Solitary Tract Nuclei in Acute Heart Failure

Raffaele De Caro, MD; Anna Parenti, MD; Massimo Montisci, MD; Diego Guidolin, PhD; Veronica Macchi, MD

Background and Purpose—Symmetrical necrosis of the brain stem nuclei has been described as a consequence of severe transitory cerebral hypoxia mainly in neonates or young adults who experienced an episode of acute ischemia due to transitory acute heart failure. We report selective bilateral lesions of the solitary tract nuclei in 5 adults with short survival intervals after acute heart failure.

Methods—In 5 patients who died due to cardiovascular pathology, histological examination was performed on multiple samples of cerebral hemispheres, on transverse sections of the midbrain and pons, and on transverse serial sections of the medulla stained with hematoxylin-eosin, Klüver-Barrera, and Luxol fast blue. The 3-dimensional reconstruction of the extension and topography of the medullary lesions was obtained with computed image analysis.

Results—In 4 subjects who died soon after an episode of acute heart failure (range of survival 10 hours to 2 days), the dorsal portion of the solitary tract nuclei showed an eosinophilic roundish aspect bilaterally. In their context, the neurons showed changes characteristic of ischemic coagulation necrosis. In a fifth patient, a 32-year-old man who died 15 days after an episode of cardiac arrest, 2 circumscribed symmetrical infarcts with macrophagic and astrocytic reactions were found at the same level. The topography of the lesions and the inflammatory reaction and gliosis of patient 5 suggest that the findings in the other 4 patients correspond to initial features of selective lesions of the solitary tract nuclei after acute heart failure: the short interval of survival prevented the evolution of the reactive process. The nucleus is localized at the watershed zone between the terminal branches of the medullary collateral vessels of the vertebral arteries, thus representing the last meadow in the case of sudden fall of the systemic blood flow due to acute heart failure. The absence of lesions of other medullary and pontine nuclei accounts for a selective vulnerability of the neurons of the solitary tract nuclei, and the selective dendritic lesions suggest an excitotoxic component to ischemic cell death.

Conclusions—The commonly accepted resistance of the medullary centers to ischemic hypoxia in adults apparently could be due to the rapidity of death, which prevents the evolution of lesions that can be diagnosed. In addition, minor lesions in the medullary tegmentum after acute heart failure could play a role in the prevention of the resumption of autonomous cardiac and respiratory functions despite life-saving procedures. (Stroke. 2000;31:1187-1193.)

Key Words: brain stem ■ heart arrest ■ nucleus tractus solitarii ■ pathology

The nuclei of the medulla involved in the continuous monitoring and autonomic regulation of respiratory and cardiovascular functions are the nucleus of the solitary tract, the dorsal vagal nucleus, and the intermediate reticular zone, which includes the region of the ventrolateral medulla adjacent to the surface. The nucleus of the solitary tract is presumed to act presynaptically to regulate respiratory reflexes.1-3 In the rat and the cat, the intermediate third of the nucleus, at the level of the obex, assumes a critical role in the central neural integration of cardiovascular activity.4 This portion of the solitary nucleus presumably integrates a number of important cardiovascular reflexes, including the baroreflexes and chemoreflexes.5-7

Symmetrical necrosis of the brain stem has been described in neonates with perinatal hypoxia.8-14 Similar necrotic lesions of specific brain stem nuclei with cerebral involvement have been only occasionally reported in adults.10,15-19 Although Gilles10 postulated that the brain stem lesions were “directly related to the sudden acute transient circulatory failure and not to hypoxia or hypoxemia per se,” a primary role of the cardiac arrest was underlined by Janzer and Friede,12 and they proposed the term “cardiac arrest encephalopathy.”

Brierley et al16 described the neuropathology of “neocortical death” after cardiac arrest in adults. This definition refers to persistently isoelectrical EEGs and the absence of sensory evoked responses in the neocortex, together with the resumption of spontaneous respiration and of certain brain stem reflexes.

Because the incidence of hypoxic-ischemic brain stem lesions is 10 times greater in infants than in adults,12 the
Clinical Data and Pathological Findings in Patients With Lesions of the Solitary Tract Nuclei

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Neuropathological findings

- In cerebral cortex: Hemorrhagic infarction in occipital lobes
- In the medullary tegmentum: 2 Roundish eosinophilic areas

Methods

During the course of a systematic study of the vessels of the brain base, in 5 patients we found recent lesions at the level of the medulla. In all 5 patients, death was due to cardiovascular pathology (Table), and there was no evidence of previous neurological pathology. Autopsy was performed within 24 hours of death. The brain was cut after fixation in 10% formalin for 15 days. Histological examination was performed on multiple samples of cerebral hemispheres, on transverse sections of the midbrain and pons, and on transverse serial sections of the medulla stained with hematoxylin-eosin, Klüver-Barrera, and Luxol fast blue.

In patient 5, on 22 transverse sections taken at 0.5-mm intervals, the contours of the medulla and the lesions were delineated to obtain the 3-dimensional reconstruction of the extension and topography of the lesions with computed image analysis (VIDS V; AMS).

Results

Case 1

A 65-year-old woman was admitted to the hospital for restaging of breast cancer 2 years after a mastectomy and chemotherapy. She had chest pain, and an ECG showed an ischemic area in the posterior wall of the left ventricle. She experienced profound hypotension (persistent <60 mm Hg for 4 hours) and died 2 days later due to tachyarrhythmia with ventricular fibrillation.

The pathological findings showed an old scar in the lateral wall of the left ventricle and an area with contraction bands and undulations of muscle bundles with pallor of muscle cells at the Azan-Mallory stain at the level of the posterior wall of the left ventricle.

The neuropathological examination showed the presence of 2 hypereosinophilic areas in the bulbar tegmentum. They were located symmetrically dorsal to the solitary tract in the sections at the level of the obex (Figures 1a to 1c). The 2 areas showed a roundish shape and a mean transverse diameter of nearly 1 mm. At their level, the neurons were shrunken, staining darkly with cresyl violet, and the cytoplasm was markedly eosinophilic. The nuclei and the nucleoli were relatively preserved. The dendrites were clearly recognizable due to intense eosinophilia (Figure 1d).

Hemorrhagic infarction of the cortex of the occipital lobes was found.

Case 2

A 52-year-old man, a physician, lost consciousness returning home from the hospital. He was immediately resuscitated. After 1 day, he underwent a surgical procedure for dissecting aneurysm of ascending aorta but died at the end of the operation. For 6 hours before surgery, his blood pressure was <70 mm Hg.

The necropsy findings showed extension of the dissection to the bulbus aorticus with occlusion of the coronary ostia.

The neuropathological examination showed 2 symmetrically lesions dorsal to the solitary tract at the level of the obex. Their largest diameter was ~1 mm. At their level, the neurons were shrunken with eosinophilic cytoplasms and nuclear pyknosis. The dendrites were intensely eosinophilic, and they appeared short with a curved course describing reentrant profiles at the periphery between the involved neuron nuclear group and its enviroms.
Case 3
After a 2-week history of fatigue, a 55-year-old man came to the emergency department with a complaint of dyspnea; after 1 hour, he loss consciousness. Resuscitation maneuvers were immediately performed. An ECG showed the presence of an ischemic area at the level of the lateral wall of the left ventricle. The patient was hypotensive for 3 hours (<75 mm Hg) and died 10 hours later.

The pathological findings showed diffuse coronary atherosclerosis with narrowing of the lumen. The histological examination showed widespread myocardial fibrosis. The neuropathological examination showed 2 symmetrical lesions in the medullary tegmentum at the level of the dorsal portion of the solitary tract nucleus. The neurons were shrunken with eosinophilic cytoplasm. The nuclei and the nucleoli were relatively preserved. The dendrites showed intense eosinophilia, and they presented with a curved course at the periphery of the involved neuron group.

Case 4
A 70-year-old woman was admitted for a left bronchopneumonia. She had ischemic dilated cardiomyopathy. She complained of palpitations and dyspnea; she had low blood pressure (<80 mm Hg) for 2 hours and died 18 hours later.
The pathological findings showed diffuse coronary atherosclerosis and an area with contraction bands and undulations of muscle bundles with pallor of muscle cells at the Azan-Mallory stain at the level of the lateral wall of the left ventricle.

The neuropathological examination showed 2 hypereosinophilic symmetrical lesions in the bulbar tegmentum, dorsal to the solitary tract (Figures 2a and 2b). They were roundish with a mean transverse diameter of nearly 1 mm. At their level, the hypereosinophilic neurons were shrunken, with relatively preserved nuclei. The dendrites showed intense eosinophilia, and they appeared short with a curved course at the periphery of the involved neuron group (Figures 2c and 2d).

**Figure 2.** Patient 4 (18-hour survival interval after myocardial infarction). a, Transverse section of the medulla shows the topography of the lesions (arrows) dorsal to the solitary tract (Klüver-Barrera, magnification ×1). b, Left side of the subependymal medullary tegmentum. The dorsal portion of the solitary tract nucleus (STN) exhibits a roundish aspect. ST indicates solitary tract; DVN, dorsal vagal nucleus (Klüver-Barrera, magnification ×4). c, Dorsal portion of the STN. The roundish aspect is due to a particular evidence of the dendrites, which show a curved course describing reentrant profiles at the periphery between the involved neuron nuclear group and its environs (Klüver-Barrera, magnification ×10). d, Roundish area in the dorsal part of the STN showing the presence of shrunken, dark-staining neurons (Klüver-Barrera, magnification ×16).

Diffuse cerebral cortical atrophy was present.

**Case 5**

A 32-year-old male drug addict was found unconscious in cardiorespiratory arrest. He was ventilated mechanically and treated with naloxone, epinephrine, bicarbonate, and mannitol. Cardiac activity recommenced after 10 minutes of resuscitation procedures, while assisted ventilation was initiated. His blood pressure was <70 mm Hg for 5 hours. Toxicological tests with the use of gas chromatography on a blood sample revealed 1.9 µg/mL morphine and 5.0 µg/mL oxazepam. The patient’s clinical conditions remained unchanged (Glasgow Coma Scale score E1, V tube, M1) for 2 weeks. On the 10th day, he was feverish (40°C), and *Staphylococcus*
**aureus** and **Candida albicans** were found in bronchial excretions. On the 15th day, there was a sudden fall in blood pressure, which did not respond to therapy, accompanied by anuria, and followed shortly afterward by death.

The pathological findings showed bilateral bronchopneumonia and a recent subendocardial lesion in the lateral wall of the left ventricle. Histological examination of the cardiac lesion showed myocytolysis with leukocytes and red blood cell infiltration and vascular proliferation.

The neuropathological examination showed cerebral edema with small ventricles. Histological examination showed 2 small, roundish, symmetrical infarcts in the medullary tegmentum (Figure 3a). The lesions were characterized by macrophagic and astrocytic reactions with capillary proliferation (Figures 3b and 3c). The 2 areas of ischemic necrosis were consistent with infarctions of about 2 weeks’ duration. They were located at the level of the nuclei of the tractus solitarius and of the adjacent portion of the medial vestibular nuclei. On the 3-dimensional reconstruction, these lesions presented a transverse diameter of nearly 1.5 mm each and a rostrocaudal extension of 13 mm from the mid olivary level down and were interrupted by a thin band of normal tissue at nearly the same level. Furthermore, the rostral portion of the 2 lesions was located posteromedially in comparison with the caudal portion (Figures 3d and 3e).

**Discussion**

Predominant involvement of the brain stem with limited or absent cerebral lesions in adults has been described “under exceptional circumstances.” In these cases, the absence of cortical lesions was attributed to a protective effect of drugs or hypothermia.

Our patients show a symmetrical columnar damage of brain stem tegmentum in 5 adults. The lesions are circumscribed to the medulla, and in the transverse sections, they appear as roundish areas with a limited extension. In their context, the neurons are shrunken, with eosinophilic cytoplasm and pyknotic nuclei, characteristic of ischemic coagulation necrosis. The roundish aspect of the lesions depends on particular evidence of the intense eosinophilic dendrites,
which are short and curved and pursue reentrant courses at the perimeter of nervous group, defining a boundary between it and the neighboring nervous tissue. Schneider et al proposed a correlation between the extension of the involved gray matter of the diencephalon, brain stem, and spinal cord of their patients and the “isodendritic core” described by Ramón-Moliner and Nauta. In our patients, the limited axial (bulbar) and transverse (tegmental: nuclear) extension of the lesions accounts for the circumscribed group of neurons with “isodendritic configuration” (ie, neurons whose dendrites are curved with a reentrant course at the periphery of the nuclear group). In both situations, the pathophysiology of the lesions can be ascribed to a reduced perfusion of the brain stem tegmentum, but in our patients, the limited extension of the lesions accounts for a selective necrosis of a group of neurons with a greater vulnerability.

In all of the cases reported here, the sudden decrease in the cardiac output and the fall in systemic blood pressure caused a consequent diminution of the cerebral blood flow. In the 4 patients with a short survival interval, small, roundish, symmetrical eosinophilic areas of neuronal damage were found at the level of the dorsal portion of the solitary tract nuclei. In patient 5, the lesions were represented by isolated symmetrical infarcts in the medullary tegmentum, a district that is considered resistant to ischemic insults in adults. In this patient, the presence of macrophagic and astrocytic reactions at the level of the solitary tract nuclei after a 15-day survival interval, without effective spontaneous respiration, suggests that the findings in the other 4 patients correspond to the initial features of hypoxic damage of the solitary tract nuclei due to a critical reduction in blood flow: the rapidity of death prevented the onset of inflammatory reaction and gliosis.

Thus, due to the intense metabolic activity, the subependymal portion of the bulbar tegmentum, mainly the solitary tract nuclei, could be particularly vulnerable to ischemia after a critical decrease in cardiac activity.

The location of the lesions at the level of the solitary tract nuclei after acute heart failure can be explained with reference to vascularization of the medullary tegmentum. Foix and Hillemand described 3 areas of vascularization in this district: a median area fed by the paramedian arteries for the motor nuclei, a middle area that is very small and is fed by the short circumferential arteries for the ala cinerea, and a lateral area fed by the posterior inferior cerebellar artery for the restiform body. Because the solitary tract nucleus is localized at the watershed zone between the terminal branches of these arteries, it is predictable that the nucleus should be particularly exposed to ischemia after acute heart failure. Thus, it could represent the “most distant field” in the medullary tegmentum according to the theory of Optitz and Schneider. However, in prior studies in animals and humans, extensive ischemic changes were described in many brain stem nuclei after an episode of acute heart failure, hypotension, or both. The involvement of the solitary tract nucleus, always associated with lesions of other medullary and pontine nuclei, was reported in few cases and the histological findings corresponded to infarcts of various timing.

In our patients, the limited extension of the symmetrical medullary lesions suggests that cerebral ischemia could not be the only factor responsible for these lesions. In fact, the absence of lesions of other brain stem nuclei accounts for a selective vulnerability of the neurons of the solitary tract nuclei. Furthermore, the selective dendritic lesions are characteristic of neuronal death due to hyperexcitation. This suggests an excitotoxic component to ischemic cell death, which could be ascribed to hyperactivity of neurons of the solitary tract nuclei in the postischemic period possibly due to enhanced sensitivity of postischemic neurons to afferent stimuli after acute heart failure. Thus, the findings in the 4 patients with a short survival interval could be interpreted as aspects of incipient selective neuronal necrosis of part of the solitary tract nuclei.

Our findings suggest that in the case of an acute decrease in verteobasilar blood flow due to acute heart failure, the rapidity of death makes the onset of evident initial, although irreversible, ischemic lesions in the medullary tegmentum extremely difficult. The very low incidence of extensive ischemic changes in the brain stem contrasts with the frequency of episodes of acute heart failure among the population. Therefore, the commonly accepted resistance of the medullary centers to ischemic hypoxia in adults apparently could be due to the rapidity of death, which prevents the onset of lesions that can be diagnosed. Small, roundish, symmetrical, eosinophilic areas in the medullary tegmentum should be evaluated as possible locations of initial features of selective neuronal necrosis when death is due to acute heart failure. Thus, the failure of recovery of cardiac and respiratory automatism, despite life support, after an episode of acute heart failure could be ascribed to secondary irreversible ischemic lesions in the medullary tegmentum.

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References


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