiological imaging in Wallenberg syndrome are thought to have reduced the number of autopsy reports.

The main clinical symptoms in the original case reported by Adolf Wallenberg in 1895 were crossed sensory disturbance, cerebellar ataxia and bulbar palsy. However, a variety of symptoms in Wallenberg syndrome have been reported as more case reports have been accumulated. Hata et al. classified clinical symptoms of Wallenberg syndrome into 5 group categories.[2] Group 1 is crossed sensory disturbance; Group 2 is cerebellar ataxia; Group 3 is bulbar palsy; Group 4 is autonomic symptoms and Group 5 is other symptoms. Group 1 involves disturbance to thermal and pain sensibilities on the face on the same side of the infarct lesion and disturbance to thermal and pain sensibilities on the trunk and limbs on the opposite side of the infarct. According to Hata et al., Group 1 is observed in 97% of cases, and they considered crossed sensory disturbance an essential symptom. Sensory disturbances of the limbs and trunk are considered to be caused by impairment of the lateral spinothalamic tract, while sensory disturbances of the face are considered to be due to impairment of both the spinal tract of the trigeminal nerve and the nucleus of the spinal tract of the trigeminal nerve. The cerebellar ataxia symptoms of Group 2 include ataxia, vertigo, nystagmus and giddiness. Ataxia of the limbs is caused by disturbance of the inferior cerebellar peduncle and spinocerebellar tract, while vertigo and nystagmus are caused by disturbance of the vestibular nucleus. Bulbar palsy in Group 3 is considered to be due to disturbance of the nucleus ambiguus. Kurono et al. reported that the rostral region within the nucleus ambiguus had the strong relationship with swallowing.[11] Of the autonomic symptoms of Group 4, Horner's syndrome is observed in 66% in cases, which is considered to be due to disturbance of the sympathetic descending tract. The symptoms in Group 5 include a very wide variety of manifestations. Headache is reported to make up 60% of these symptoms, double vision 13% and facial palsy 11%.[2] Headaches are supposed to arise from transient vasospasms of the blood vessels that supply the nucleus of the spinal tract of the trigeminal nerve.[2] As these vasospasms are transient, the headaches disappear after several days. Takahashi et al. reported that headache was related to disturbance of both nucleus of the spinal tract of the trigeminal nerve and the spinal tract of the trigeminal nerve.[12] In double vision, it is supported that the trochlear nucleus is disturbed as the infarct lesion spreads rostrally upward to the trochlear nucleus of the midbrain. Similarly in facial palsy, as the infarct spreads rostrally upward to the facial nucleus of the pons, it disturbs the facial nerve nucleus. Taken together, as a infarct lesion expands, symptoms of the nerve nuclei and tracts in the disturbed region could appear. Since only the lateral MO is affected in Wallenberg syndrome, there is no disturbance of the pyramidal tract or the medial lemniscus. This is the mechanism that hemiplegia from disturbance of the pyramidal tract or deep sensory disorder due to disturbance of the medial lemniscus do not appear. Therefore, this mechanism results in only the crossed sensory disturbance without hemiplegia and deep sensory disturbance.

The 2 autopsy cases that we pathologically analyzed in detail exhibited the 3 main symptoms reported by Adolf Wallenberg—crossed sensory disturbance, cerebellar ataxia and bulbar palsy. As shown in the results of the analysis of the correlation between the clinical symptoms and the pathologic lesions, we confirmed that the appearance of crossed sensory disturbance was due to pathological disturbance of the lateral spinothalmic tract, nucleus of the spinal tract of the trigeminal nerve and spinal tract of the trigeminal nerve. We also verified that cerebellar ataxia appeared due to pathological disturbance of the inferior cerebellar penduncle and spinocerebellar tract. Similarly, we showed that pathologically verifiable damage in the nucleus ambiguus caused the clinical symptom of bulbar palsy. In both autopsy cases, we were able to verify a 1-to-1 correspondence between the clinical symptoms and the neuropathological lesions. Neuropathologically, our analysis of the correlation between the clinical symptoms and the neuropathological lesions verified the validity of the clinical 5 symptom categories reported by Hata et al. As shown in Table 1, our analysis of the literature found 24 autopsy reports that provided neuropathological examinations of Wallenberg syndrome. An analysis of these 24 autopsies with the 3 major symptoms verified a 1-to-1 correlation between clinical symptoms and the neuropathological lesions. However, it has been indicated that the clinical symptoms that are actually observed are more varied than the putative symptoms based on the neuropathological disturbances.[13] Among a wide variety of symptoms,

Table 1. Autopsy cases of Wallenberg syndrome in Japan

	Age (yr)	Sex	Cause	Laterality	Origin	Sensory disturbance	Cerebellar ataxia	Bulbar palsy	Dysautonomia	Vertigo	Headache	Others
Case 1	67	m	Thrombosis, anomaly	lt	PICA, hypoplasia in lt PICA	○: crssd	○	○		○		lt facial palsy, lt hypoglosssal palsy
Case 2	84	f	Thrombosis	lt	PICA	○: crssd	○	○	○	○	○	Dysuria
Case 3	35	f	nd	lt	nd	○: crssd	○	○				Double vision, lt hemiplegia
Case 4	42	f	Tumor (Neurinoma)	rt	Tumor compression	○	○	○		○	○	Double vision, lt hemiplegia, memory disturbance
Case 5	64	m	Thrombosis	lt	PICA	○: ipsi	○	○	○	○	○	Double vision, dysuria
Case 6	62	m	Thrombosis	rt	PICA VA	○: ipsi	○	○	○		○	Double vision, lt hemiplegia, eye movement disturbance
Case 7	nd	nd	Thrombosis	rt	nd	○	○	○	○	○		rt facial palsy, rt hypoglossal palsy
Case 8	63	m	Thrombosis	lt	PICA	○: crssd	○	○	○	○	○	lt facial palsy
Case 9	60	m	Thrombosis	lt	PICA, hypoplasia in rt PICA	○: crssd	○	○	○	○		
Case 10	40	f	Anomaly, thrombosis	rt	Defect of PICA	○: crssd	○	○	○	○		
Case 11	54	m	Thrombosis	lt	nd		○	○	○	○	○	lt hypoglossal palsy
Case 12	48	m	Thrombosis	rt	VA	○: crssd	○	○	○	○	○	rt facial palsy, rt hypoglossal palsy
Case 13	76	m	Thrombosis, anomaly	rt	lt VA, hypoplasia in rt VA, rt PICA branched from lt VA			○				
Case 14	38	m	Tumor (astrocytoma)	lt	Tumor infiltration		○	○		○	○	lt facial palsy, lt deafness
Case 15	49	f	Thrombosis	rt	VA, no remarkable findings in PICA	○: bi	○	○	○	○	○	Dysuria
Case 16	58	m	Embolism	nd	PICA, VA	Typical type						
Case 17	58	f	Thrombosis	rt	VA	○: ipsi	○	○	○		○	lt hypoglossal palsy
Case 18	58	f	Tumor (metastasis)	rt	Tumor infiltration	○: bi	○	○	○	○		bi deafness
Case 19	70	m	Embolism	rt	Not detected emboli in VA and PICA	○: crssd	○	○	○	○	○	
Case 20	84	m	nd	rt	nd	○: ipsi	○	○		○		
Case 21	64	m	nd	rt	nd	○: crssd	○	○				rt facial palsy, respiratory distress, hallucination
Case 22	50	m	Dissection of aneurysm	lt	VA	○: crssd	○	○	○	○	○	Double vision
Case 23	70	m	Thrombosis	lt	VA	○: ipsi	○	○				lt facial palsy, apnea
Case 24	83	m	Thrombosis, embolism, anomaly	lt	VA to BA, hypoplasia in rt VA, rt PICA branched from BA, lt AICA branched from lt VA	Wallenberg syndrome						
Patient 1	56	m	Thrombosis, anomaly	rt	VA, hypoplasia in rt VA	○: crssd	○	○	○	○		
				lt			○	○		○		
Patient 2	79	m	Embolism	rt	PICA	○: crssd	○	○	○	○	○	

○, present; AICA, anterior inferior cerebellar artery; BA, basilar artery; *bi*, bilateral; *crssd*, crossed; f, female; *ipsi*, ipsilateral; *lt*, left; m, male; N, nucleus; *nd*, no description; PICA, posttterior inferior cerebellar artery; *rt*, right; V, trigeminal nucleus; VA, verteblar artery; VI, tolochler nucleus; VII, facial nuclues; X, dorsal vagal nucleus; XII, hypoglossal nucleus.

Table 1—Continued

Neuropathological lesions

Spinothalamic tract	N. of spinal tract of trigeminal nerve	Spinal tract of trigeminal nerve	Inferior cerebellar peduncle	Spinocerebellar tract	Nucleus ambiguus	Sympathetic discending tract	Medial vestibular nucleus	Others	Reference
nd									16
○	○	○	○	○	○			lt cerebellar hemisphere	17
nd									18
nd									19
					○			lt cerebellar hemisphere	20
○	○	○	○	○	○			V, VI, X, XII, pyramidal tract, medial lemniscus, dentate N in rt cerebellum	21
nd								lt cerebellar hemisphere	22
○	○	○	○	○	○	○	○	VII, X	23
○	○	○	○		○		○	X, XII, medial lemniscus	24
nd									25
○	○	○	○	○	○		○	XII, lt cerebellar hemisphere	26
nd								VII, lt cerebellar hemisphere	27
○	○	○		○	○		○	X, rt cerebellar hemisphere	28
nd									29
nd									30
nd								Cerebellum	31
nd									32
○	○	○	○		○		○	XII	33
nd								bi cerebellar hemisphere	34
○	○	○			○	○			35
	○		○		○				36
nd									37
					○				38
nd								lt cerebellum	39
○	○	○	○	○	○	○		rt cerebellar hemiephere	
			○		○				
○	○	○	○	○	○	○	○	X, rt cerebellar hemisphere	

Footnotes, refer to the previous page

there were some symptoms that appeared transiently in the initial stage of the disease and then eventually disappeared.[13] Tissue edema is presumed to be a cause of symptoms that appear transiently only in the initial stages of the disease.[13] This applies to our Patient 1, he experienced vertigo at both the 1st and the 2nd attacks, but the vertigo disappeared. No clear histopathological abnormalities were observed in the vestibular nucleus. Tissue edema is presumed to be a pathological mechanism able to explain the discrepancy between the presence of this vertigo symptom and histopathologically normal findings. It is thought that edema occurred in the vestibular nucleus at the initial stage of the disease, which caused a functional disturbance in this nucleus, leading to the transient appearance of vertigo. As time passed, edema itself disappeared from the vestibular nucleus, which caused the vertigo to disappear.

In Adolf Wallenberg's article in 1901, he recorded an occlusion of PICA at the location of 4 mm distal from the PICA bifurcation, as well as an infarct of the lateral MO.[1] In Patient 2 that we describe above, the area of right PICA occlusion was 3 mm distal from the PICA bifurcation, only 1 mm different than in the original autopsy case reported by Adolf Wallenberg. Therefore, the autopsy case of Patient 2 is considered equal to the original autopsy case reported by Adolf Wallenberg. On the other hand, advancements in neuroradiological diagnosis have led to reports that cases of Wallenberg syndrome with the 3 major symptoms (crossed sensory disturbance, cerebellar ataxia and bulbar palsy) more often exhibit VA blockage.[3–6] Of the 24 Wallenberg syndrome autopsies in Table 1, 8 cases were caused by PICA blockage, 9 cases by VA blockage, 1 case by BA blockage, 4 cases by blood vessel dysplasia, 1 case by dissection of an aneurysm, 3 cases by a tumor, 1 case without clear vessel blockage and 5 cases where the causative vessel blockage was not recorded (including overlap). Moreover, our search of the overseas literature using PubMed only yielded 4 autopsies of Wallenberg syndrome.[7–10] One case was caused by dissection of the VA,[7] 1 case by meningioma[9] and 2 cases in which the causative vessel blockage was not recorded.[8, 10] Neuroradiologically, Matsumura et al. used angiography to examine 10 patients with Wallenberg syndrome, finding only 1 case of PICA blockage, with the other 9 cases exhibiting VA blockage.[3] In an MRA investigation, Watanabe et al. reported that among 12 patients with Wallenberg syndrome, VA blockage was observed in 9 cases.[4]

The PICA supplies the lateral 1/3 of the MO, as well as the lower part of the cerebellar hemisphere, including the cerebellar tonsilla and vermis. Therefore, as recorded by Adolf Wallenberg, blockage of the PICA causes an infarct in the lateral MO, leading to Wallenberg syndrome. However, individual differences in the architecture of the PICA are frequent, with the defect of the PICA itself even being reported.[14] There are many variations in the arterial architecture system that supplies the cerebellum.[14] Among these variations, unilateral PICA defect or hypoplasia is observed in 42%, and unilateral anterior inferior cerebellar artery defect or hypoplasia is observed in 30%. In contrast, variation of the superior cerebellar artery is rare. In 12% of cases with unilateral PICA defect, the normal-side PICA alone supplies the cerebellar region supplied by both PICA. The type of blood vessel dysplasia called "a VA-PICA variation", which was observed in Patient 1, is reportedly seen in 21% of cases.[14] In addition to many variations in the cerebellar arterial architecture system, there are also well-developed formations of arterial anastomosis. Based on this arterial anastomosis, the frequent defects and hypoplasia found in cerebellar arteries are often compensated by other arterial systems. Thus, a congenital PICA defect or hypoplasia would not necessarily directly cause clinical symptoms.[14] However, acquired atherosclerotic lesions in the PICA with variations are supposed to arise earlier and be more severe compared to those in normal.[15] Moreover, cases of VA-PICA variations exhibit a small diameter in the thin VA portion from the PICA bifurcation to the BA. In such cases, since BA is supplied only by the opposite-side VA, blood-flow dynamics could easily lead to blockage lesions in the thin VA.[14]

Next, considering the arterial system that supplies the MO from an anatomical standpoint, it has been reported that the lateral MO is more often supplied by branches from the VA than from the PICA.[5, 6] For this reason, congenital abnormalities in VA formation might to play an important role in Wallenberg syndrome. From the detailed analysis of the 2,200 autopsy cases performed at our Neuropathology Division, however, we are convinced that only the differences in the diameter of the left and right VAs are normal variations with no pathological significance. The results of our literatural analysis of 24 past autopsy cases found 4 cases of abnormal vessel formation (cases 1, 10, 13, 24 in Table 1). Including overlap, the PICA abnormality was involved in all 4 cases (cases 1, 10, 13, 24 in Table 1) and the VA abnormality in 1 case (case 24 in Table 1). The vessel abnormality directly contributed to the Wallenberg syndrome was involved in 3 cases (cases 1, 10, 13) of the 4 cases. Analyzing our 2 autopsy cases, hypoplasia of the right VA in a VA-PICA variation is considered to be a factor that caused the 1st infarct in the right MO in Patient 1. In contrast, the left VA was well developed, and the lumen of the left VA was maintained despite

the presence of severe atherosclerosis. If the left and right VAs had the same degree of atherosclerosis, the 1st would be a thin lumen of the right VA in a VA-PICA variation. In fact, the right VA did become occluded first, causing right Wallenberg syndrome.

The clinical symptoms corresponding to the 2nd infarct in the left lateral MO in Patient 1 were only ataxia and exacerbated dysphagia. Since left crossed sensory disturbance was not observed, a clinical diagnosis of Wallenberg syndrome was not able to be made while the patient was alive. Pathologically, the infarct lesion in the left lateral MO was disturbing the inferior cerebellar peduncle and nucleus ambiguus. At the time of the 2nd infarct onset of the left lateral MO, there had already been disturbance to the right inferior cerebellar peduncle, the right spinocerebellar tract and the right nucleus ambiguus. The 2nd infarct caused bilateral cerebellar ataxia and severe dysphagia, leading to the 2nd hospitalization. In the end, the patient died from aspiration pneumonia caused by severe dysphagia. Regarding the vessel lesions corresponding to the 2nd infarction in the left lateral MO, occlusion to the left VA or left PICA was not pathologically identified. Although a clinical diagnosis of left Wallenberg syndrome was not able to be given, a pathological diagnosis of left Wallenberg syndrome should be made in this case from a pathological standpoint. Patient 2 had an infarct in the lateral MO and showed the typical 3 major symptoms of crossed sensory disturbance, cerebellar ataxia and bulbar palsy, which was caused by occlusion of the PICA: this Patient 2 was the same as the original case reported by Adolf Wallenberg. Of the 24 autopsy cases, only 3 cases displayed this kind of original Wallenberg syndrome (Table 1).

Taken together with the original Wallenberg syndrome, we would like to call the cases that fulfill the following 3 criteria "definite pathologic Wallenberg syndrome". The 1st criterion is that a pathological obstruction of the PICA or VA can be confirmed. The 2nd is that an infarct in the lateral MO based on obstruction of the PICA or VA can be pathologically identified. The 3rd is that there is a 1-to-1 correspondence between the clinical symptoms and the neuropatholoical lesions. Both the 1st infarct in the right lateral MO in Patient 1 and the infarct in the right lateral MO in Patient 2 correspond to "definite pathologic Wallenberg syndrome". Although the 2nd infarct in the left lateral MO in Patient 1 was pathologically identified, pathological occlusion of the left VA or left PICA caused this infarct was not observed. A variety of reasons could have caused the 2nd infarct in the left lateral MO, including transient occlusion by a thrombus (or an embolus) that dissolved naturally or a hypodynamic infarction. Although it is not possible to identify occlusion to the left VA or the left PICA in Patient 1, pathological infarct do exist in the left lateral MO, which is the region supplied by these vessels. As shown in Table 1, the clinical symptoms of Wallenberg syndrome also appear in a case with no clear vessel occlusion (case 19 in Table 1). Moreover, there are cases in which the cause is something besides a blood vessel lesion, such as tumor infiltration (cases 15 and 18 in Table 1). It is possible to pathologically identify a disturbance other than an infarct in the lateral MO on the occasion of autopsy analysis. Therefore, in the patients with the typical 3 major symptoms (crossed sensory disturbance, cerebellar ataxia and bulbar palsy) recorded by Adolf Wallenberg in 1895, an autopsy analysis might be required.

The authors declare no conflict of interest.

REFERENCES

1 Wallenberg A. Anastomischer Befund in rinen als "acute Bulbaraffection (Embolie der Art. Cerebellar. Post. Inf. Sinister.)?" beschriebenen Falle. Arch Psychiat Nervenkr. 1901;34:923-59. German.

2 Hata Y, Kawamura A, Suzuki K. [Two cases of Wallenberg syndrome—an analysis of 151 cases from Japan]. Shindan To Chiryo. 1969;57:1259-68. Japanese.

3 Matsumura K, Tamaoka A, Sonoh M, Sakuma M. Clinical and neuroradiological investigation of Wallenberg's syndrome. Rinsho Shinkeigaku. 1986;26:1206-9. Japanese with English abstract. PMID: 3829523.

4 Watanabe M, Takahashi A, Hashizume Y, Motegi Y, Furuse M. Magnetic resonance angiography in 12 patients with Wallenberg's syndrome. Rinsho Shinkeigaku. 1992;32:1186-92. Japanese with English abstract. PMID: 1301318.

5 Fisher CM, Karnes WE, Kubik CS. Lateral medullary infarction – The pattern of vascular occlusion. J Neuropathol Exp Neurol. 1961;20: 323-79. PMID: 13699936.

6 Currier RD, Schneider RC, Priston RE. Angiographic findings in Wallenberg's lateral medullary syndrome. J Neurosurg. 1962;19:1058-67. PMID: 14024327.

7 De Caro R, Parenti A, Munari PF. Fenestration of the vertebrobasilar junction. Acta Neurochir. 1991;108:85-87. PMID: 2058433.

8 Amantini A, Arnetoli G, Rossi L, Fenzi, Salviati A, Rizzuto N, et al. BAEP and autopsy findings in Wallenberg syndrome. Ital J Neurol Sci. 1982;3:237-40. PMID: 7161039.

9 Kleinshmidt-DeMasters BK, Avakian JJ. Wallenberg syndrome caused CSF metastasis from malignant intraventricular meningioma. Clin Neuropathol. 1985;4:214-9. PMID: 4064387.

10 Moffie D, Hamburger HL. Pain and neuroma formation in

Wallenberg's lateral medullary syndrome. Clin Neurol Neurosurg. 1986;88:217-21. PMID: 3780111.

11 Kurono H, Uesaka Y, Kunimoto M, Imafuku I. The correlation between dysphagia and involvement of the ambiguous nucleus on MRI in acute-phase lateral medullary syndrome. Rinsho Shinkeigaku. 2006;46:461-6. Japanese with English abstract. PMID: 17061698.

12 Takahashi J, Jimi T, Wakayama Y. [An investigation of headache with Dejerine syndrome]. Nihon Zutsu Gakkai Zasshi. 1999;26:75-6. Japanese.

13 Wakayama Y, Takahashi A, Asano H, Kuriyama K, Ando T. [Three cases of Wallenberg syndrome with diabetes—an analysis of 213 cases of Wallenberg syndrome from the Japanese literature]. Saishin Igaku. 1973;28:336-43. Japanese.

14 Kameyama M. [Variations of the cerebellar arteries: a vascular pattern responsible for cerebellar infarction]. Rinsho Shinkeigaku. 1966;6: 95-100. Japanese.

15 Moossy J. Development of cerebral atherosclerosis in various age groups. Neurology. 1959;9:569-74. PMID: 14423917.

16 Asano K, Yamada T. [An interesting case with embolism of the posterior inferior cerebellar artery]. Naigai Chiryo. 1933; 28:930-4. Japanese.

17 Nakamura H, Toyokura Y, Aki M, Kameyama M, Yamamoto H, Kuroiwa Y, et al. [A case of Wallenberg syndrome (a clinicopathological study)]. Seishin Shinkeigaku Zasshi. 1953;55: 890. Japanese.

18 Murata T, Ushio H. [Infarct in Medulla oblongata, particularly in Wallenberg's lateral medullary syndrome]. Rinsho Naika Shonika. 1957;12:1133-6. Japanese.

19 Tahara Y, Ito K. [A case of Wallenberg syndrome with a brain tumor]. Seishin Shinkeigaku Zasshi. 1958;60:798. Japanese.

20 Nishino T, Oda K, Nakade R, Hatano S. [An autopsy case of a Wallenberg syndrome]. Rinsho No Nippon. 1960:6:296-303. Japanese.

21 Maekawa M, Sawami H, Seriu Y, Fujiwara T, Matsuoka T, Inanami M, et al. [An autopsy case of Wallenberg syndrome]. Shinkei Shinpo. 1960;5:206-9. Japanese.

22 Ikeda T. [An autopsy case of Wallenberg syndrome]. Nagasaki Igaku Zasshi. 1962;37:35. Japanese.

23 Nose J, Inoue J. [An autopsy case of Wallenberg syndrome]. Rinsho Naika Shonika. 1963;18:949-52. Japanese.

24 Tanabe H. [Wallenberg syndrome]. In: Okinaka S, editor. Naika Rinsho To Boken. Tokyo: Nanzando; 1963. p. 50-67. Japanese.

25 Kokubun K, Irei T, Hara K, Shiono K, Watari H, Koshikawa T, et al. [Three cases of Wallenberg syndrome]. Fukushima Igaku Zasshi. 1966;16:161-8. Japanese.

26 Abe M, Yamagami T, Gondo Y, Yano M. [Clinicopathological analysis on nervous system. 3. An autopsy case of Wallenberg syndrome]. Kyushu Shinkei Seishin Igaku. 1966;12:312-8. Japanese.

27 Murakami F, Yasutake K, Yamamoto T, Honbo Z, Hirano N, Tachikawa Y, et al. [An autopsy case of Wallenberg syndrome]. Chiryo. 1965;47:1755-61. Japanese.

28 Itahara K, Tominaga T, Kutsuzawa N, Suwa N, Arai S. [Clinicopathological conference. 179. A case of Wallenberg's syndrome modified by a congenital arterial anomaly]. Saishin Igaku. 1965;20:2622-8. Japanese. PMID: 5888325.

29 Murata J, Takamizawa K. [A case of astrocytoma with Wallenberg syndrome-like symptoms]. Nihon Naika Gakkai Zasshi. 1966;54:1227. Japanese.

30 Oshima M, Mikuni C, Ujiie T, Furuya K. [An autopsy case of Wallenberg syndrome]. Nihon Naika Gakkai Zasshi. 1967;56: 291-2. Japanese.

31 Kodama R, Ota T, Ato N, Matsuoka K. [Four cases of Wallenberg syndrome]. Nihon Naika Gakkai Zasshi. 1967;56: 1046. Japanese.

32 Tazawa W. [An autopsy case with Wallenberg syndrome with abdominal angina]. Shindan To Chiryo. 1970;45:138-40. Japanese.

33 Ogawa M, Yamanouchi H, Togi H, Tomonaga M, Kameyama M. Autopsy case of Wallenberg's syndrome caused by metastasis of lung neoplasm to medulla oblongata. Rinsho Shinkeigaku. 1977;17:25-30. Japanese with English abstract. PMID: 191226.

34 Oiwake H, Kametani T, Miyamoto S, Imura M, Takeuchi N, Shinozaki K, et al. [An autopsy case of Wallenberg syndrome with a myocardial infarction]. Japanese Circulation Journal. 1982; 46(suppl 2):314. Japanese.

35 Tsuchiya I, Nakao N, Sahashi K, Takahashi A, Ikeda H. [An autopsy case of Wallenberg syndrome with 13-year disease duration]. Rinsho Shinkeigaku. 1983;23:628. Japanese.

36 Takehara M, Ishikawa K, Hiroi T, Fujimura H, Yorifuji S. Central type of sleep apnea syndrome caused by unilateral lateral medullary infarction. Rinsho Shinkeigaku. 1992;32:511-5. Japanese with English abstract. PMID: 1458729.

37 Abe H, Kamei H, Nobuhara K, Takebayashi S, Nishimaru K. An autopsy case of idiopathic vertebral artery dissecting aneurysm with analysis of MRI changes. No Socchu. 1993;15: 144-50. Japanese with English abstract.

38 Osano H, Terao S, Fukuoka T, Miura N, Yoshida M, Sobue H. [An autopsy case of lateral medulla oblongata infarct with rapid respiratory failure]. Rinsho Shinkeigaku. 2001;41:257. Japanese.

39 Okamoto Y, Yamashita M, Yamamoto T. [An autopsy case of Wallenberg syndrome with cerebellar infarction: an MRI analysis]. Rinsho Shinkeigaku. 2007;47:545. Japanese.