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Analysis of the Histopathology of the Irradiated Rat Brain with or Without Cisplatin in the First Post-Irradiation Month

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= Abstract =

The histopathology of the brains of rats killed was studied, following various doses of 20 to 30 Gy X rays with or without cisplatin(cis-diamminedichloroplatinum II) treatment. Choroid plexus in lateral ventricles, neuropil, and neuronal changes were evaluated in coronal sections of the brain. The changes were different depending on survival days regardless of dosage of irradiation or cisplatin treatment. At 4 days after irradiation, the changes of choroid plexus were marked and associated with diffuse perivascular edema. At 6 days after irradiation, choroid plexus showed congestion of blood vessels with no changes in epithelial cells and neuropil. The degenerative changes in neurons were marked at 6 days and minimal after 7 days, which suggests the reversible changes of neurons in radiation damage of rat brain. Those rats with 20 Gy irradiation, killed at 3 or 9 days, showed mild to moderate vacuolization of epithelial cells and dilatation of capillaries with no perivascular edema. Cisplatin treatment showed mild to moderate changes in choroid plexus with no changes in neurons and neuropil.

INTRODUCTION

An appreciation of effects of radiation on normal brain and on brain adjacent to intracranial tumor is very important in both the clinical and pathologic point of view, which led to throughful clinical and experimental studies. The clinically concerned irradiation-induced effects are usually delayed and can be devided into early- and late-delayed types. Early delayed effects have been described in cases of brain stem and spinal cord irradiation within 2 to 13 weeks [1-3] after the initial dose of irradiation. The changes consist of multiple punched out foci of demyelination with axonal break down and perivascular infiltration of lymphocytes and plasma cells[4]. The late delayed effects of irradiation are usually seen months or years after initial radiotherapy and consists of coagulative necrosis of all elements, demyelination with marked macrophagic reaction, and fibrinoid necrosis of blood vessel walls with vascular thrombosis and telangiectases[5]. Reactive swollen astrocytes with bizarre abnormal nuclei are also present. The late changes in the architecture and perfusion of blood vessels of the rat brain were also well documented in experimental studies[6-8].

In experimental conditions, the death of rats following irradiation of large volumes of the brain has been used to measure dose effect relationship for irradiation damage to the brain. Previous studies showed that after irradiation of rat brain animals die primarily as a result of white matter necrosis 5 to 10 months post-irradiation associated with loss of reproductive ability of cells of the subependymal

plate[9-11]. In other study, histological examination of the brains of rats dying before 200 days showed no damages to the mid-brain and cerebral hemispheres[11-13]. Since the changes in early post-irradiation period have not been well analyzed in the literature, I carefully evaluated the findings of histolopathological examination in this study to give a better insight into the cause of death during the first month following irradiation of the rat brain.

The effects of cisplatin alone or combined effects of irradiation and cisplatin in early days after treatment were also evaluated in this study, because combined effects of irradiation and cisplatin have not been well known in rat brains so far.

MATERIALS AND METHODS

Sprague-Dawley rats of both sexes weighing 200-250 gm were used for the present study. Each rat was allowed free access to food and water before and after the irradiation. The rats were lightly anesthetized with ketamine(50mg/ml) intraperitoneal injection(100mg/kg). Whole brain was irradiated by 6 MV linear accelerator(NEC 1000x) through anterior 1 portal with shielding of both eyes.

This work was part of a study of combined effects of irradiation and cisplatin in the brain. The treatment schedules involved single doses of 20, 25, and 30 Gy of irradiation. In combined group of radiation and chemotherapy, cisplatin(8mg/kg, Cisplan, Dong-A Pharmacy Co) was injected intraperitoneally immediately after irradiation and subsequently 3 ml of 0.9% NaCl was injected intraperitoneally for hydration.

The animals, 14 in all(Tables 1-3), were killed in extremis for histologic analysis when they were so ill as to be likely to die within 24 hours. They showed symptoms attributed to the irradiation and the major signs were loss of weight with a general weakness and abnormal movement. 2 age-matched rats were used as a control without any treatment and 2 were injected saline intraperitoneally(sham operation). Additional 13 cases were included in this study for comparison, consisting of 8 cases of 20 Gy irradiation group, 4 of them were sacrificed after 3 days and 4 after 9 days(Table 4). Another 2 rats were treated with cisplatin and and 3 with combined 20 Gy irradiation and cisplatin. Those 5 rats were sacrificed after 7 days. The rats were killed by an overdose of ketamine and perfused through the left

Table 1. Histopathological findings at 4 days after irradiation with or without cisplatin

animal no	cortex	hippocampus			choroid plexus			white matter
condition	f-p	CA1-2	CA3-4	DG	cong	vacuo	dilat	edema
N-9 30Gy	1+	1+	0	0	2+	2+	2+	3+, bil
N-5 20Gy+cis	1+	0	1+	1+	1+	2+	2+	3+, bil
N-6 20Gy+cis	1+	1+	0	0	2+	3+	2+	3+, bil
N-7 20Gy+cis	2+	0	1+	0	2+	3+	2+	3+, uni+midline
N-8 20Gy+cis	1+	0	1+	1+	2+	3+	2+	3+, bil

no : number
f-p : frontoparietal
CA : cornus ammonis
DG : dentate gyrus
cong : congestion of blood vessels
vacuo : vacuolation of epithelial cells
dilat : dilatation of blood vessels
uni : unilateral
bil : bilateral
cis : cisplatin

ventricle of 4% paraformaldehyde following perfusion with isotonic saline to remove blood from the cerebral vasculature. The brains were removed and fixed in the same solution for a further 24 hours. Coronal sections of the supratentorial portion of each brain were taken and embedded in paraffin. Routine sections were stained with hematoxylin-eosin(H-E), cresyl violet, and luxol fast blue to demon-

Table 2. Histopathological findings at 6 days after irradiation

animal no	cortex	hippocampus			choroid plexus			white matter
condition	f-p	CA1-2	CA3-4	DG	cong	vacuo	dilat	edema
N-1	1+	3+	3+	3+	3+	0	0	0
20Gy								
N-2	2+	3+	1+	3+	3+	0	1+	0
20Gy								
N-3	2+	1+	2+	2+	3+	0	0	0
30Cy								
N-4	1+	0	0	2+	3+	0	0	0
30Gy								

no : number
f-p : frontoparietal
CA : cornus ammonis
DG : dentate gyrus
cong : congestion of blood vessels
vacuo : vacuolation of epithelial cells
dilat : dilatation of blood vessels

Table 3. Histopathological findings at 7 to 15 days after irradiation with or without cisplatin

animal no	cortex	hippocampus			choroid plexus			white matter
condition	f-p	CA1-2	CA3-4	DG	cong	vacuo	dilat	edema
N-20	1+	0	1+	1+	0	3+	2+	3+, uni
20Gy+cis					2+	1+	1+	
7d								
N-18	1+	1+	0	0	3+	0	0	3+, uni
25Gy					0	3+	2+	
9d								
N-17	1+	0	1+	0	1+	3+	2+	3+, uni
20Gy+cis		0	0	0	2+	1+	1+	
9d								
N-21	1+	1+	0	0	3+	1+	0	1+, bil
25Gy								
14d								
N-15	2+	0	0	0	2+	2+	1+	1+, bil
25Gy								
15d								

no : number
f-p : frontoparietal
CA : cornus ammonis
DG : dentate gyrus
cong : congestion of blood vessels
vacuo : vacuolation of epithelial cells
dilat : dilatation of blood vessels
uni : unilateral
bil : bilateral
d : days
cis : cisplatin

Table 4. Histopathological findings of miscellaneous groups of irradiation and/or cisplatin

animal no	cortex	hippocampus			choroid plexus			white matter
condition	f-p	CA1-2	CA3-4	DG	cong	vacuo	dilat	edema
20Gy, 3d								
N-36	0	0	0	0	0	2+	2+	0
					0	1+	2+	
N-37	0	0	0	0	0	2+	2+	0
					0	1+	2+	
N-38	0	0	0	0	0	2+	2+	0
N-39	0	0	0	0	1+	2+	2+	1+, uni
20Gy, 9d								
N-54	0	0	0	0	1+	1+	1+	0
N-66	0	0	0	0	2+	1+	2+	0
N-67	0	0	0	0	2+	2+	2+	0
N-68	0	0	0	0	2+	2+	2+	1+, uni
					2+	3+	2+	
cis, 7d								
N-64	0	0	0	0	1+	2+	2+	0
N-65	0	0	0	0	1+	2+	2+	0
20Gy+cis, 7d								
N-55	0	0	0	1+	1+	2+	2+	0
N-56	0	0	0	1+	0	2+	0	1+, bil
					1+	1+	0	
N-57	0	0	0	1+	0	2+	1+	2+, uni
					0	0	1+	

no : number
f-p : frontoparietal
CA : cornus ammonis
DG : dentate gyrus
cong : congestion of blood vessels
vacuo : vacuolation of epithelial cells
dilat : dilatation of blood vessels
uni : unilateral
bil : bilateral
d : days
cis : cisplatin

strate Nissl substance of neurons and myelin as well as immunohistochemical study with anti-glial fibrillary acidic protein(GFAP) antibody to evaluate the changes of astrocytes. The antiserum for GFAP from human brain, raised in mouse, was purchased from Dako(Glostrup, Denmark) and diluted to 1 : 100.

RESULTS

Autopsy

At death, the animals in Tables 1-3 showed considerable emaciation and the body weight was reduced 10-20gms(average 16gms) at 4 days, 35~40gms(average 37.5gms) at 6 days, and 20~75gms(average 53 gms) at 7 to 15 days, respectively. 2 rats with cisplatin treatment showed 40 and 50gm weight loss, respectively, after 7 days. 3 rats with 20 Gy irradiation and cisplatin treatment showed 80gm weight loss in 2 rats and 20gm weight gain in 1 rat after 7 days. External lesions observed were hair loss within irradiation field and crusty deposits around the eyes. The rats in control group and Table 4 did not show gross anomalies.

Histopathology

All fractionation schedules were included in the samples taken and no relationship was seen between the irradiation dosage and cisplatin treatment and

the type or onset of the lesions.

The histopathological analysis was performed in anatomical regions of interest, which have known as main target of irradiation in the brain, white matter and blood vessels in choroid plexus in lateral ventricles, according to number of days after irradiation with or without cisplatin treatment. The changes of blood vessels and perivascular edema were graded

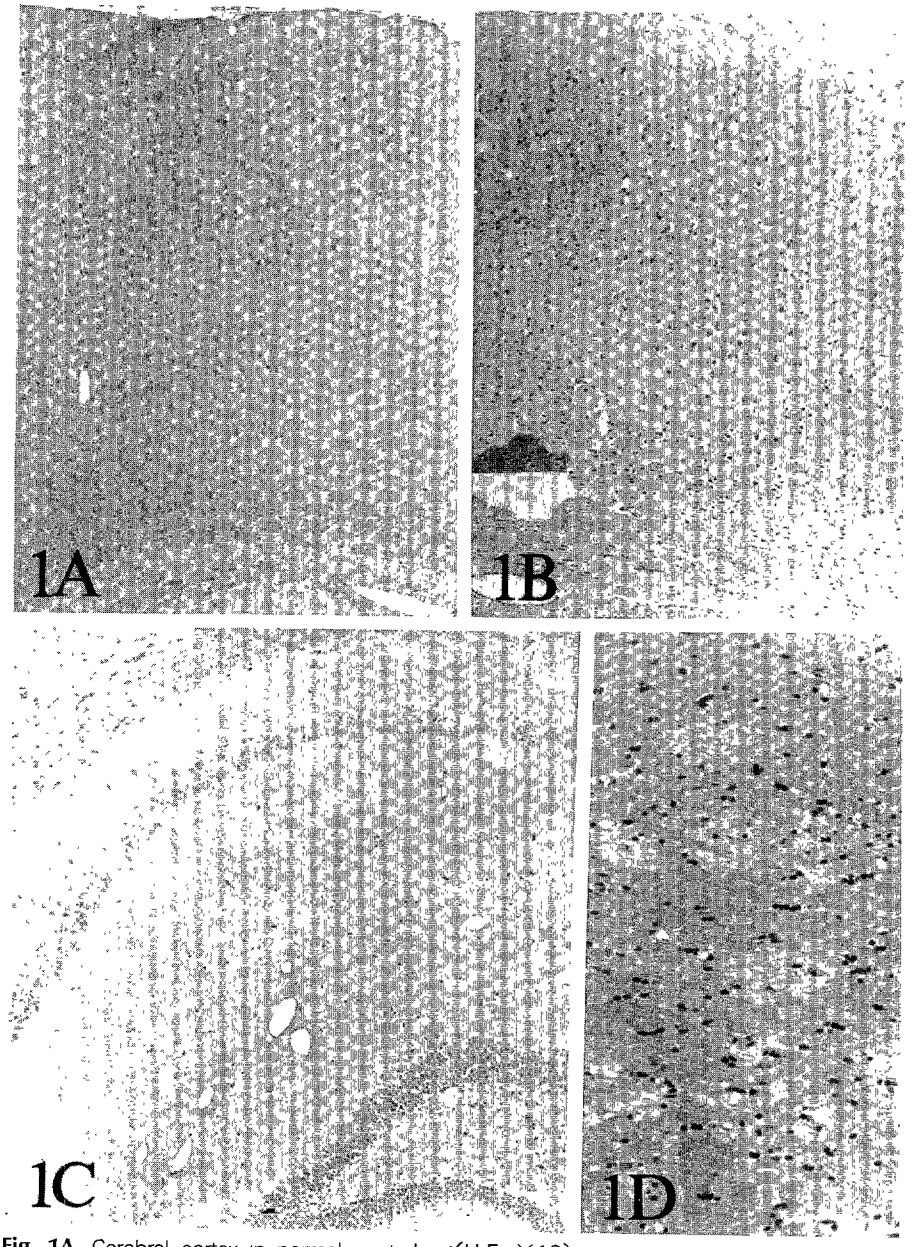

Fig. 1A. Cerebral cortex in normal control rat(H-E, ×10).
1B. Marked perivascular edema in cerebral cortex at 4 days after 20 Gy irradiation and cisplatin treatment(H-E, ×10).
1C. Marked perivascular edema in hippocampus at 4 days after 20 Gy irradiation and cisplatin treatment(H-E, ×16).
1D. Marked perivascular edema in corpus callosum at 4 days after 20 Gy irradiation and cisplatin treatment(H-E, ×50).

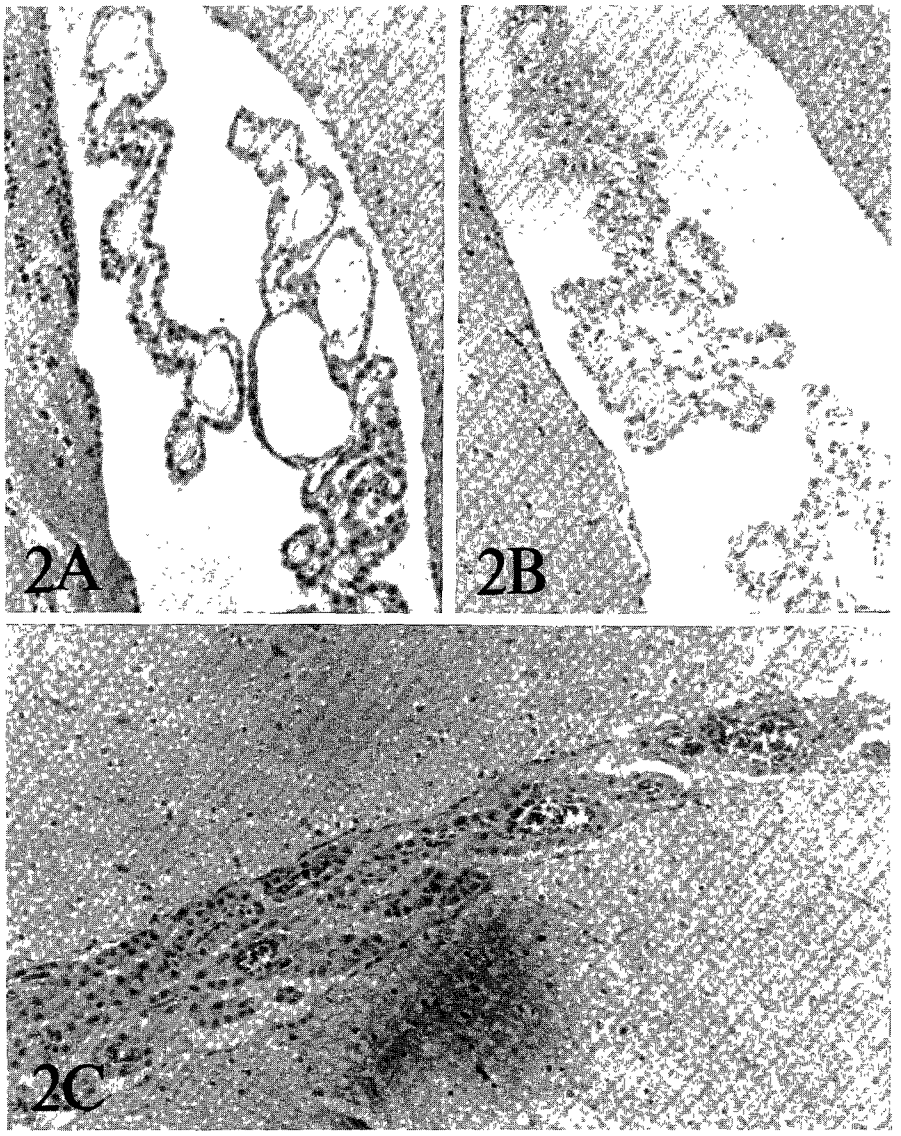

Fig. 2A. Choroid plexus in lateral ventricle of normal control rat(H-E, ×33).
2B. Marked vacuolization of epithelial cells at 4 days after 20 Gy irradiation and cisplatin treatment(H-E, ×50).
2C. Marked congestion of blood vessels at 6 days after 20 Gy irradiation(H-E, ×50).

0 to 3+ where 0 was normal and 1+, 2+, and 3+ were mild, moderate, and severe changes, respectively. The hippocampi and frontoparietal cerebral cortex were also evaluated for presence of degenerated neurons. Neuronal damages in those areas were graded 0=normal, 1+=less than 25% of neurons were degenerated, 2+=25~50% of neurons were degenerated, or 3+=more than 50% of neurons were degenerated.

1) **Control animals with or without sham operation**

2 age-matched rats with no treatment and 2 with saline intraperitoneal injection showed no histopathological changes(Fig. 1A and 2A).

2) **4 days after irradiation with or without cisplatin**

treatment(Table 1)

4 rats killed in extremis at 4 days after irradiation or combined irradiation and cisplatin showed similar changes, consisting of diffuse marked perivascular edema involving cortex, deep gray matter, and hippocampi(Fig. 1B-D). The blood vessels in choroid plexus of lateral ventricles showed marked vacuolation of epithelial cells and dilatation and congestion of blood vessels(Fig. 2B). The changes were bilateral in 3 rats and unilateral with involvement of thalamus and basal ganglia in 1 rat. The hippocampi and frontoparietal cortex showed only occasional pyknotic neurons.

3) 6 days after irradiation(Table 2)

4 rats killed in extremis at 6 days after irradiation of 20 or 30 Gy showed similar changes, consisting of marked congestion of blood vessels of choroid plexus with no vacuolation of epithelial cells(Fig. 2C). White matter changes were absent in all 4 rats. 3 rats showed moderate to marked degenerative changes of neurons in hippocampi(Fig. 3). The cerebral cortex showed mild to moderate numbers of pyknotic neurons. The changes were similar in both hemispheres.

4) 7 to 15 days after irradiation with or without cisplatin treatment(Table 3)

3 rats killed in extremis at 7 or 9 days showed unilateral marked perivascular edema and unilateral changes of blood vessels in choroid plexus(Fig. 4A and 4B). Changes of neurons in cerebral cortx and hippocampi were minimal. One rat(N-18, 25 Gy, 9 days) showed marked bilateral cranial nerve vacuolation and rarefaction in section of brain stem(Fig. 5).

2 rats killed in extremis at 14 or 15 days showed moderate to marked congestion of blood vessels, mild to moderate vacuolation of epithelial cells, and minimal perivascular edema. The changes were similar in both hemispheres.

5) 3 or 9 days after 20 Gy irradiation(Table 4)

8 rats sacrificed after 3 or 9 days after irradiation(4 each) showed similar changes in blood vessels in choroid plexus, which were dilatation of capillaries and vacuolation of epithelial cells, although congestion was severer in 9-day group. The changes of choroid plexus were asymmetrical in 4 rats. Only 2 rats

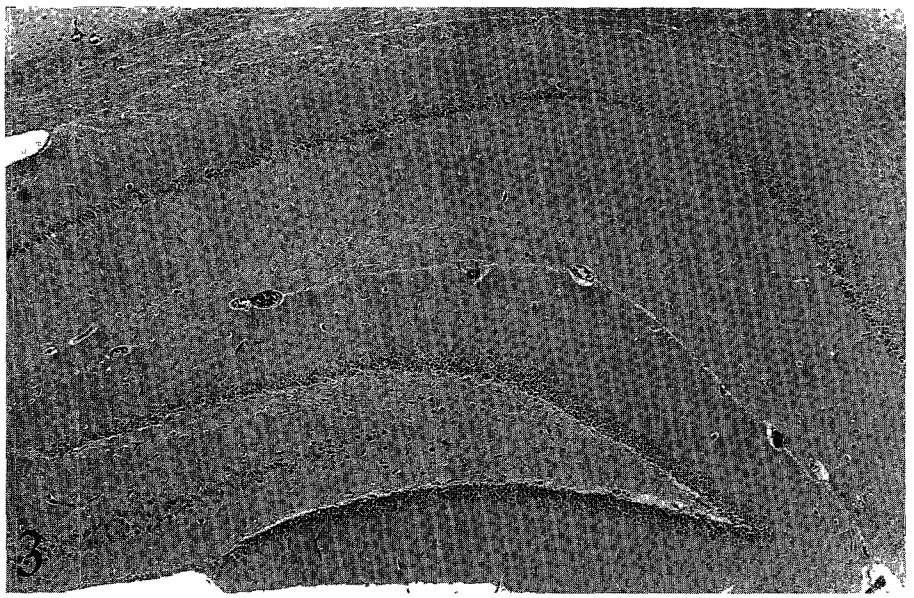

Fig. 3. Marked degenerative changes of neurons in hippocampus at 6 days after 20 Gy irradiation(H-E, ×13).

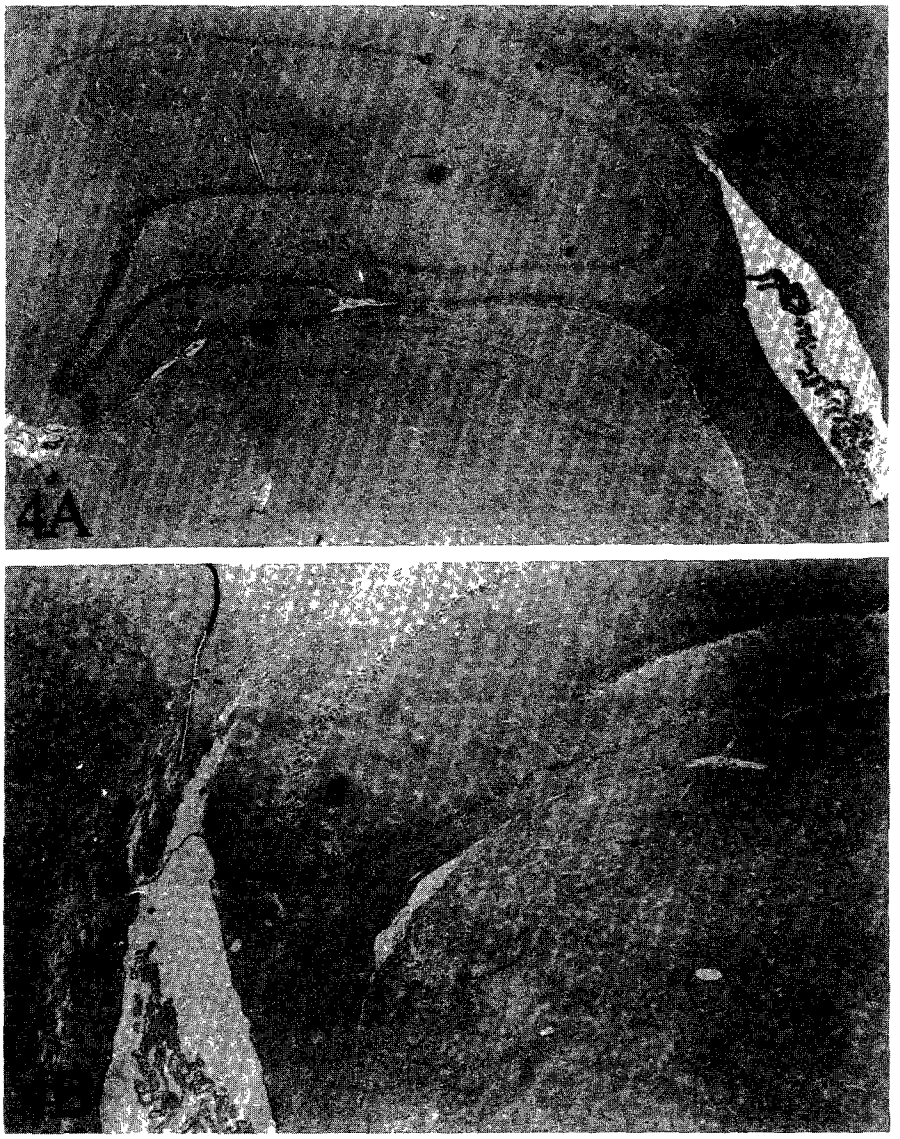

Fig. 4. Well preserved right hippocampus and thalamus(4A) and marked perivascular edema in left hemisphere(4B) at 9 days after 25 Gy irradiation(H-E, ×8).

showed mild perivascular edema in one hemisphere. Neuronal damages were absent in this group.

6) 7 days after cisplatin treatment(Table 4)

2 rats sacrificed 7 days after cisplatin treatment showed bilateral symmetrical blood vessel changes, moderate vacuolation of epithelial cells and dilatation of capillaries with mild congestion. Neuronal damages or perivascular edema were absent in this group.

7) 7 days after 20 Gy irradiation and cisplatin treatment(Table 4)

3 rats sacrificed 7 days after combined treatment showed moderate vacuolation of epithelial cells of choroid plexus in all 3 cases and mild to moderate perivascular edema in 2 cases. The changes were slightly asymmetrical in 2 rats. Neuronal changes were absent.

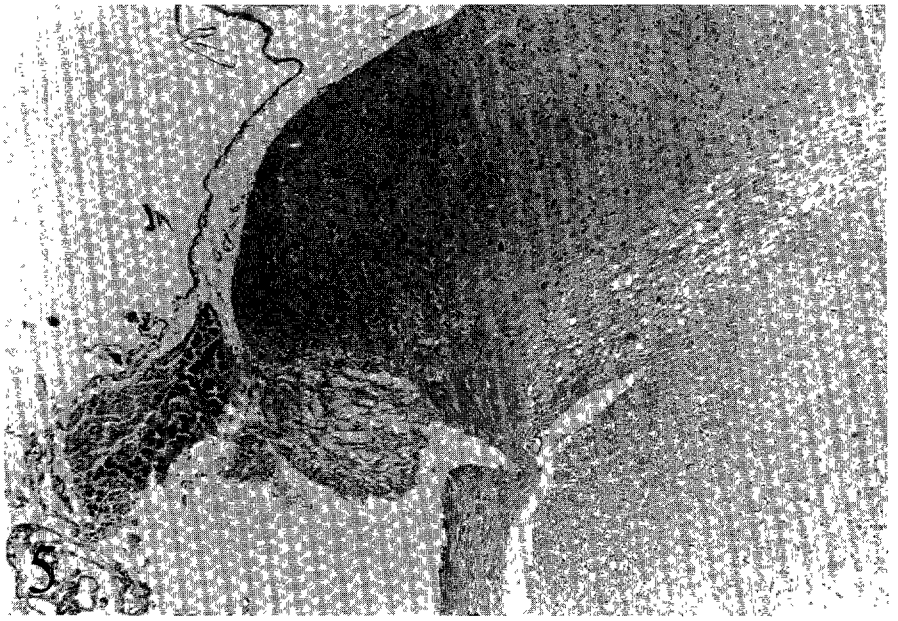

Fig. 5. Marked vacuolation and rarefaction of cranial nerve of brain stem at 9 days after 25 Gy irradiation(H-E, ×16).

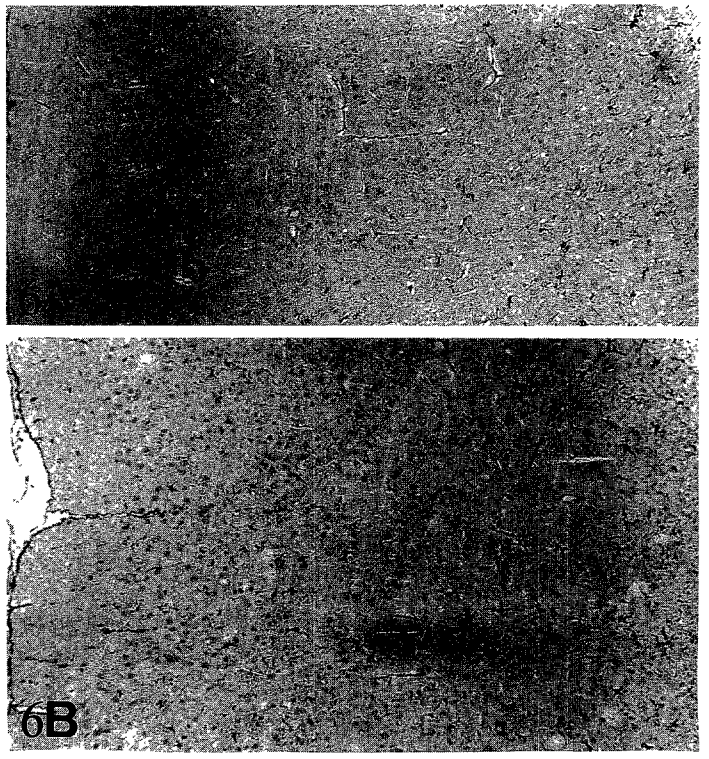

Fig. 6-A. GFAP positive glial cells in cerebral cortex of normal control rat(GFAP, ×25).
6-B. Increased GFAP positive glial cells in cerebral cortex at 9 days after 20 Gy irradiation and cisplatin treatment(GFAP, ×25).

8) GFAP immunoreactivity(IR)

13 rats in Tables 1-3 showed scattered positive cells similar to control. Only 1 rat(N-17, 20 Gy irradiation combined with cisplatin, 9 days) showed increased IR in one hemisphere with marked perivascular edema(Fig. 6A and 6B).

DISCUSSION

The changes observed in this study were similar in rats with or without cisplatin treatment but different depending on survival days(Tables 1-3). Body weight was markedly decreased in all animals, which was similar to previous studies[9)11)14)].

The changes of choroid plexus, consisting of vacuolation of epithelial cells and dilatation of blood vessels were marked at 4 days post-irradiation, which showed positive relationship with perivascular edema(Table 1). When the choroid plexus showed marked congestion of capillaries with no vacuolization of epithelial cells, perivascular edema was absent(Table 2). When the changes of choroid plexus were asymmetrical in both cerebral hemispheres, perivascular edema was also unilateral(Table 3). Only 1 rat showed slightly increased GFAP IR cells in unilateral hemisphers with perivascular edema at 9 days post-irradiation. There was no evidence of demyelination or myelin break down with macrophagic reaction or perivascular infiltration of lymphocytes or plasma cells. The positive relationship between changes in choroid plexus and perivascular edema suggested intimate relationship between these two. Further study at later consequent period would be helpful to relate sequential changes in the early and late changes after irradiation. The neurons in hippocampi and cerebral cortex showed marked degenerative changes at 6 days post-irradiation and less changes thereafter, which suggested the reversible changes of the neurons.

Compare to above mentioned animals killed in extremis, those rats with 20 Gy irradiation, killed at 3 or 9 days, showed mild to moderate vacuolization of epithelial cells and dilatation of capillaries with no perivascular edema(Table 4). The neurons in hippocampi and cerebral cortex were normal.

Previous experimental works indicated differences between species as well as between different regions of the brain and spinal cord[8)]. The threshold single dose for white matter lesions in most species was 20~25 Gy and the higher the irradiation dose the shorter the delay before the appearance of lesions in the cord and roots[15)16)]. The principal early-delayed changes in the cervical cord were demyelination and necrosis of white matter and damage to nerve roots was the main changes in lumbosacral region. Ultrastructural studies showed breakdown of paranodal myelin or nodal widening at as early as 2 weeks after irradiation and more prominent changes over 2 months[17)]. With increasing survival time increased numbers of remyelinating thinly myelinated fibers were observed. Pathogenesis of myelin changes in early-delayed spinal lesions is not clearly understood, although a primary effect on oligodendrocytes has been postulated. The difference in histopathological findings in this study from previous studies was most likely due to difference of examination time of the brains after irradiation.

Early experimental works on radiation effects on the nervous system done with large doses of x-rays showed rapidly developing cell necrosis, brain hemorrhages and breakdown of blood-brain barrier, which were also different from findings of this study [18)]. The principal biologic changes after irradiation are considered to be mediated by its effects on cell division, which may include delay of cell cycle by inhibition of mitosis after DNA synthesis, cell death during or after one or several mitotic divisions, or non-lethal damage to chromosome[19)]. The central nervous system has been considered as more radioresistant tissue of the body due to a low rate of cell turnover confined to glial and endothelial cells, which could explain the main changes in myelin and blood vessel by irradiation with subsequential

changes in central nervous system.

The pathogenesis of the late-delayed radiation injury is not yet clearly understood and the possibilities of infarction[20] and related changes to cell kinetics[21-23] have been speculated. The findings of cell kinetic studies suggested that glial and endothelial cell death occurred because of the mitotic proliferation of these cells induced by irradiation effects on DNA. They speculated that the mitotic activity and cell death proceed very slowly and at a certain critical low point a sudden acceleration of the process('avalanche effect') leading to necrosis occurs. Calvo et al[24] showed reduction of endothelial cells and subsequent necrosis without any reduction in numbers of oligodendrocytes. They also observed that the epithelial cells of choroid plexus were reduced in numbers at 13 weeks and normal at 39 weeks, suggesting the regeneration.

Cisplatin has been used as a chemotherapeutic agent for various malignant neoplasm including central nervous system since 1970s. Clinical studies showed sensory peripheral neuropathy[25], ototoxicity with tinnitus and high frequency hearing loss, and local nerve damage following intra-arterial administration[26][27], and damage to central nervous system following intracarotid administration[28]. Histopathologic changes included loss of axons of large and unmyelinated fibers in sural nerve[29][30] and gliosis with loss of axons in the posterior columns of spinal cord[31]. Direct toxic effects of platinum to peripheral nerve fibers as well as vasculopathy were considered as pathogenesis of these lesions. Experimental studies in rats also showed axonal degeneration in peripheral nerves and abnormal axons in the optic disc, retrolaminar optic nerve, and long tracts of the spinal cord[32]. Also noted were cellular changes in rat spinal ganglion cells by intraperitoneal injection of cisplatin in doses of 0.5~2mg, which consisted of focal clearing of nucleoplasm and disorganization of ribosomes[33]. Earliest changes were started as early as 6 hours after the injection of 2 mg. Their study did not include the brain. Present study showed only mild to moderate vacuolization of epithelial cells and dilatation of capillaries with no perivascular edema(Table 4). The neurons in hippocampi and cerebral cortex were normal. The effects of cisplatin treatment on radiation-induced brain damage in rat could not be evaluated in this study because of limitation of numbers in each group and will be accomplished later.

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