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CNS CHANGES IN THE MECONIUM ASPIRATION SYNDROME

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INDEXING WORDS

meconium aspiration syndrome (MAS); hypoxic brain; perinatal brain damage; neuropathological study

SYNOPSIS

Pathological study on the central nervous system (CNS) were performed in cases of the meconium aspiration syndrome (MAS) in order to elucidate hypoxic changes of the neonatal CNS.

Thirty-eight autopsied MAS cases showed clinically severe and prolonged hypoxia during the perinatal period, and pathologically severe MAS changes in more than 2 lobes. The brain/body weight ratios at autopsy were estimated in short-lived cases within 7 days, and they were classified into group A showing higher ratios than normal control ratios, and group B showing lower than normal ratios in order to evaluate the effects of brain edema.

There were degeneration and decrease of neuronal cells, and the edematous or spongy changes of the stroma in addition to various degrees of degeneration in axons and myelinated fibers in the brains of all cases. Those changes were more severe and more widely spread in group A especially in the cerebral gray matter

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and the cerebellum. Thus it is considered that brain edema injures the hypoxic brain and that the cerebral gray matter and the cerebellum are not easily to be injured by hypoxia but to be injured by edema.

The brains in long-lived cases of over 14 days showed mostly diffuse and marked edema with neuronal necrosis and GFAP positive microglial infiltration in the gray and white matters, and simultaneously revealed more marked atrophy of the whole brain than that of both short-lived groups. So it is proved that the long lasting hypoxia affects the whole brain severely.

INTRODUCTION

Perinatal hypoxia injures neonatal CNS, and becomes a major cause of neurological sequelae such as cerebral palsy, mental retardation and epilepsy.[5, 17] Among many diseases causing perinatal hypoxia, MAS is not a so infrequent case which occurs following fetal distress and causes severe dyspnea clinically.

Many clinicopathological studies of the hypoxic effects on CNS have been reported,[2, 3, 9] but the causes of hypoxia in those reports were not definite and the differences between primary hypoxic changes and secondary ones were not discriminated. In this study, we restricted the cause of hypoxia to MAS and elucidated the hypoxic changes of the neonatal CNS, especially about the effects of brain edema and of the length of hypoxia.

MATERIALS AND METHODS

Thirty-eight autopsied MAS cases were studied; they were admitted to Kobe Children's Hospital from 1970 to 1985 and showed clinically severe and prolonged hypoxia during the perinatal period, and pathologcally severe MAS changes in more than 2 lobes.

The gestational ages at birth of these cases were from 34 to 43 weeks.

The body weights at birth ranged from 2220 g to 4600 g (3110 g ± 90 g), the small for dates babies were not included in this study to exclude the influence of intrauterine disorders such as malnutrition and infection.

The ages at autopsy were as follows;

1) 33 cases within 7 days; short-lived cases

2) 5 cases from 14 to 30 days; long-lived cases

The cases which had well-defined episodes of fetal distress and/or an Apgar score of 3 or less at one or five minutes after delivery were 17 cases, but 11 cases had no defined episodes at birth. Respiratory assistance was carried out in 24 cases.

The brain/body weight ratios at autopsy were estimated as an index of brain edema in short-lived cases, and they were classified into group A showing higher ratios than normal ratios and group B showing lower than normal ratios (Fig. 1). The pathological differences were estimated in order to study the influence of brain edema to CNS between group A and group B, and in order to study the influence of the length of hypoxia between short-lived cases and long-lived cases.

The autopsied brains were fixed in 10% formalin solusion, then embedded in paraffin and sectioned 4 m thick for microscopic examination.

The sections were stained with hematoxyline-eosin (HE), Holzer, Bodian-Weigert, iron HE in addition to monoclonal PAP methods: S-100 protein, neuron specific enolase (NSE), glial fibrillary acidic protein (GFAP).

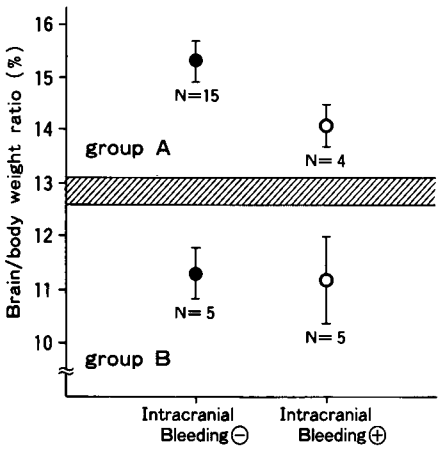

Fig. 1
Brain/body weight ratio in short-lived cases.

RESULTS

1) Pathological findings of group A

The brains of this group showed edematous changes of the gray and white matters, of which degree was proportional to the increase of brain/body weight ratios. The boundary between the

gray and white matter was unclear with capillary congestion and microscopic petechiae in the white. Figure 2 reveals severe edema in the cerebrum with petechiae in the thalamus.

The structures of the cortical layer were destroyed markedly with the degeneration and the decrease of cortical neuronal cells (Fig. 3). They showed pyknosis or karyorrhexis, decrease of Nissl substance and swollen axons with loss of cytoplasmic processes (Fig. 4).

There were severe edematous changes, involved focal or diffuse spongy degeneration in the cerebral white matter, and one case of them showed the periventricular leucomalacia (PVL). The myelinated fibers in the white matter decreased in number, and their successions were interrupted severely (Fig. 5). Microglial infiltration could be found in the white matter of all cases, but stained negatively with GFAP staining. In the thalamus and the basal ganglia, neuronal cells were preserved almost normally, but degenerated or necrotized in some cases. The degree of the changes was not always correlated to the degree of the damage of the gray and white matters.

The pontosubicular neuronal necrosis (PSN) were seen massively in the brainstem of two cases, but the columnar tegmental necrosis was not seen in any cases. Among the nuclei of the brainstem, the vestibular nuclei were injured in all cases.

There were marked degeneration of Purkinje cells and decreased number of granular cells in the cerebellum. Interstitial edema was very severe in this group (Fig. 6). Corpora amylacea were seen in the thalamus and the cerebellar vermis of one case, which were frequently seen in senile brains and thought to be the ghost or end-stage of glial cells (Fig. 7). Neutrophilic infiltration into the granular layer of the cerebellum was seen in two cases (Fig. 8, 9). The degenerative changes of dentate nuclei were more marked than those of cerebellar Purkinje and granular cells (Fig. 10).

In the spinal cords, the ganglionic cells of the anterior horn were preserved almost normally, but those of the posterior horn showed few number and small sized nuclei in all cases. Nerve fibers in the spinal tracts showed slightly retarded myelination especially in the dorsal roots (Fig. 11).

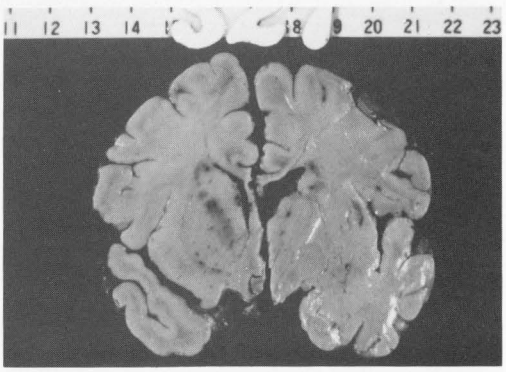

Fig. 2 Sectioned cut surface of the brain of group A, showing severe edema with petechiae in the thalamus.

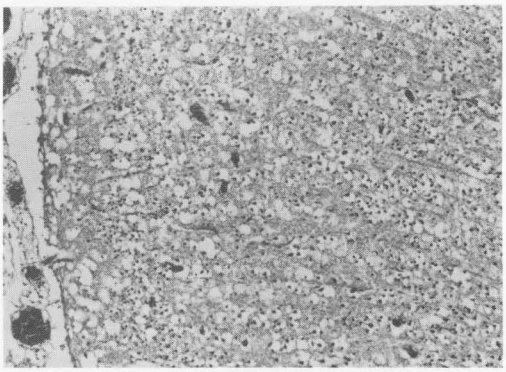

Fig. 3 Cerebral cortex of group A, showing severe edema and destroyed layer structure. HE staining, x 58

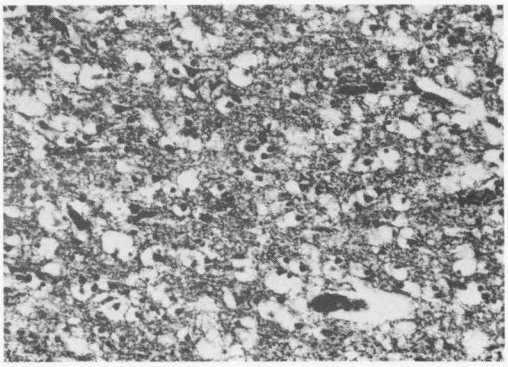

Fig. 4 Cerebral cortex of group A, showing degeneration and decrease of neuronal cells. Weigert's acid iron chloride hematoxylin staining, x 117

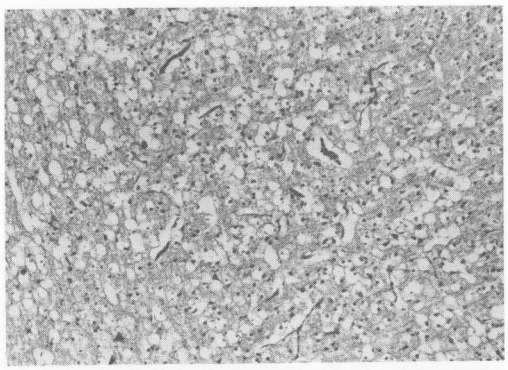

Fig. 5 Cerebral white matter of group A, showing severe edema with microglial infiltration. HE staining, x 58

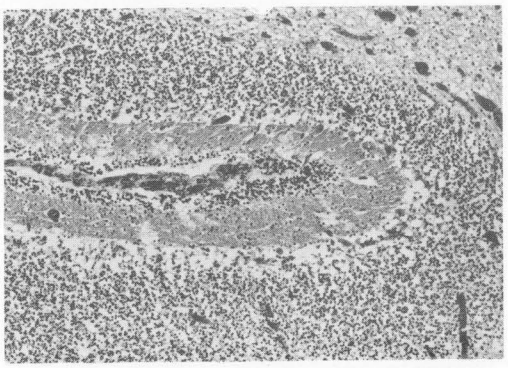

Fig. 6 Cerebellum of group A, showing degeneration of Purkinje cells and decreased number of granular cells. HE staining, x 58

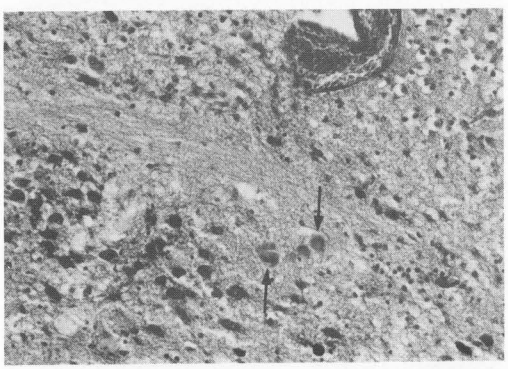

Fig. 7 Thalamus of group A, showing corpora amylacea (↑). HE staining, x 58

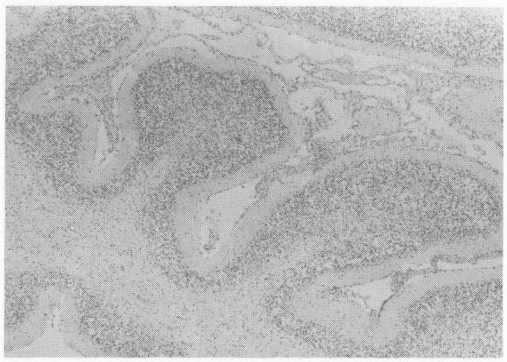

Fig. 8 Cerebellum of group A, showing neutrophilic infiltration. HE staining, x 23

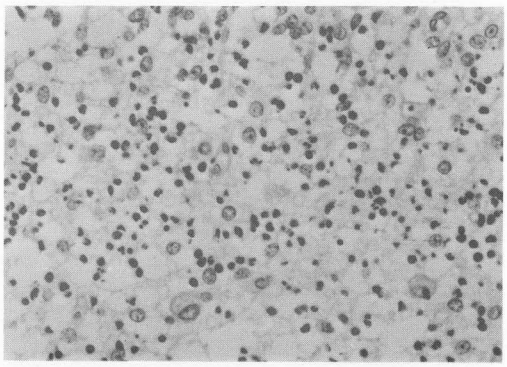

Fig. 9 Cerebellum of group A, showing neutrophilic infiltration. Naphthol acetate esterase staining, x 58

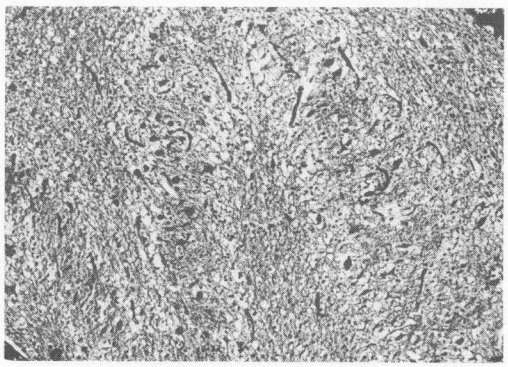

Fig. 10 Dentate nucleus of group A, showing degeneration of neuronal cells. Bodian's staining, x 58

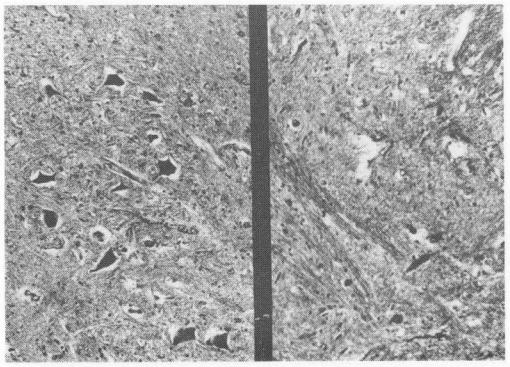

Fig. 11 Spinal cord of group A, showing ganglionic cells of the anterior (left) and the posterior horn (right). Weigert's acid iron chloride hematoxyline staining, x 58

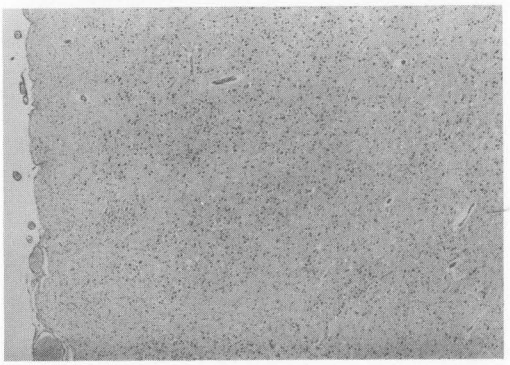

Fig. 12 Cerebral cortex of group B, showing almost normal structure of cortical layer. HE staining, x 23

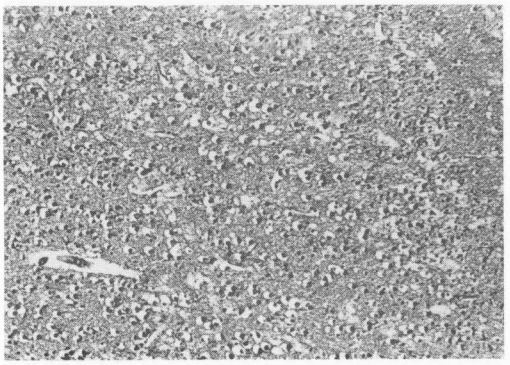

Fig. 13 Cerebral cortex of group B, showing swelling and degeneration of axons and myelinated fibers. Bodian's staining, x 58

II) Pathological findings of group B

The gross features of the brain in this group were normal or slightly atrophic. No conspicuous changes were found in any areas of this group.

Edematous changes in the gray and white matters were not so severe compared with them in group A. The structures of the cortical layer were well preserved, but numbers of cortical neuronal cells were slightly decreased (Fig. 12). Their axons and myelinated fibers were apparently preserved, but exhibited various degrees of swelling and degeneration by LFB and Bodian's staining (Fig. 13).

There was neither spongy degeneration nor PVL in the white matter. Microglial infiltration was also seen in this group (Fig. 14), but stained negatively with GFAP staining.

There were the degeneration of neuronal cells in the thalamus, the basal ganglia and the nuclei of the brainstem as well as seen in group A.

In the cerebellum, Purkinje cells and granular cells were preserved normally. Cerebellar edema was not so severe as in group A, but atrophic changes of foliae were always seen in this group (Fig. 15). The degeneration of dentate nuclei were marked though cerebellar cortices were preserved normally (Fig. 16).

The spinal cord showed intact ganglionic cells of the anterior horn but few of them of the posterior horn.

III) Pathological findings of long-lived cases

The brains of this group showed atrophic features without delineated boundaries between the gray and white matters but with any lesions of hemorrhage or necrosis after 14 days of life (Fig. 17).

Severe changes in the gray matter were seen, showing necrotic foci and marked edema with microglial infiltration positively stained with GFAP staining (Fig. 18). The cortical structures were variously destroyed in all cases (Fig. 19). The white matter showed also severe damages such as PVL and the subcortical leucomalacia (Fig. 20). PVL were seen in all of 4 cases, and subcortical leucomalacia were seen in two cases. There were swollen axons and retarded myelination especially in the area of spongy changes.

Degenerative neuronal cells in the thalamus, the basal gan-

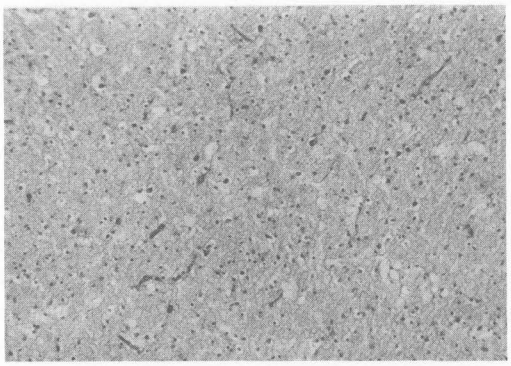

Fig. 14 Cerebral white matter of group B, showing slight edema with microglial infiltration. HE staining, x 58

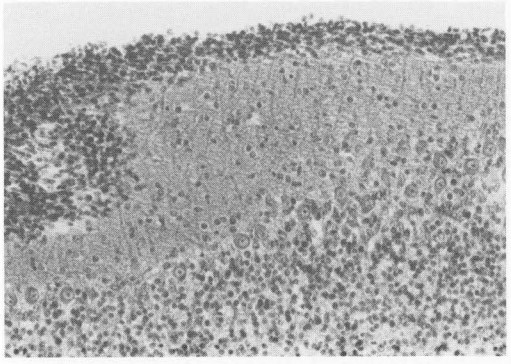

Fig. 15 Cerebellum of group B, showing normally preserved Purkinje and granular cells. NSE staining (PAP method), x 117

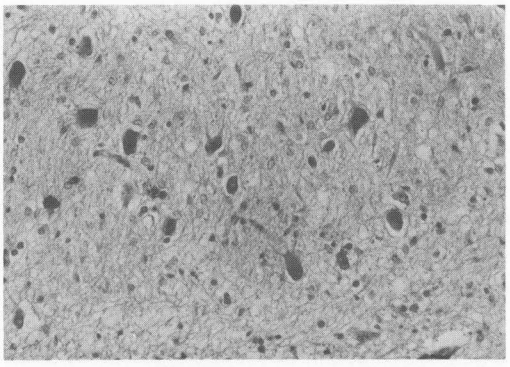

Fig. 16 Dentate nucleus of group B, showing degenerated neuronal cells. NSE staining (PAP method), x 117

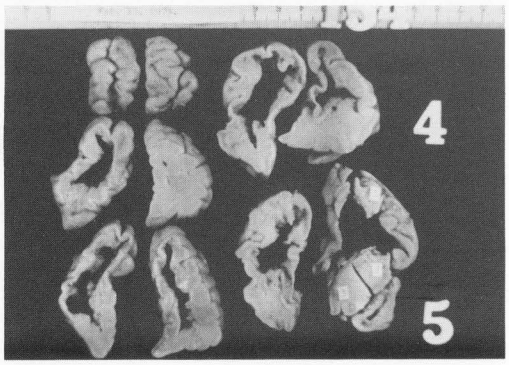

Fig. 17 Sectioned cut surface of the brain of long-lived case, showing marked atrophy and secondary hydrocephalus.

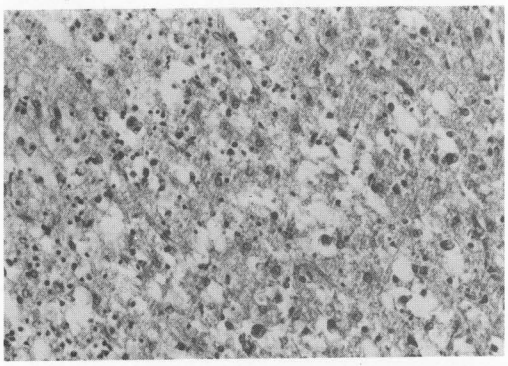

Fig. 18 Cerebral cortex of long-lived case, showing marked edema and focal necrosis with microglial infiltration. GFAP staining, x 117

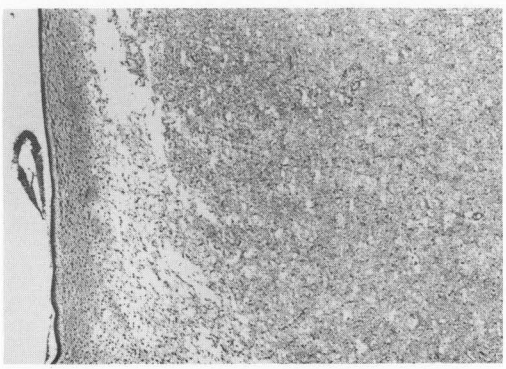

Fig. 19 Cerebral cortex of long-lived case, showing destroyed layer structure. Bodian's staining, x 23

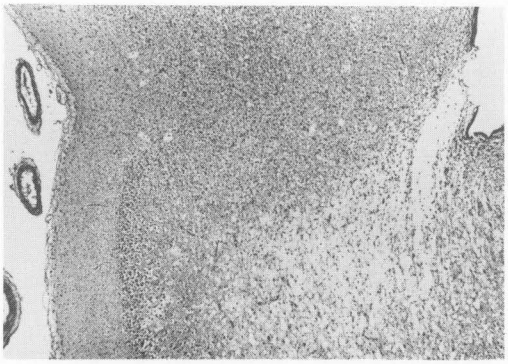

Fig. 20 Cortical gray and white matter of long-lived case, showing periventricular and subcortical leucomalacia. Bodian's staining, x 23

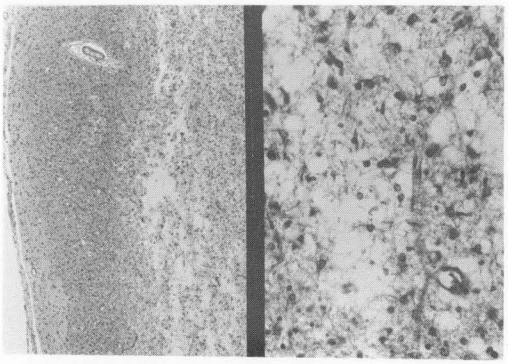

Fig. 21 Thalamus long-lived case, showing pontosubicular necrosis. HE staining, x 23 (left), x 117 (right)

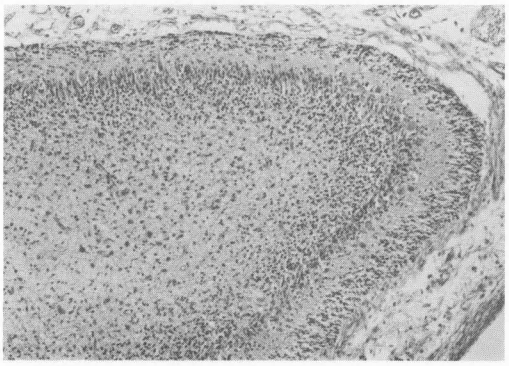

Fig. 22 Cerebellum of lon-lived case, showing degeneration of Purkinje cells and a decreased number of granular cells. HE staining, x 58

glia and the nuclei of the brainstem were seen in this group and their degree was more severe than that of the short-lived cases. PSN was seen in 3 cases (Fig. 21).

In the cerebellum, there was marked degeneration of Purkinje cells, a decreased number of granular cells, and interstitial edema was severe, especially in the layer of Purkinje cell (Fig. 22).

In the spinal cord, the anterior horn cells were almost preserved normally, but the posterior horn cells showed retarded tendency in their maturation as well as in short-lived cases. The fibers of the spinal tracts were also swollen and interrupted.

DISCUSSION

Clinicopathological studies about 38 autopsied MAS cases were performed in order to elucidate the hypoxic changes on the neonatal CNS, especially about the influence of brain edema and of the length of hypoxia. The results are follows;

1) The hypoxic brain damage is grown much worse in association with brain edema.
2) The longer the length of hypoxia lasts, the more severe the damages of CNS become.
3) The cerebral gray matter and the cerebellar cortices comparatively resist the hypoxic condition but are liable to be injured by edema.
4) Brain edema is considered to be one of the causes of PVL.
5) GFAP positive glia is not a cause of the leucomalacia but a result of it.
6) The dentate nuclei are more easily affected by hypoxia than the cerebellar cortices.

Myers[7, 10] investigated the effects of brain edema associated with hypoxia to CNS and reported that brain edema made hypoxic brain injury more severe because of the diminution in the blood flow. Myers[9] also classified various conditions of oxygen deprivation into four patterns and showed them as corresponding to pathological findings; 1. Anoxia (total asphyxia) leads to the brainstem damage, 2. Hypoxia (partial asphyxia) with acidosis leads to the cortex damage and brain edema, 3. Hypoxia without acidosis leads to the white matter damage, 4. Hypoxia plus anoxia lead to the basal ganglia damage. Because the degree of brain

edema correlated best with the length of hypoxia, hypercarbia with a pCO_2 greater than 70 mmHg, and pH below 7, Myers[7] attributed brain edema to those factors. We adopted brain/body weight ratio as an index of brain edema, and examined the effects of brain edema to the hypoxic brain. Group A with higher brain/body weight ratio showed more severe pathological changes than those of group B with lower ratio. This indicated that edema causes severe damage of brain. Furthermore, because the cortical gray matter and the cerebellar cortices were injured much more severely in group A, these regions are liable to be affected by brain edema.

Leech[6] classified the anoxic ischemic encephalopathy to the cortical injury pattern and the brainstem injury pattern, and reported that the cortical gray matter, the cerebellar cortices and the hippocampus are mainly injured in the cortical injury pattern. Group A corresponds to the cortical injury pattern of his classification. Volpe[17] advocated the conception of hypoxic-ischemic encephalopathy (HIE), and suggested that the hypoxic damages of CNS became worse by ischemia associated with edema and hypotension. Major neurological varieties of neonatal HIE are as follows; 1. Selective neuronal necrosis, 2. Status marmoratus, 3. Parasagittal cerebral injury, 4. Periventricular leucomalacia, 5. Focal ischemic brain necrosis. Among those categories, the status marmoratus is always found only in the long survivors, so it cannot be found in our study. The parasagittal cerebral injury and the focal ischemic brain necrosis are not characteristic only of the neonatal hypoxia but of the adult's hypoxia. So those findings are common in the hypoxic brain damages. Among the selective neuronal necrosis, PSN is characteristic of the neonatal asphyxia. Fried[3] observed 22 cases of perinatal distress showing a characteristic lesion of selective neuronal necrosis in the pontine gray matter and in the subiculum of the hippocampal region, and named these findings as PSN. He also suggested in cases of PSN that fetuses were older than 30 weeks' gestation and infants were younger than the second postnatal month. In our study, all cases of PSN have the same conceptional ages as his cases. Ahdab-Barmada and co-workers[1] reported that the cases with PSN had a history of higher atrial pO_2 level than 150 mmHg, and attributed PSN to hyperoxemia. In our study, all of 5 cases with PSN had no hyperoxemic episodes as far as we examined. PVL was seen in one case of group A and 4 of long-lived cases in our

study, and is considered to be characteristic of the longstanding hypoxia and of the hypoxia with brain edema. Banker and Larroche[2] indicated the hypoxia associated with repeated apneic spells as the cause of PVL, and suggested that the anatomical prematurity of the vascular system encouraged its aggravation, to be known as the vascular borderzone theory. PVL was reported at first to be characteristic of premature babies,[16] but Banker and Larroche[2] suggested PVL was seen even in full term babies as well as in premature babies. In our study, PVL was rather correlated to the degree of brain edema.

Schneider and co-workers[13] reported subcortical lesions in 7 newborn babies after transient circulatory arrest and/or asphyxia, that is, basal ganglia, diencephalon, tegmentum of the brainstem and spinal gray matter exhibited extensive necrosis in a columnar pattern (the columnar tegmental necrosis). They maintained columnar tegmental necrosis as the characteristic findings of neonatal hypoxia. But it could not be seen in our cases because their cases were not primarily the cases with asphyxia but the cases following cardiac arrest. Gilles[4] and Miller [11] also suggested that the cases from cardiac arrest or severe hypotension were mainly damaged in the brainstem, and did not show the same findings as the cases with asphyxia.

Many studies[5, 8, 12, 14, 15] reported about the brainstem lesions caused by hypoxia. They are in agreement with the lesion of the vestibular nuclei, but they are divided in opinion about other regions. So it is considered that the vestibular nuclei are liable to be affected by hypoxia. The same findings were seen in our study. The result clinically corresponds to the fact that the vestibular dysfunction is relatively common among cerebral palsy patients.

Volpe[17] reported that Purkinje and granular cells in the cerebellum were injured by hypoxia as well as dentate nuclei, but dentate nuclei were injured more markedly than Purkinje and granular cells in our study. Furthermore, Purkinje and granular cells were liable to be affected by edematous changes associated with hypoxia.

In the spinal cords, anterior ganglionic cells were seldom destroyed, but there was a retardation of maturation in posterior ganglionic cells and of myelination in the dorsal roots.

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