

A CLINICO-NEUROPATHOLOGICAL STUDY ON BRAIN DEATH

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ABSTRACT

A clinico-neuropathological study was conducted on 60 cases of brain death, 36 males and 24 females, ranging in age from 11 to 81 years, the average being 49.4 years. Of these, 29 patients died of cerebrovascular disease. The average duration of brain death was 99 hours. The mean weight of the brain was 1466 g. Neuropathological findings were brain edema, congestion, herniation and various subarachnoid hemorrhages. Histologically, the cytoplasm of neurons was pale and ghost-like. In the white matter, myelin staining was pale, and nuclei of the glial cells were shrunken and piknotic. Autolysis of the cerebellar granular layer and the pituitary gland was evident in all cases. No reactive astrocytosis or infiltration of the cells in or around necrotic tissue could be seen. In eight cases, there was laminar infiltration of neutrophils in the superficial area of the cerebrum and brain stem, possibly due to temporary or partial recirculation. Correlation between the degree of autolysis and duration of brain death was observed, but no relationship between the degree of autolysis and the difference of underlying disease could be found. Autolysis in the cerebral cortex, thalamus, tegmentum of the brain stem, cerebellar granular layer and pituitary gland was most prominent. However, neuropathological diagnosis of underlying diseases could be made even in brain death. Histologically, the cases of brain death differed from those of cardiac arrest-induced encephalopathy and from those of long postmortem autopsy.

Key Words: Brain death, Neuropathology, Cardiac arrest, Encephalopathy

INTRODUCTION

Brain death is a major subject from the socio-medical view point.¹⁾⁻⁴⁾ Although it is highly desirable to confirm brain death by autopsy in each case, such autopsy is not common in Japan. Moreover, it is often difficult to study neuropathologically the autopsied brain in detail because of autolysis, and only a few reports have been presented concerning the neuropathological findings of brain death in Japan.⁵⁾⁻⁷⁾ We have performed neuropathological examinations during the past 15 years at eight hospitals in Aichi Prefecture of autopsy cases in which brain death had been diagnosed. Many of these cases were treated before the Japanese Ministry of Public Health and Welfare established the criteria of brain death in 1985.⁸⁾ Unless organ donation is expected, invasive tests such as the strict apnea test or cerebral angiography are usually not performed in clinical fields. Therefore, many of the present cases did not completely meet the criteria of brain death (1985),⁸⁾ although all of them met the criteria set by the Japanese Association of Electroencephalography in 1974.

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MATERIALS AND METHODS

The subjects of the present study were 60 patients who died and were autopsied at the Nagoya University Hospital and its affiliated hospitals and in whom a state of brain death had been diagnosed on the basis of their terminal clinical and neuro-pathological records during the period 1976 to 1991. Brain death was diagnosed as by careful investigation of the patients' clinical records using the criteria of the Japanese Association of Electroencephalography.

In the present study, the clinical factors investigated were age, underlying disease, duration of mechanical respiration, duration of brain death, and postmortem time. For neuropathological findings, the cerebrum (cortex, white matter, basal ganglia, thalamus, hippocampus), brain stem (tegmentum, base), cerebellum (molecular layer, granular layer, white matter), and pituitary gland were examined. The intensity of changes that occurred after the onset of brain death, i.e., autolysis, was evaluated according to the tendency toward tissue destruction, decrease in the staining of cells, myelinated fibers and neuropils, ghostly cytoplasm of cells, and atrophy, dark staining, and disintegration of the nucleus. The results of Klüver Barrera (KB) staining were also taken into account in some cases.

For purposes of comparing with brain death, the clinico-pathological findings of 11 patients with cardiac arrest-induced encephalopathy were investigated. Pathological findings of the brain in patients autopsied long after death were investigated to compare the autolysis of the brain in brain death with that long postmortem autopsy.

RESULTS

Clinical background factors

Age, underlying disease, clinical course: A total of 60 patients were studied. They consisted of 36 males and 24 females ranging in age from 11 to 81 with an average of 49.4 years. The majority of patients were in their forties, fifties and sixties (39 cases). The underlying diseases were classified as follows: Group a) primary brain lesions (47 cases) and Group b) secondary brain lesions (13 cases). The relative incidence of underlying diseases was as follows: subarachnoid hemorrhage (15 cases), secondary brain lesion (13 cases), intracerebral hemorrhage (10 cases), head injury (10 cases) and brain tumor (7 cases). Of seven brain tumor patients, three had glioblastoma multiforme two had astrocytoma, and two had pineal tumor. In the patients classified in Group b, brain death occurred when cardiopulmonary arrest, shock during anesthesia, or asphyxia were followed by the deterioration of general condition. Two patients with Shy-Drager syndrome (SDS), a degenerative disease in the central nervous system, were classified in Group b because respiratory or cardiac arrest was followed by brain death.

The use of mechanical respiration averaged 153 h with a spread of 11.5 to 1,008 h. the duration of brain death averaged 99 h with a spread of five to 648 h, lasting within five days in 19 (80%) and within ten days in 55 (92%) patients, and as long as two weeks or more in three patients; the longest duration was 27 days. The postmortem time averaged 6.6 h with a spread of one to 48 h. Table 1 shows the number, age, and time course of brain deaths by underlying disease.

Neuropathological findings

1) Macroscopic findings

The weight of the brain averaged 1466 g with a range of 1090 to 1770 g. In patients with short-term brain death (within 24 hours), brain edema, gyral flattening, marked congestion of

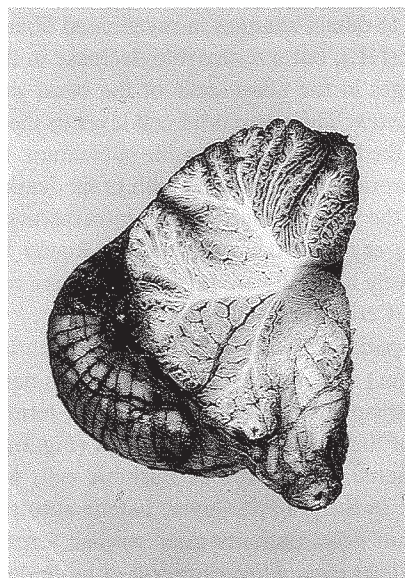
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Table 1. Relationship Between Underlying Disease and Clinical Features in Brain Death.

| Underlying diseases | Cases (male, female) | Age (average) | Time on respirator (average)[hours] | Duration of brain death (average)[hours] | Postmortem time (average)[hours] |
|---------------------------|----------------------|-------------------|-------------------------------------|--|----------------------------------|
| Primary brain lesion | | | | | |
| subarachnoid hemorrhage | 15 (11, 4) | 38 ~ 76 (54.8) | 43 ~ 491 (147.6) | 5 ~ 480 (105.4) | 2 ~ 24 (8.0) |
| intracerebral hemorrhage | 10 (6, 4) | 33 ~ 70 (52.4) | 48 ~ 264 (142.2) | 19 ~ 168 (76.8) | 1 ~ 18 (4.3) |
| brainstem infarction | 2 (2, 0) | 55, 65 (60.0) | 72, 109 (90.5) | 24, 72 (48.0) | 2, 4 (3.0) |
| Moyamoya disease | 2 (1, 1) | 31 (31) | 16, 22 (19.0) | 5, 17 (11.0) | 1 (1) |
| head injury | 10 (5, 5) | 15 ~ 81 (43.9) | 18 ~ 336 (122.9) | 5 ~ 264 (73.7) | 1 ~ 8 (2.4) |
| brain tumor | 7 (3, 4) | 11 ~ 77 (40.7) | 12 ~ 1008 (248.9) | 6 ~ 648 (172.3) | 1 ~ 15 (3.9) |
| meningitis · encephalitis | 1 (1, 0) | 37 | 70 | 96 | 14 |
| Secondary brain lesion | 13 (7, 6) | 13 ~ 73 (51.9) | 21 ~ 456 (176.0) | 5 ~ 360 (114.2) | 1 ~ 45 (12.1) |



a



b

Fig. 1. Macroscopic findings of the brain deaths

- a. Pontine astrocytoma: Death after 27 days of brain death; 15- y.o. girl. The brain (after fixation in formalin) shows, marked autolysis and the appearance is hardly preserved.
- b. Subarachnoid hemorrhage: Death after two days of brain death; 71-y.o. man. In the cerebellar slice (after fixation in formalin), depressions of the cerebellar granular layer are noted.

veins in the brain surface, cerebral herniation, filling with coagulation in the sinus of the dura mater and subarachnoid hemorrhage were noted in all of them. In patients with long-term brain death (Fig.1-a), the structure of the brain was not maintained at autopsy and the brain weight could not be measured in eight cases.

In brain slice, the cortex was not sharply demarcated from the white matter. The ventricles were narrowed, and the brain parenchyma was cloudy and brown. The tissue tended to be cracked, and petechiae were prominent. Autolysis of the cerebellar granular layer (Fig.1-b) and secondary brainstem hemorrhage were noted in various degrees. In brain death, subarachnoid hemorrhage was not extensive except in brain death following a ruptured aneurysm.

2) Microscopic findings

a) Cerebrum

The principal changes in the cerebrum of the brain dead patients with mild autolysis were dilated pericellular spaces and decreased staining (Fig.2-a). In severer cases, the tissue was cracked and nerve cells were greatly decreased in staining and nearly undetectable (Fig.2-b). These findings were obviously different from those in patients with cardiac arrest-induced encephalopathy (Fig.2-c) or in patients autopsied long after death (Fig.2-d).

In some patients, laminar leukocyte infiltration, parallel to the surface of cortex and principally perivascular, was noted in the superficial layers (Fig.3-a) (8 cases). The nuclei of infiltrating leukocytes were disintegrated (Fig.3-b). The underlying diseases and duration of brain death varied among these patients.

Bleeding spots were often observed principally in the superficial layers. No particular layer-related difference was noted. The structure of layers was preserved relatively well in patients with autolysis. In the cerebral white matter, the nuclei of glia cells were atrophied and darkly stained in relatively mild autolysis, but crushed in more advanced autolysis (Fig.3-c). It was difficult to detect changes in myelinated fibers in the white matter by staining with hematoxylin and eosin (HE), but a noticeable decrease in the staining of such fibers was detected by KB staining. Changes in the nerve cells of the basal ganglia and thalamus were almost the same as those in the cortex. The pyramidal cell layer in the hippocampus showed a decrease in staining, diffusely from the terminal plate to the subiculum. Loss of cells in the Sommer sector in the hippocampus was prominent in patients with brain death after cardiac arrest induced encephalopathy.

In the subarachnoid space, intravascular erythrocyte filling was noted in all patients. In brain death, erythrocytes were usually foamy in appearance. However, erythrocytes that appeared relatively normal were observed in some regions even in cases of severe autolysis.

b) Cerebellum

In patients with short-term brain death (within 24 h), autolysis of the granular layer (status bullosus) was most prominent and was noted from the central part to the surface of the cerebellar hemisphere. In patients with long-term brain death, autolysis of the molecular layer, rarefaction of the cerebellar white matter (Fig.3-d), and ghostly nerve cells of the dentate nucleus were also noted. The shape of Purkinje cells was preserved for relatively extended periods of brain death. In the granular layer, patchy autolysis was observed in some cases (Fig.3-e). In the brains of brain dead patients after cardiac arrest-induced encephalopathy, loss of Purkinje cells was prominent even when duration of brain death was short.

c) Brain stem

Autolysis of nerve cells showed no obvious difference between the tegmentum and base of the brain stem, but the intensity of tissue rarefaction tended to be high in the tegmentum. Furthermore, superficial leukocyte infiltration as in the cerebral cortex was noted in three cases. Lesions in the peripheral cranial nerve roots were milder than those in the parenchyma of the brain stem.

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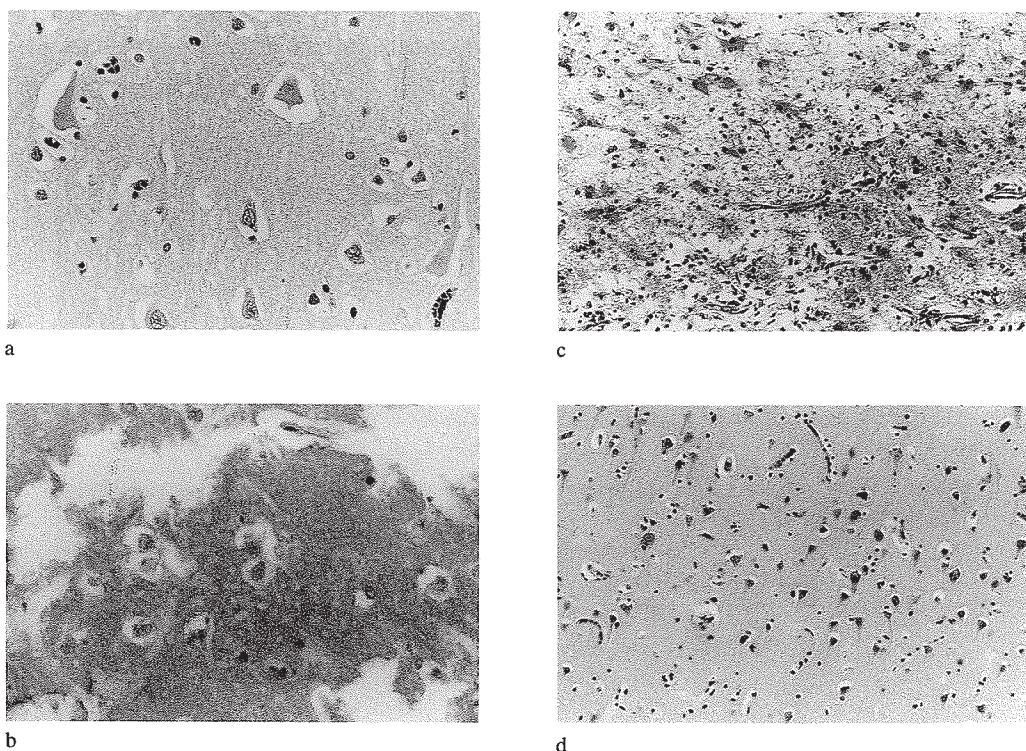


Fig. 2. Findings of the cerebral cortex

- a. Infarct in brain stem: Death after three days of brain death; 55-y.o. man; HE stain $\times 314$.
Mild autolysis is noted. Pericellular spaces are dilated and the nuclei and cytoplasm of nerve cells are discolored.
- b. Secondary brain lesion (hypotension during vulvular displacement): Death after eight days of brain death; 23-y.o. man; HE stain $\times 314$.
Severe autolysis is noted. A number of fissures are seen in the tissue and many nerve cells are ghostly or have disappeared.
- c. Cardiac arrest-induced encephalopathy (cardio-pulmonary arrest for about 15 min due to asphyxia during treatment of the rupture of thoracic aortic aneurysm): Death after about one month of cardiac arrest-induced encephalopathy; 78-y.o. woman; HE stain $\times 157$.
The cerebral cortex shows laminar necrosis and marked proliferation of blood vessels and astrocytes. Loss of nerve cells is marked.
- d. Patient autopsied 48 hours after death from traumatic intraperitoneal hemorrhage: 40-y.o. man; HE stain $\times 157$.
No particularly abnormal findings are noted in the cerebral cortex.

d) Pituitary gland

Bleeding was often observed in the pituitary gland. The central part of the anterior lobe showed autolysis, but the marginal part was spared (Fig.4-a). In some patients autopsied after less than ten days of brain death, there was patchy autolysis. In all patients with prolonged brain death of ten days or more, autolysis had spread to involve the marginal part of the pituitary gland.

When the relationship of the duration of brain death to the intensity of autolysis was assessed for each region of the brain, the intensity of autolysis in the thalamus and cerebral cortex was found to be high in patients with short-term brain death. And the intensity of autolysis in the

tegmentum of the brain stem, cerebellar granular layer and pituitary gland was found to increase with time. The intensity of autolysis of Purkinje cells was relatively low even in patients with considerably prolonged brain death.

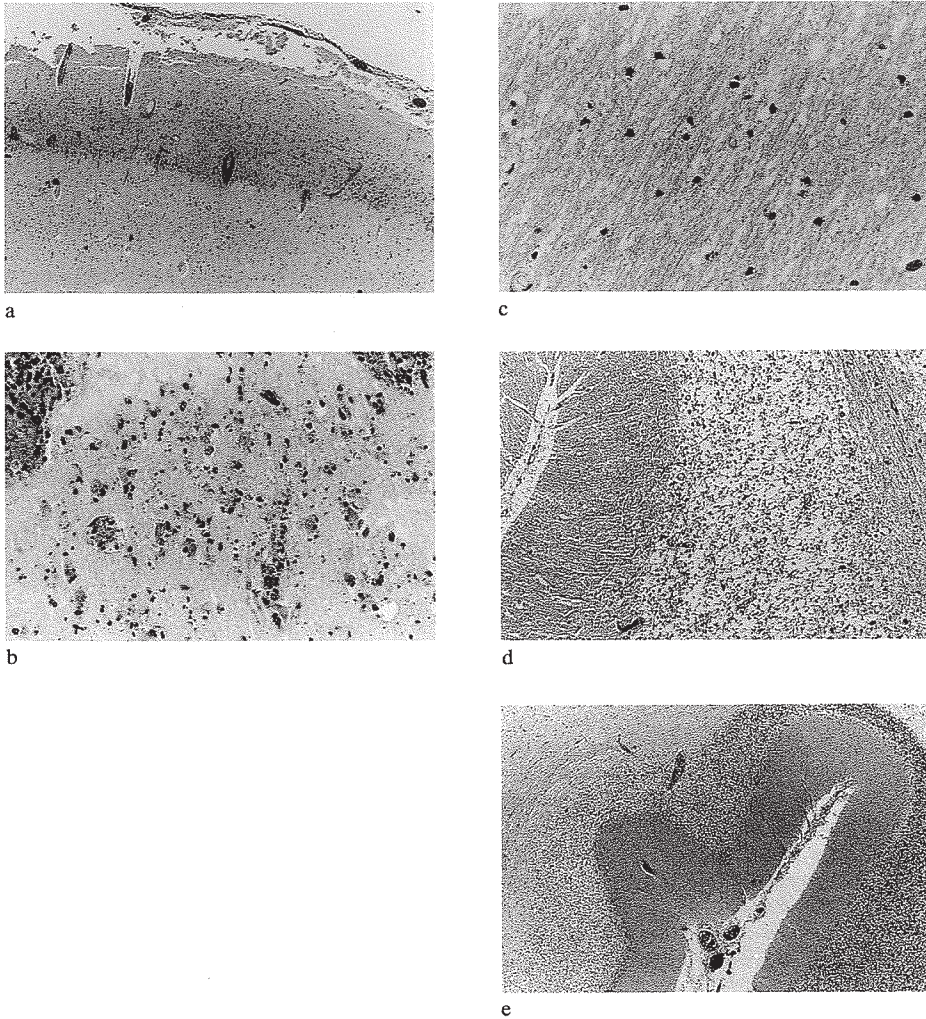


Fig. 3. a. Secondary brain lesion (hypotension after vulvular displacement): Death after four days of brain death; 64-y.o. man; HE stain $\times 114$.
Laminar leukocyte infiltration into the superficial layer of the cerebral cortex is noted.

b. Secondary brain lesion (hypotension after vulvular displacement): Death after four days of brain death; 64-y.o. man; HE stain $\times 228$.
Autolysis of infiltrated leukocytes is observed at high magnification.

c. Extensive brain stem infarct due to the obstruction of the basilar artery: Death after three days of brain death; 55-y.o. man; KB stain $\times 274$.
In the cerebral white matter, the myelin shows rarefaction and a decrease in staining. The nucleus of oligodendroglia is atrophied, darkly stained and crushed.

d. Secondary brain lesion (cardio-pulmonary arrest for about 15 min during treatment empyema): Death after two days of brain death; 52-y.o. woman; HE stain $\times 85$.
Autolysis of the cerebellar cortex and rarefaction of the cerebellar white matter are observed.

e. Glioblastoma multiforme: Death after six hours of brain death; 50-y.o. woman; HE stain $\times 23$.
Uneven autolysis of the cerebellar granular layer is seen.

Clinical and pathological findings of cardiac arrest-induced encephalopathy

There were 11 patients with cardiac arrest-induced encephalopathy, nine men and two women, aged 27 to 80 years (average: 59.2 yr). Their underlying diseases included brain tumors, dissecting aortic aneurysm, and interstitial pneumonitis. In all of the patients, cardiac arrest was followed by severe disturbances of consciousness. The duration of cardiac arrest was five to 30 min (average: 15 min).

The duration of cardiac arrest-induced encephalopathy ranged from one day to two years and three months. If the one case of prolonged encephalopathy (two years and three months) were excluded, the average duration was 23 days. The time from death to autopsy was one to 15 h (average: 7.9 h). The weight of the brain was as low as 820 g and marked cerebral atrophy was noted in the one patient who experienced prolonged cardiac arrest-induced encephalopathy for two years and three months. In the other patients, brain weight averaged 1300 g, ranging from 1110 to 1480 g.

Microscopically, the cerebral cortex showed ischemic changes, that is, eosinophilic staining of the cytoplasm of nerve cells in patients with slight changes. Laminar necrosis was seen in patients with more pronounced changes. Proliferation of astrocytes, swelling of the vascular endothelium, and loss of nerve cells were prominent in prolonged survivors (Fig.2-d). Gliosis was noted in the cerebral white matter. Marked rarefaction and reactive proliferation of astrocytes were noted in prolonged survivors. Specific loss of pyramidal cells in the Sommer sector of the hippocampus was characteristic. A number of nerve cells showing the same changes due to ischemia as in the cerebral cortex were observed in the basal ganglia, thalamus, brain stem, and cerebellar dentate nucleus. In the cerebellum, loss of Purkinje cells was prominent, but the molecular and granular layers were preserved satisfactorily. There was little significant change in the pituitary gland, or erythrocytes. Intravascular erythrocyte filling was not noted in the sinus or subarachnoid space.

Pathological findings of two patients autopsied long after cardiac arrest

Two patients were autopsied 48 and 40 hours after death, respectively. They were 40- and 57-year-old patients who died of traumatic intraperitoneal hemorrhage and heart failure, respectively. There were no pathological or autolytic findings in the cerebral cortex (Fig.2-d), white matter, brain stem, pituitary gland, or erythrocytes, and staining was maintained satisfactorily in KB staining. In the cerebellum, only the granular layer showed autolysis (Fig.4-b). The intensity of this change was slightly higher in the central part of the cerebellar hemisphere.

Pathological findings of underlying diseases in the brain of brain dead patients

Subarachnoid and intracerebral hemorrhage: Secondary subarachnoid hemorrhage and intracerebral bleeding spots were common in brain death. In subarachnoid hemorrhage, hemorrhage was marked and diffuse and was often particularly intense in the cerebral base, while secondary subarachnoid hemorrhage due to brain death was mild and macular. In intracerebral hemorrhage, massive hematomas were noted, and infiltration with neutrophils and macrophages, appearance of reactive astrocytes, and hemosiderin deposits were noted around hematomas. On the other hand, secondary intracerebral hemorrhage was mild and spotty, and cell infiltration or appearance of astrocytes in response to hemorrhage was not noted in intracerebral hemorrhage due to brain death.

Infarct in the brain stem: The intensity of tissue destruction of the brain stem was severer in the brain dead patients who had brain stem infarction than in other brain dead patients. It was confirmed that reactive cell infiltration into the area of infarct occurred before the onset of brain death, and that was different from the superficial leukocyte infiltration observed in some

cases of brain death.

Head injury: The sites and spread of cerebral contusion and extradural and subdural hemorrhage were consistent with clinical findings. Neither secondary extradural nor subdural hemorrhage due to brain death was noted.

Brain tumor: It was possible to make a histologic diagnosis of brain tumor in the brain dead patient (Fig.4-c). Autolysis was generally milder in tumor cells than in normal tissues. Accurate determination of the spread of tumor cells was difficult, however, because tissue was brittle and broke down easily because of cerebral edema and autolysis.

Encephalitis and meningitis: Inflammatory changes due to encephalitis and meningitis could be recognized as perivascular infiltration of cells including lymphocytes in the subarachnoid space and cerebral parenchyma.

Degenerative disease: In SDS, loss of cerebellar Purkinje cells and neurons in the pontine and inferior olive nuclei was greater than the ghostly changes and was associated with marked gliosis (Fig.4-d). The presence of fibrous gliosis was confirmed even in brain deaths.

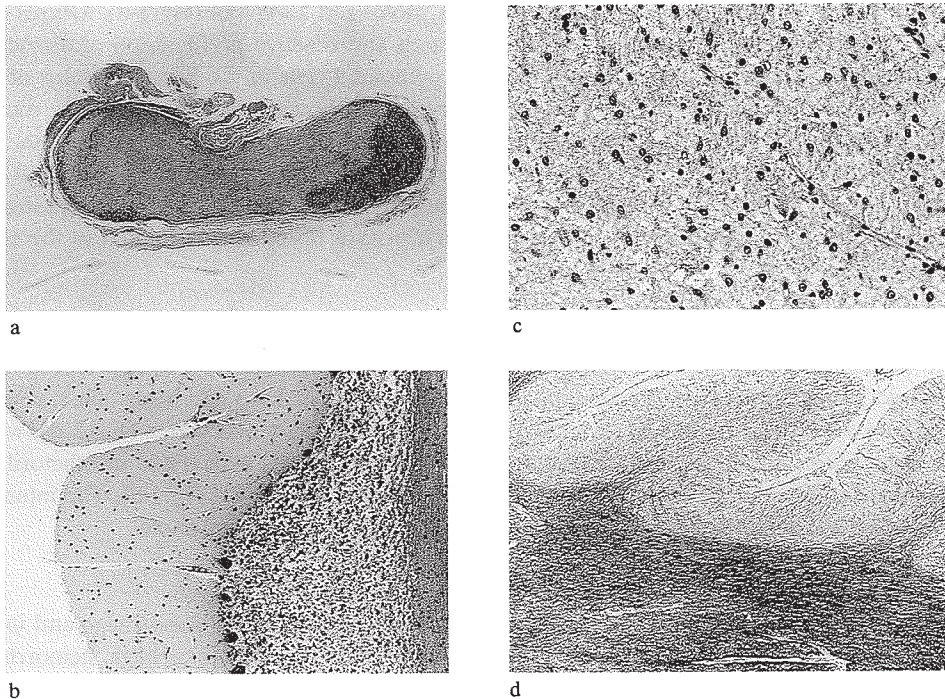


Fig. 4.a. Secondary brain lesion (severe hypotension during anesthesia): Death after eight days of brain death; 41-y.o. woman; HE stain $\times 5$.
Aside from the marginal part, the pituitary gland shows hemorrhagic necrosis.

b. Patient autopsied 48 hours after death from traumatic intraperitoneal hemorrhage; 40-y.o. man; HE stain $\times 85$.
In the cerebellum, the granular layer shows autolysis, but the molecular layer, Purkinje cells, and white matter are satisfactorily preserved.

c. Glioblastoma multiforme: Death after four days of brain death; 54-y.o. woman; HE stain $\times 170$.
Changes due to autolysis are milder in tumor cells than in normal glia cells.

d. Shy-Drager syndrome: Death after six days of brain death from asphyxia; 60-y.o. man; Holzer stain $\times 28$.
Gliosis in the cerebellar white matter is observed.

DISCUSSION

Underlying diseases and age distribution in brain deaths somewhat differ in each report.^{5)-7), 9)-11)} In the present study, more than half of the patients had cerebrovascular disorders as underlying diseases and about half of them had subarachnoid hemorrhage. These results were similar to the age distribution and incidence of the underlying diseases in brain deaths reported by Ikuta et al.^{5), 6)} as experienced at general hospitals. Many studies report that age or underlying diseases were not correlated with the time course of brain death.^{10), 12), 13)}

The characteristic pathological finding was autolysis, which was correlated with the duration of brain death. As a rule, neither reactive cell infiltration nor gliosis is noted.¹⁴⁾ These results indicate the cessation of intracranial blood flow. However, whether or not complete cessation of intracranial blood flow persisted during brain death, was a controversial point. Focal and transient intracranial blood flow were clinically reported after the diagnosis of brain death by cerebral angiography or contrast enhanced CT.¹⁵⁾ Pathological examination disclosed perivascular leukocyte infiltration suggestive of the presence of intracranial blood flow in the superficial layer of the brain in a state of brain death.^{16), 17)}

There was no obvious correlation between the degree of autolysis and the difference of underlying disease. But the relationship between the duration of brain death and intensity of autolysis was obvious, although it slightly varied with each region of the brain. According to Ikuta et al.,⁶⁾ the tegmentum of the brain stem was damaged earlier, while the hypothalamus was preserved for longer periods of time in short-term brain deaths with slight histological changes. In the present study, the cerebral cortex, nerve cells of the thalamus, tegmentum of the brain stem, cerebellar granular layer and pituitary gland tended to show marked changes in patients with short-term brain death or those with mild autolysis, and we could not find a clear difference in histological changes between the tegmentum of the brain stem and the hypothalamus.

Necrosis of the anterior lobe is a well-known change in the pituitary gland during brain death. According to McCormick et al.,¹⁸⁾ acidophils showed the most notable changes. In the present study, however, the intensity of autolysis showed no difference among acidophils, basophils, and chromophobe cells. The rim of the pituitary gland is preserved longer and patchy autolysis is often observed. This has been explained by the characteristics of vessels supplying blood to the pituitary gland. Namely, the central part of the anterior lobe is perfused by the superior hypophysial artery branching after the entrance of the internal carotid artery into the cranium, while the peripheral part and subcapsular area in the inferior surface of the anterior lobe are perfused by the inferior hypophysial and capsular arteries branching before the entrance of the internal carotid artery into the cranium. Therefore, there is a difference in the influence of intracranial pressure. Necrosis in the central part is not even because of its complicated vascular anastomosis.

In brain death, obvious autolysis in the cerebellar granular layer has long been known as a postmortem change. Autolysis in the cerebellar granular layer of brain death differs from the usual postmortem change, because it occurs even in the surface of the cerebellar hemisphere exposed to a sufficient amount of formalin.²⁰⁾

Brain death is known clinically and pathologically to be quite different from cardiac arrest-induced encephalopathy.²¹⁾ Pathologically, marked cerebral congestion and edema are noted in brain death, while the brain is rather atrophied with time in cardiac arrest-induced encephalopathy. Microscopically, the whole brain is diffusely autolysed in brain death, while laminar necrosis of the cerebral cortex, specific loss of pyramidal cells in the Sommer sector of the hippocampus and cerebellar Purkinje cells, and reactive gliosis are observed in cardiac arrest-induced encephalopathy. These are obviously different from the neuropathological findings in brain

death.

Pathological findings in patients who died and were autopsied long after death are also different from findings in brain death. This may be partly due to the fact that the environmental temperature of the brain tissue in brain death is higher than room temperature, because extracranial blood circulation is present.

Neuropathological changes of underlying diseases in the brain of brain dead patients could be found fairly easily. However, it was difficult even in short-term brain death to determine accurately when each lesion of hemorrhage was formed. In the diagnosis of inflammatory diseases, superficial leukocyte infiltration noted in some cases of brain death could be clearly discriminated from cell infiltration in encephalitis and meningitis having induced brain death. Brain tumors were usually identified even in severely damaged brain because the histological changes of tumor tissues due to autolysis tended to be milder than those of normal tissues. Such findings were also reported by Nagashima.²¹⁾ Pathological findings of underlying diseases in brain death with degenerative diseases in the central nervous system are maintained for considerably extended periods of time²²⁾. In fact, gliosis in SDS was observed clearly even in the brain of brain death with advanced autolysis.

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