An experimental model for chronic communicating hydrocephalus

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A reliable technique is described for producing chronic communicating hydrocephalus in experimental animals. This involves the injection of Silastic into the basilar cisterns by way of a cisterna magna puncture. This model proves to be very useful in studying the physiology of chronic communicating hydrocephalus and allows the evaluation of the condition by isotope cisternography.

KEY WORDS: communicating hydrocephalus, experimental model, cisternography, Silastic injection

CURRENT investigations of the pathophysiological mechanisms involved in communicating hydrocephalus have been limited by the lack of a satisfactory animal model. Several methods to produce communicating hydrocephalus have been reported. Some proved to be too traumatic to the animal to be utilized in a chronic time frame; others produced inflammation and closure of the outlets of the fourth ventricle and non-communicating hydrocephalus. The rest did not reproduce the clinical circumstances of chronic communicating hydrocephalus.\(^\text{3,5,6,7,13}\)

This report describes a simple, successful, and relatively atraumatic technique to produce chronic communicating hydrocephalus. This model allows differentiation of the various phases in a manner similar to that employed in patient evaluation.

Materials and Methods

We used 64 dogs, 2 cats, and 12 primates under intravenous sodium pentobarbital or light inhalation anesthesia, with and without tracheal intubation. The animals were placed in the right lateral recumbent position. By using the external occipital protuberance and wings of the atlas as anatomical landmarks, the middle of the cisterna magna was identified, and the overlying skin was shaved, washed with an aseptic solution, and draped. A longitudinal skin incision of 3 to 5 mm was made, and the midline was punctured with a 17-gauge Bardic needle* whose inside diameter would accept a 19-gauge polyethylene catheter; the

*Bardic needle manufactured by C. R. Bard Corporation, Murray Hill, New Jersey.
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needle was angled laterally and superiorly to avoid the medulla and to facilitate subsequent passage of the polyethylene catheter into the area of the basal cisterns (Fig. 1 left). After clear cerebrospinal fluid had appeared at the needle hub, the catheter (the tip of which had been made radiopaque by dipping in powdered tantalum*) was advanced under fluoroscopic control into the area of the pontine and interpeduncular cisterns. Proper subarachnoid placement of the catheter was monitored by fluoroscopy and radiography; the flow of CSF through the catheter and CSF pressure were recorded by a pressure transducer.†

One to 2 cc of a Silastic material was injected into the basal subarachnoid space (Fig. 1 right). The mixture contained 3 cc of polysiloxane polymer, 3.5 cc of dimethylpolysiloxane, 2 drops of the catalyst stannous octoate, and 1 cc of powdered tantalum. The animal was then placed supine with the head hanging for 20 to 30 minutes to aid flow of the mixture anteriorly and superiorly.

An alternate technique for accurate injection of the Silastic material was used with the primates. Under basal anesthesia (Sernylan‡) the animals were placed in a skull-fixation device for posterior fossa exploration. A midline skin incision was made from the base of the occiput to the upper cervical spine, and dissection was carried down to the arch of the atlas. The cisterna magna was opened, and under direct vision a small Silastic catheter was passed through the subarachnoid space around the brain stem into a prepontine position (Fig. 2). The Silastic material was

*Powdered tantalum obtained from Fansteel Corporation, Baltimore, Maryland.
†Sanborn model 267A pressure transducer manufactured by Hewlett Packard, Waltham, Massachusetts.
‡Sernylan (phencyclidine hydrochloride) manufactured by Bio-ceptic Laboratories, Inc., St. Joseph, Missouri.

Fig. 1. Catheter technique of Silastic implantation in a rhesus monkey. Left: Artist's impression. Hatched area shows usual location of the Silastic at the time of the sacrifice. Right: Lateral skull radiograph in monkey for in vivo localization of the injected mixture (arrows).

Fig. 2. Drawing of surgical placement of polyethylene catheter. After posterior fossa exposure the catheter is threaded lateral to the medulla and cephalad prior to silastic injection.
then injected, the catheter withdrawn, and fascia and muscle were closed anatomically over the cisterna magna.

Serial cisternograms and measurements of transfer of the injected radiopaque mixture from the subarachnoid space into the blood were made to monitor the development of communicating hydrocephalus, which took 30 days in dogs and cats and 45 to 60 days in primates. Cisternograms were performed by injection of radiopharmaceutical medium (150 μCi 131I, 1 mCi 99mTc serum albumin, 500 μCi 111In, or 169Yb diethylenetriaminepentaacetic acid) into the subarachnoid space of the cisterna magna; lateral and vertex x-ray views were subsequently made at 30 minutes, 4 hours, and 24 hours.

Measurement of the transfer of labelled albumin into the blood was made by counting serial samples of whole plasma at various time intervals up to 24 hours, using the technique described by van Wart, et al.Ⅻ Chromatographic studies were obtained to determine the amount of “free” radionuclide not attached to the albumin label. (Greater than 2% “free” radionuclide was found to give spurious results regarding transfer. Thus, radiopharmaceutical quality was determined prior to the subarachnoid injection.)

Following documentation of the establishment of communicating hydrocephalus, the animals were sacrificed and various pathological and autoradiographic studies obtained. The methodology and results regarding serial CSF pressures, extracellular space calculations, and quantitative autoradiography will be presented in subsequent communications.

Results

The animals tolerated the procedure well. The Silastic mixture did not appear to cause any significant meningeal irritation if the puncture of the cisterna magna was atraumatic. Proximal localization of the injection was followed by rapid development of hydrocephalus with clinical signs of increased intracranial pressure. However, these symptoms had abated after several days of supportive therapy. In 7 to 10 days, the physical signs of the procedure had disappeared, and the neurological signs of developing hydrocephalus became evident; these included depression of mental alertness, and muscle incoordination, and were much more dramatic in dogs than in primates.

As hydrocephalus developed, the cisternograms revealed entry of the radiopharmaceutical into the ventricles. At first there was evidence of distal subarachnoid radioactivity and ventricular “clearing” in the delayed views. However, as the ventricles continued to enlarge they retained the radioactivity on the CSF images at 4 and 24 hours (Fig. 3). Following the initial ventricular enlargement, the hydrocephalus progressed for a period of time and then appeared to become arrested. With development of the chronic communicating hydrocephalus, measurement of transfer of radiopharmaceutical from the subarachnoid space into the blood was delayed in each time period sampled in 14 dogs (Fig. 4).

At autopsy the entire ventricular system was found to be enlarged (Fig. 5). Measurement of the distance between the dorsolateral angle of the ventricles revealed

![Fig. 3. Left lateral cisternogram in monkey 60 days after silastic implantation and following cisterna magna injection of 500 μCi 111In in diethylenetriaminepentaacetic acid (DPTA). This 6-hour study shows ventricular radiopharmaceutical entry.](image-url)
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Fig. 4. Graph of transfer of radio-pharmaceutical from the subarachnoid space in normal animals (N) compared with those with chronic communicating hydrocephalus (CH). Shaded area represents ± standard deviation.

an average width of 23.6 mm in the dogs studied (normal for dog is 11.8 mm). The range was 18 to 35 mm. In dogs, the Silastic mixture obliterated the subarachnoid spaces near the ambient cisterns, over the cerebral convexities, or in the parasagittal region, while primates showed a more proximal distribution.

Histologically the ventricular ependyma was flattened and denuded in some areas, especially at the ventricular angles (Fig. 6 left). There was periventricular edema, both intercellular and perivascular (Fig. 6 right); this differed from the normal control animals prepared in the same manner.

Detailed ultrastructural studies will be reported later. In general, there was loss of myelinated fibers. In the periventricular area there were electron-dense oligodendroglia and distented astrocytes with proliferation of glial filaments and prominent cytoplasmic pigment granules. The choroid plexus showed cytoplasmic granules and expansion of intercellular spaces. The endothelial cells of the capillaries appeared edematous. Inflammatory meningeal reactions, fibrosis, or histological evidence of a ventriculitis were all conspicuously absent.

Discussion

Initial reports have indicated that patients with chronic communicating hydrocephalus may benefit dramatically following a CSF diversionary shunt, and as a result there has been renewed interest in the pathophysiology of this disorder. Reconstruction of the clinical circumstances of chronic communicating hydrocephalus is obviously important in any related experimental study. The most common pathological findings have been obliteration of the subarachnoid space in the basal cisterns, the communicating CSF pathways (such as the ambient cisterns), the tentorial region, or over the cerebral convexities and around the arachnoid villi;4,12 these findings correlate well with reported pneumoencephalographic manifestations and appearance on CSF images (cisternograms). Although the clinical history in many patients with chronic communicating hydrocephalus is often incomplete, antecedent episodes of subarachnoid hemor-

Fig. 5. Left: Sagittal section of brain of rhesus monkey sacrificed 83 days after Silastic injection showing enlargement of the entire ventricular system. Right: Coronal section of brain of animal sacrificed at 113 days showing dilatation of the body and temporal horns of the lateral ventricle.
rhage, meningitis, or trauma can frequently be elicited.\textsuperscript{10,12,13}

Thus, the most common background for chronic communicating hydrocephalus is obliteration of the peripheral subarachnoid pathways. Silastic, introduced by a noninflammatory procedure, effects this obstruction with minimal morbidity or mortality in the experimental animal. By employing the proper mixture of rubber, diluting fluid, and catalyst, the required properties of flow and localization can be obtained. With a silicone oil it is difficult to control the anatomical localization of the obstruction;\textsuperscript{14} in larger animals the silicone oil, in our experience, will either surround the cerebellum and collapse the fourth ventricle or enter the fourth ventricle through the outlet foramina and produce a noncommunicating hydrocephalus. When a mixture is used that is viscous when injected but becomes solid in a predictable time, obstruction of these outlets can be avoided.

Several animal models have been proposed to produce communicating hydrocephalus.\textsuperscript{1,7,8,14} Some cause such an inflammatory meningeal response that many animals die as a result of the procedure.\textsuperscript{7} In animals that survive, histological and ultrastructural changes secondary to the inflammatory process are difficult to separate from those due to the communicating hydrocephalus. Other preparations that have been reported to produce communicating hydrocephalus do so only rarely; thus, the yield is too low to be useful. More commonly the ventricular outlets are obstructed, and noncommunicating hydrocephalus results. Other models, such as occlusion of the venous return, produce a very mild type of nonprogressive communicating hydrocephalus.\textsuperscript{2} Thus, none of these models duplicates the anatomical substrate of chronic communicating hydrocephalus as it is encountered clinically. On the other hand, the ventricles in our Silastic model progressively enlarge.
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for 4 to 6 weeks in the dog and 6 to 12 weeks in the primate before some type of compensatory level is reached. Whether this time difference represents a relation between the amount of injected Silastic to the size of the peripheral subarachnoid space or to a species difference is unknown.

The use of CSF-imaging by subarachnoid injection of a proper radiopharmaceutical is well established clinically as a reliable method to detect and characterize hydrocephalus. It has been effectively employed in dogs\textsuperscript{9,10} and primates.\textsuperscript{1,4} Serial patterns showing progression from ventricular entry with clearing to ventricular entry with stasis correlate with those encountered clinically in patients following subarachnoid hemorrhage\textsuperscript{13} and meningitis.\textsuperscript{10} The change in transfer rate is less commonly employed clinically but appears to correlate well with ventricular entry at cisternography.\textsuperscript{5} The relation of both the image and quantitative abnormalities to communicating hydrocephalus is supported by pathological documentation. Minimal ventricular enlargement can be present without entry of the radiopharmaceutical at cisternography or a change in the transfer curve. However, when these abnormalities are present in the diagnostic studies, moderate-to-marked ventricular dilatation has been seen in all animals pathologically.

Certain fundamental alterations associated with chronic communicating hydrocephalus have not been elucidated because a model for long-term observations has not been available. The alternative pathways of CSF absorption in chronic communicating hydrocephalus have not been identified. Coexistence of markedly dilated ventricles, peri-ventricular edema, and normal CSF pressure measurements remains unexplained,\textsuperscript{5} and the reason why certain patients respond dramatically to CSF diversionary shunts is not known.

References


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