Radioactive tissue changes induced to control experimental hydrocephalus

MARTIN H. WEISS, M.D., AND UROS ROESSMANN, M.D.
Division of Neurosurgery, University Hospitals, Veterans Administration Hospital, and Division of Neuropathology, Institute of Pathology, Case Western Reserve University, Cleveland, Ohio

Hydrocephalic animals were given an intraventricular infusion of radioactive colloidal gold and then sacrificed up to 7 weeks after infusion. Histological evaluation revealed progression from a marked hemorrhagic necrosis of choroid plexus vessels and stroma to eventual replacement by fibrous connective tissue, sclerosis, and fibrinous degeneration of stromal vessels. Particulate colloid was found engulfed in perivascular spaces in the subependymal periventricular tissues, but there was no evidence of vascular damage, gliosis, or demyelination. These findings may play a role in decreasing cerebrospinal fluid production.

Keywords: hydrocephalus, radioactive colloidal gold, choroid plexus necrosis, subependymal colloid

Various investigators have attempted to alter the rate of production of the cerebrospinal fluid (CSF) or to influence the dissemination of malignant cells in the CSF by instillation of radioactive materials directly into the subarachnoid system. The acute pathological effects of these agents showing selective damage to the choroid plexus have been reported, but there has been little note of the pathological findings in animals with longer survival.

To define the subacute and chronic pathological changes, we studied hydrocephalic dogs sacrificed at 5, 21, and 49 days after intraventricular infusion of radioactive colloidal gold.

Materials and Methods

Six adult mongrel dogs, weighing 12 to 15 kg, were made hydrocephalic by intracisternal injection of a 12.5% sterile suspension of kaolin (50 to 60 gm/kg) after removal of an equivalent volume of CSF from the cisterna magna. All dogs developed hydrocephalus, verified by serial ventriculography. Two weeks after the injection of kaolin, each dog was again anesthetized (pentobarbital sodium 30 mg/kg) and a Holter ventricular silicone catheter attached to a capped Rickham reservoir was inserted into the right lateral ventricle through a standard convexity trephine. The cannula was fixed in the subgaleal tissues and the animal allowed to recover. The indwelling catheter gave easy access to the lateral ventricles by percutaneous tapping through the Rickham cap, thereby enabling serial ventriculograms to confirm progression of hydrocephalus. Intraventricular pressures measured from the same reference levels rose from an average of 116 mm of CSF to an average of 176 mm of CSF. Two weeks after placement of the catheter, 12 mc of colloidal gold (Au198 suspended in 2 to 3 ml of aspirated CSF) were instilled into the lateral ventricle through the catheter. Barbotage was used to assure complete delivery and even distribution. The animals were killed at 5, 21, and 49 days after infusion of radioactive material, and the brains were removed and fixed in formalin.
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Coronal sections through cerebral hemispheres were stained with hematoxylin and eosin, Luxol fast blue, PTAH, Holzer, and Masson trichrome stains.

Results

Gross inspection of the basal cisterns showed them to be completely obliterated by a firm cast of kaolin, with obstruction of the outlet foramina of the fourth ventricle. On sectioning, the ventricles were dilated. The choroid plexus in the dogs killed 5 days after injection of radioactive material appeared grossly hemorrhagic, dark red, with obliteration of the normal granular appearance. In animals that survived for 21 to 49 days, the entire plexus was enclosed in a firm, rubbery coagulum that filled large parts of the ventricular system. No other focal lesions were observed in the brains.

Microscopic changes in untreated hydrocephalus produced experimentally by kaolin have been described previously. The ependyma appeared attenuated, but there were no significant changes in the underlying parenchyma.

Histological preparations from animals killed 5 days after injection showed ventricular dilatation with stretching of the ependymal cell layer of the ventricular walls. Portions of the walls were denuded as were considerable segments of the choroid plexus. The ependymal nuclei were frequently dark and hyperchromatic and their cytoplasm vesicular. The stroma of the choroid plexus was edematous (Fig. 1); the cells appeared pyknotic and nearly submerged into the mass of polymorphonuclear leukocytic cells. Blood vessels were distended and congested. The subependymal tissue was spongy, and polymorphonuclear exudate was present in the perivascular spaces as well as in the tissue itself. There was no glial reaction nor evidence of demyelination demonstrated by appropriate stains.

Twenty-one days after injection of radioactive substance the ventricles were filled with coagulum containing many polymorphonuclear leukocytes. The ependyma of the choroid plexus had enlarged and showed vesicular nuclei surrounded by small amounts of eosinophilic cytoplasm (Fig. 2). The cells were quite flat. The stroma was edematous; the cellular exudate now contained numerous

Fig. 1. Photomicrograph of the choroid plexus 5 days after radioactive gold injection. Stroma is swollen, hyperemic, and completely covered by cellular exudate. The ependyma is stretched, the cells flattened, and the nuclei small and dark. H & E, x 80.

Fig. 2. Photomicrograph of the choroid plexus, 21 days after injection. Ependymal nuclei are large and vesicular; there is vascular and endothelial proliferation. Cellular exudate now includes many monocytes and macrophages. H & E, x 370.
macrophages, many of which were filled with dark granular material consistent in appearance with colloidal gold particles. There was vascular and endothelial proliferation. The number of fibroblasts appeared increased. Perivascular leukocytic infiltrates in the subependymal tissue diminished greatly. The blood vessels showed slight endothelial proliferation. There was no glial reaction demonstrable by Holzer stain.

At 7 weeks after injection the ventricles were distended and, in part, contained an acellular coagulum. The plexus was covered by a thin but highly excessive layer of ependyma (Fig. 3). Ependymal nuclei now appeared large with normal chromatin content; the cytoplasm, however, remained scant. By light microscopic examination there was no evidence of cilia. The choroid plexus now consisted of extensive fibrous connective tissue with heavy deposits of coarse collagenous strands and a few fibroblasts. The blood vessels were numerous but, at this stage, showed no endothelial proliferation. Instead, they appeared sclerotic and a few showed evidence of fibrinous degeneration. Cellular exudate was greatly diminished, consisting for the most part of macrophages and focal accumulations of mononuclear cells.

The ventricular walls showed marked flattening of the ependyma, with a few denuded areas. Dark granules of colloidal gold could be seen in perivascular spaces of the subependymal tissues, apparently engulfed in macrophages (Fig. 4). No glial reaction or demyelination could be detected in the periventricular white matter, nor were there any changes demonstrable in the blood vessels.

Discussion

Few reports are available on the chronic pathological findings following radioactive material infusion into the ventricular system. Rish and Meacham noted that hydrocephalic animals allowed to survive 2 to 3 months after intraventricular infusion of radioactive colloidal gold showed more "chronic fibrotic necrosis" with less acute hemorrhagic reaction affecting the choroid plexus than the animals sacrificed up to 10 days after the colloid infusion; they did not note the subependymal perivascular colloid. McClure, et al., followed one animal for 29 days after radiocolloid gold infusion and...
found minimal histological changes in the choroid plexus; however, the animals used in their series did not have obstructive hydrocephalus.

Haymaker reported delayed radionecrosis of the brain in monkeys 1 to 17 weeks following high-level doses of external radiation to the brain. The effect was primarily on the white matter, although scattered lesions were found in the cortex and hypothalamus. The significant finding, however, appeared to be a predilection for blood vessels, with perivascular lesions and calcific deposits. Our results similarly implicate vascular toxicity as the mechanism underlying the pathophysiological changes observed in the areas apparently exposed to the radiocolloid.

Au198 is a beta and gamma ray emitter, with approximately 95% of its energy yielded as beta rays. Its half life is 2.7 days, and 90% of its activity is dissipated within 10 days. Since the penetration of the beta rays is only approximately 0.4 mm, the significant effect is limited to the immediate vicinity of the colloid particles at the ependyma and at the site of their penetration through the ependymal cell layer. Our observations suggest that the particles penetrate through the ependyma into the brain substance for a short distance, since inflammatory exudate was seen in the subependymal tissue in the early specimens, and macrophages containing colloid particles were present in the perivascular spaces after longer survival. The findings were limited to a narrow zone of periventricular tissue; we saw no evidence of cell death, gliosis, or demyelination in the area.

The largest part of the injected material definitely accumulated at and within the choroid plexus. This fact may be due to a selective affinity of the material for the plexus, easier penetration of the plexus ependyma, or its greater sensitivity to radiation. The ependyma of the choroid plexus showed marked changes initially; its cells, however, either recuperated or regenerated, as the plexus was lined by an excessive layer of cells by the end of 7 weeks after injection. The most significant changes were found in the blood vessels and stroma of the choroid plexus. As expected, ionizing radiation caused necrosis of the blood vessel walls, with endothelial and fibrous proliferation, hyalinization, and disappearance of small vessels. These vascular changes and the dense fibrosis of the stroma may be potential factors in the inhibition of CSF formation.

References

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