Morphological study of experimental syringomyelia with kaolin-induced hydrocephalus in a canine model

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In this morphological study the authors investigated whether spinal cord cavitation, produced in young mongrel dogs that had been rendered hydrocephalic by cisternal injection of kaolin, consists of a dilated central canal or intramedullary cavities. Hydrocephalus was noted in 50 of 56 dogs treated with kaolin. Of the 50 hydrocephalic young dogs, 29 were shown to have central canal dilation that was prominent at the thoracic level and 21 to have cervical intramedullary cavities in the posterior column and/or the posterior horn. In 11 dogs from the latter group these cavities were demonstrated to have no communication with the central canal. This finding could not be explained by the hydrodynamic theory.

On histopathological examination, myelomalacia and hemorrhagic infarction following ventricular shunting were noted adjacent to the cervical cavities, which suggested vascular impairment. A perfusion study revealed insufficient blood flow within the cerebral cord at the level of the intramedullary cavities. A close correlation between the vascular insufficiency of the cervical cord and the pressure cone resulting from significant hydrocephalus was observed. The latter may cause cervicomedullary compression at the foramen magnum, affecting the venous drainage of the cervical cord below that level, resulting in intramedullary cavitation.

Accordingly, vascular impairment was thought to play a significant role in the development of cervical syrinx formation in our kaolin model. The current results may provide a reasonable explanation for the formation of noncommunicating cervical syringomyelia in Chiari I malformation.

KEY WORDS • experimental syringomyelia • hydrocephalus • pressure cone • vascular impairment

The pathogenesis of syringomyelia associated with Chiari I malformation has been the subject of much debate. Currently, the most widely accepted hypothesis is based on the hydrodynamic mechanism proposed by Gardner and its later modification by Williams and colleagues according to which this lesion is believed to be hydrosyringomyelia consisting of central canal dilation and resultant intramedullary cavitation. The hydrodynamic mechanism is valid only if the syrinx communicates directly with the fourth ventricle. However, in the majority of patients with syringomyelia associated with Chiari I malformation, no definite cerebrospinal fluid (CSF) channel between the two chambers has been established by pathological investigations. These observations cast doubt on the validity of the hydrodynamic theory with respect to the pathogenesis of syringomyelia associated with Chiari I malformation.

Although several models of experimental syringomyelia have recently been proposed, syringomyelia produced by kaolin-induced hydrocephalus is the most popular and widely used model for communicating syringomyelia. This model has been used to demonstrate downward movement of CSF within the dilated spinal central canal, the pathogenesis of which has been attributed to the hydrodynamic mechanism of Gardner. However, using the same model we have demonstrated microscopically that some of the cervical syrinxes are noncommunicating. This morphological discontinuity cannot be explained by the hydrodynamic theory. In this study we analyzed the morphological results of experimental syringomyelia produced in kaolin-induced hydrocephalus in young mongrel dogs to determine the pathogenesis of the noncommunicating cervical syrinx.

Materials and Methods

Animal Preparation

Sixty young mongrel dogs, aged approximately 1 month and weighing 1 to 1.5 kg, were used for this study. All animals were maintained in accordance with the Guiding Principles for the Care and Use of Animals approved by the faculty meeting of the University of Occupational and Environmental Health in 1987. All procedures were performed while the animals were under pentobar-
bital-induced anesthesia. Hydrocephalus was produced by a percutaneous injection of kaolin solution (200 mg/ml/kg) into the cisterna magna. One month after kaolin injection, computerized tomography (CT) scanning was performed to determine the degree of ventricular enlargement. Fifty-six kaolin-treated dogs were divided into three groups depending on their degree of ventricular enlargement: 24 dogs with gross hydrocephalus comprised Group A; 22 with moderate hydrocephalus Group B; and 10 with minimal hydrocephalus Group C (Fig. 1). Eighteen dogs in Group A underwent ventriculoperitoneal (VP) shunting using a one-piece catheter with cephalus Group C (Fig. 1). Eighteen dogs in Group A underwent ventriculoperitoneal (VP) shunting using a one-piece catheter with a distal slit valve at low pressure (20–30 mm H2O) via a right parietal burr hole. Four of these animals died of unknown causes soon after the shunting procedure and autopsies were performed. The 14 dogs that survived were killed 1 month after placement of the shunts when cerebral mantle reconstitution was confirmed by CT scan. The six remaining dogs from Group A, the 22 dogs from Group B, and the 10 from Group C did not receive shunts but were killed for histological evaluation within 2 months after kaolin injection. Four animals did not undergo kaolin injection and were used as normal controls (Group D).

Histological Preparation

Five dogs each from Groups A, B, and C and two dogs from Group D were reserved for microangiographic study prior to use in the histological investigation. The other animals were perfused via the abdominal aorta with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer. The brain and spinal cord were removed and immersed in 15% formalin solution. Macroscopic examination was performed after brain and spinal cord sectioning, followed by contact microangiography using a supersoft x-ray apparatus. All of these sections were also used for histological evaluation.

Results

Pathology of Brain and Spinal Cord

In all dogs treated with kaolin, a marked thickening of the meninges was observed in the basal cisterns and the subarachnoid space of the posterior fossa and rostral cervical spinal cord. Outlets of the fourth ventricle were obstructed by the thickened meninges. In Group C, however, obstruction of the lateral foramina of the fourth ventricle was incomplete. Microscopic examination of the thickened meninges demonstrated protracted granulation tissue containing kaolin particles. Spinal meningeal blood vessels showed no evidence of obstruction or narrowing and no thrombus formation.

Pathology of Syringomyelic Cavities

For the purposes of this study, we defined spinal cord cavities as matching either of two histopathological conditions: a cystic dilation of the central canal or a parenchymal cavity withoutependymal lining; the latter may communicate with the central canal.

Central canal dilation was seen in 29 animals (18 in Group A, nine in Group B, and two in Group C). The greater the cerebral ventricular enlargement, the higher the frequency of increased central canal dilation (Table 1). A remarkable dilation of the central canal was often recognized from the middle cervical to the thoracic level. At the thoracic cord level, a marked dilation and/or a parenchymal disruption of the central canal was noted in five hydrocephalic dogs (Fig. 2).

A definite intramedullary cavity of the spinal cord was recognized in 21 (16 in Group A and five in Group B) of the 56 kaolin-treated dogs (Fig. 3A). The greater the cerebral ventricular enlargement, the higher the frequency of increased parenchymal cavitation, regardless of the extent of kaolin granulomata. Six nonhydrocephalic animals treated with kaolin (in Group C) demonstrated no parenchymal cavitation or central canal dilation. Intramedullary cavitations were located mainly in the rostral portion of the cervical spinal cord and were confined to the area of the posterior column and/or the posterior horn (Fig. 3B).
In six animals the cavity extended rostrally to the medulla oblongata or caudally to the upper thoracic cord. Serial transverse sections of spinal cords with intramedullary cavitations revealed no definite communication between the cavity and the central canal in 11 of 21 hydrocephalic dogs. The most prominent histopathological findings were an increased number of reactive astrocytes and their processes in the border zone of the posterior horn and posterior column and in the cavity walls. Vasoconnective tissue was seen to bridge the cavity in one case (Fig. 3C). Furthermore, rarefaction around the cavities and in the posterior column was noted 2 or 3 weeks after kaolin injection and was associated with reactive astrocytosis (Fig. 3D), many lipid macrophages (Fig. 3E), and perivascular infiltration of mononuclear cells.

In the four animals in Group A that died of unknown causes soon after the shunting procedure, autopsy revealed massive hemorrhage associated with some hemosiderin deposits in the posterior column apart from the dilated central canal, especially in areas surrounding the cavity (Fig. 4A). These hemorrhagic lesions simulated so-called hemorrhagic infarction because the background structures, namely the microvasculature and some neural tissue, were relatively well preserved. In addition, rarefied and demyelinated white matter with some swollen or degenerated axons (Fig. 4B) and reactive astrocytosis (Fig. 4C), indicating a preexisting ischemic lesion, was located in, and adjacent to, the hemorrhagic lesions.

**Fig. 2.** Photomicrographs of sections of the thoracic spinal cord in kaolin-induced hydrocephalus in young mongrel dogs, showing remarkable dilation of the central canal (A) with resultant disruption into the posterior horn (B). H & E, original magnification × 10.

**Fig. 3.** Photomicrographs stained with H & E. A: Photomicrograph of a section of a middle cervical cord demonstrating intramedullary cavity formation in the unilateral posterior column. No definite communication with the central canal was observed in serial sections. Original magnification × 10. B: Schematic illustration showing the distribution of four representative cavities. All cavities, including these four, were located in the region of the posterior horn and/or the posterior column. C: Photomicrograph, medium magnification, of the upper cervical cord cavity showing vasoconnective tissue (arrow) crossing the cavity. Original magnification × 50. D and E: Photomicrographs, high magnification, of the spinal cord parenchyma adjacent to the cavity showing rarefaction associated with reactive astrocytosis (D) and infiltration of lipid macrophages (E), which indicate myelomalacia. Original magnification × 200.
Herniation of the cerebellar structure into the spinal canal was recognized in 10 animals (eight in Group A, two in Group B) that had both a spinal cord cavity and gross hydrocephalus (Fig. 5). In other dogs demonstrating gross hydrocephalus with or without cavitation, the cerebellum and brainstem were compressed downward to the foramen magnum but did not herniate into the spinal canal, where kaolin granulomata were thickly packed.

The results described above are summarized schematically in Fig. 6.

Perfusion Study and Microangiography

Five dogs with gross hydrocephalus (Group A) demonstrated hypoperfusion at the cervical cord level, which corresponded to the level of cavitation. In all five of the kaolin-treated animals without ventricular enlargement (Group C), no hypoperfused area was detected anywhere in the spinal cord despite prominent kaolin-induced spinal arachnoiditis. In Group B, two dogs showed a hypoperfused area at the cervical cord level. On transverse sections of the hypoperfused level, India ink staining was uniformly poor and loss of gray matter configuration was observed.

Microangiograms of cervical spinal cord sections from Group A (Fig. 7 left) revealed decreased gray matter vascularity as well as indistinct gray matter configuration. Marked attenuation of vascular densities was found in areas between the posterior horn and the posterior column, where the cavity was located. Some venous engorgement was also encountered. In Group B animals without cavitation (Fig. 7 center) and Group C animals, gray matter configuration and vascular densities were almost normal in spite of prominent kaolin granulomata. Microangiograms of thoracic spinal cord sections from Group A did not show any attenuation of vascular densities despite central canal dilation.

Discussion

Becker, et al., and Hall and colleagues18–22 found dilatation of the central canal to be prominent at the thoracic cord level in kaolin-induced hydrocephalic animals and suggested that the CSF pulse–pressure wave in the hydro-
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canal distention (hydromyelia) and disruption into the parenchyma (hydroxyryngomyelia).

The present morphological study enabled us to categorize spinal cord cavitary lesions into two types of syrinx: a distended central canal (hydromyelia) prominent at the thoracic cord level and an intramedullary cavitation (syringomyelia) located in the posterior horn and the posterior column of the cervical cord. Eleven of 21 animals with cervical intramedullary cavities revealed no definite communication with the central canal on detailed serial sections. The mechanism of the central canal dilation in our model could well be explained by the hydrodynamic theory, as Becker, et al., and Hall and colleagues have maintained, because no central canal dilation existed without significant ventricular enlargement. However, the so-called distending force cannot explain the morphological discontinuity between the cervical intramedullary cavity and the central canal in our model.

McLaurin, et al., and other investigators have proposed that vascular impairment may cause cervical cord cavitation in kaolin-hydrocephalic animals. They described myelomalacia located in the posterior half of the cervical spinal cord associated with prominent spinal arachnoid granuloma, arterial narrowing, and thrombus formation. This spinal cord region, which is supplied by the terminal branches of the anterior and posterior spinal arteries, is highly vulnerable to vascular impairment. However, subsequent studies have shown that kaolin-induced granuloma do not cause vascular impairment of spinal cord. In our model, a histopathological study of cervical cavitations demonstrated incomplete infarction, and a perfusion study revealed decreased blood flow at the level of the cavitation. However, no correlation between vascular impairment of the cervical cord and spinal arachnoiditis induced by kaolin was observed, and it was demonstrated that the kaolin-induced inflammation did not cause cervical myelomalacia. Rather, a close correlation

![Fig. 6. Schematic illustration of the present results demonstrating a herniated cerebellar structure at the level of the foramen magnum, a noncommunicating cavity with the central canal in the posterior column and/or the posterior horn in the rostral cervical cord (C), and a remarkable dilation of the central canal at the thoracic cord (Th) level.](image)

![Fig. 7. Microangiograms displaying cervical cord sections from three groups (left: Group A; center: Group B; right: normal control). Left: Microangiogram demonstrating indistinct demarcation of gray matter vascularity at the ventral portion of the posterior column as well as an avascular lesion (asterisk) corresponding to cavitation. Venous engorgement is also seen. Center: Microangiogram showing a distinct gray matter configuration similar to that of the normal control (right). C = central canal dilation. Open arrows mark the sulcal or central artery.](image)
between cervical vascular insufficiency and tonsillar herniation (pressure cone) resulting from gross hydrocephalus was detected.

A direct correlation between cervicomедулляр compression at the foramen magnum due to the herniated cerebellar structure and vascular impairment of the cervical cord at some distance caudal to that level has been hypothesized by some investigators. Based on their autopsy studies of syringomyelia associated with Chiari malformation, Lichtenstein and Foster, et al., suggested that herniated cerebellar structures compress the neuraxis as well as vessels that cross the foramen magnum and result in vascular insufficiency in the cervical cord below that level. Taylor and Byrnes, in their animal experiments of chronic compression of the neuraxis at the foramen magnum, demonstrated a disturbance in venous drainage with ischemic changes in the cervical cord and hypothesized that venous drainage of the cervical cord is directed upward. In an acute spinal cord injury model, Koyanagi and coworkers recently drew attention to hemorrhage in the posterior column and the posterior horn at a level remote from the injured site; their microangiographic study clearly demonstrated congestion of dorsal parasagittal veins with resultant extravasation. According to their theory, it is conceivable that in our model, cervicomедулляр compression by a pressure cone might cause cervical vascular impairment, particularly a disturbance in venous drainage with resultant intramedullary cavitation. Cervical intramedullary hemorrhage following ventricular shunting in our model can also be explained as follows: the shunting procedure decompressed the pressure cone at the foramen magnum, improved blood flow in the cervical cord below that level, and, ultimately, caused hemorrhagic infarction.

It is conceivable that in our model the two types of syrinx—central canal dilation prominent at the thoracic level and cervical cord cavitation in the posterior column and posterior horn—were produced in quite different ways: that is, by the hydrodynamic mechanism and by vascular impairment, respectively. Spinal cord cavitation in the kaolin-induced hydrocephalic model has been thought to be communicating in nature, as demonstrated by ventriculography. Although we did not perform ventriculography in the current study, intramedullary cavities could easily communicate with the central canal through enlarged parenchymal interspaces, because the two chambers are located close to each other. Once the syrinx in the cervical cord communicates with the central canal, the distending force proposed by Williams and coworkers could then increase the size of the syrinx.

Cavitary lesions of the spinal cord in patients with Chiari I malformation have been believed to be a form of hydrosyringomyelia resulting from the hydrodynamic mechanism. Cerebrospinal fluid from the fourth ventricle passes through the obex down into the spinal central canal and, consequently, distends (hydromyelia) or disrupts the canal into the parenchyma (syringomyelia). However, recent magnetic resonance imaging and pathological studies have demonstrated no direct communication between the syrinx and the fourth ventricle in patients with hydrosyringomyelia associated with Chiari I malformation. It is unlikely in such cases that so-called “hydrodissection” could be a cause of spinal cord cavitation. Alternatively, an explanation by Ball and Dayan that CSF flows from the spinal subarachnoid space through the interstitial spaces of the posterior horn into the syrinx is now being reappraised. Based on their experimental study using rats, Milhorat and colleagues have recently proposed that rostral flow of CSF in the central canal could be a pathogenetic mechanism of noncommunicating syringomyelia with Chiari I malformation. However, they have also shown central canal obstruction at multiple spinal cord levels of human subjects, and it remains uncertain whether CSF flow in the spinal central canal is directed upward.

Previous pathological investigations of syringomyelia associated with Chiari I malformation have clearly demonstrated that paracentral intramedullary cavity formation involving the posterior horn and/or the posterior column of the cervical cord is one of its most common features and appears to be an initial process in the occurrence of this spinal cord lesion. Although our model includes several limitations with respect to correlating it with the human condition, such as leptomeningeal granulomata induced by kaolin, hydrocephalus, hydromyelia, and the age of the syrinx, the pathological features of human subjects specified above closely resemble those of cervical cavitation in our kaolin model, and the vascular impairment of the cervical cord may provide a reasonable explanation for the initial process of noncommunicating syringomyelia associated with Chiari I malformation. Further experimental studies using other models will be required to confirm whether tonsillar herniation can affect venous drainage of the cervical cord below the level of neuraxial compression.

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