CIRCULATION OF THE CEREBROSPINAL FLUID

DEMONSTRATION OF THE CHOROID PLEXUSES AS THE GENERATOR OF THE FORCE FOR FLOW OF FLUID AND VENTRICULAR ENLARGEMENT*

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This paper presents an experimental test of the assumption that the force of formation of cerebrospinal fluid causes the cerebrospinal fluid to circulate and the ventricles to enlarge when its pathways are blocked. These experiments show that this assumption is wrong and a new description of the circulation of the cerebrospinal fluid is given.

It has always been assumed that the cerebral ventricular enlargement of hydrocephalus was caused by the back pressure of blocked circulation of the cerebrospinal fluid, but this has never been put to experimental test. The clinical facts of hydrocephalus leave no doubt that if some cerebrospinal fluid escapes from the cerebral ventricles internal hydrocephalus will be prevented or cured, if established, and experimental work has generally confirmed these facts. Dandy, in his experiments on hydrocephalus and formation of cerebrospinal fluid in dogs, removed the choroid plexus from one lateral cerebral ventricle, plugged the foramen of Monro on the same side, and then occluded the aqueduct of Sylvius. In this animal there was an enlargement of the ventricle with the choroid plexus present and the foramen of Monro open, while the other lateral ventricle remained unchanged. This was interpreted as demonstrating that the choroid plexus produced the cerebrospinal fluid, and this has remained as the basic experimental work showing that the choroid plexuses were the major source of the cerebrospinal fluid. This conclusion was based upon the assumption that a symmetrical hydrocephalus would result from the pressure of accumulated cerebrospinal fluid if the choroid plexus of one lateral ventricle was removed, the foramen of Monro left open, and the aqueduct of Sylvius occluded. However, this assumption was never tested experimentally either by Dandy or others who repeated his work.

MATERIALS AND METHODS

Mongrel dogs weighing 15 to 20 kg. were the experimental animals. The procedures carried out were unilateral and bilateral ventriculotomy, unilateral choroid plexectomy with and without occluding the foramen of Monro on the same side, and bilateral choroid plexectomy. These procedures were tested for their effect, in the otherwise normal animal, on the development of hydrocephalus and on hydrocephalus induced previously.

The surgical procedures of ventriculotomy and choroid plexectomy were done aseptically in a manner similar to that of others. Hydrocephalus was produced by intracisternal injection of 0.25 to 0.5 gm. kaolin suspended in cerebrospinal fluid which produced a sterile reaction occluding the outlets to the 4th ventricle. Three to 4 weeks were allowed between any two procedures. Measurements of pressure were made with Statham strain gauges led to a Sanborn recorder. At the time of sacrifice the animals were given a lethal dose of pentobarbital, and the carotid arteries were cannulated, washed out with saline and then irrigated with 3 or more liters of 10 per cent formalin solution. The brain then was removed, and examined for ventricular size and completeness of the choroid plexectomies.

RESULTS

Ventriculotomy. Bilateral ventriculotomies were made in 2 normal dogs which were

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sacrificed 5 and 16 weeks later. The cortical scars had healed completely. The ventricles of these dogs were slightly larger than normal in size, but they were symmetrical without any distortion of the mid-line structures.

Unilateral ventriculotomies were done on 3 dogs and after intervals of 4, 6 and 8 weeks kaolin was injected intracisternally. They then were sacrificed 3, 4 and 12 weeks later. In all 3 animals hydrocephalus had developed and the cortical scars were healed and solid. In the 3-week animal there was some intraventricular scarring around the cortical incision in the body of the ventricle with slight asymmetry of the bodies of the ventricles, but there was no shift of mid-line structures and there was complete symmetry of the anterior and temporal horns. Difference in ventricular size was not apparent in the 4- or 12-week animals. The 4th ventricle of all animals had enlarged as expected.

Bilateral ventriculotomies were made in 3 normal dogs and then after periods from 2 to 6 weeks kaolin was injected intracisternally. In all these dogs symmetrical hydrocephalus developed including enlargement of the 4th ventricle and aqueduct of Sylvius. One animal had transventricular adhesions under the cortical scar, but in spite of this there was still a symmetrical enlargement of the ventricular system. The adhesions were stretched across the ventricle without distorting the mid-line structures. There were no adhesions on the opposite side which might have had a restraining influence on distortion (Fig. 1).

Unilateral ventriculotomy was carried out in 4 dogs previously made hydrocephalic. They died or were sacrificed at 1 day, 2 days, 4 weeks, and 12 weeks. The 2 dogs that died at 1 and 2 days postoperatively were not remarkable. The other 2 both showed well healed cortical scars and symmetrical hydrocephalus. In the 12-week animal the side with the ventriculotomy was larger than the other because of atrophy around the cortical incision, but there was no mid-line distortion.

Bilateral ventriculotomy was carried out in 5 hydrocephalic dogs which were sacrificed after another 3 weeks. They all showed well healed scars with symmetrical bilateral hydrocephalus.

In summary, experiments on 13 animals showed that ventriculotomy, unilateral or bilateral, will not affect the development of a symmetrical enlargement of all the cerebral ventricles following a cisternal injection of kaolin. Particularly important was the observation that the development of transventricular adhesions following surgical procedures did not prevent ventricular enlargement nor cause distortion or shift of mid-line structures.

**Unilateral Choroid Plexectomy Without Blocking the Foramen of Monro.** Experiments with unilateral choroid plexectomy without blocking the foramen of Monro were carried out in 19 animals, with 11 satisfactory survivors with complete choroid plexectomies. Five of these animals were subjected to unilateral plexectomy and then made hydrocephalic and the other 6 animals were hydrocephalic before plexectomy.

The 5 animals that had plexectomy before production of hydrocephalus were sacrificed 3 to 9 weeks after the injection of kaolin. The cortical incisions were all healed solidly. In all animals, there was enlargement of the lateral ventricle with the choroid plexus still present while the ventricle without the

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**Fig. 1.** A coronal slice from brain of a dog which had in turn bilateral ventriculotomy, hydrocephalus produced by cisternal kaolin, and sacrifice 10 weeks later. Transventricular scarring did not prevent ventricular enlargement nor cause mid-line shift or distortion.
choroid plexus did not enlarge or was much smaller (Fig. 2).

The degree of enlargement of the lateral ventricle with the choroid plexus present was dependent upon the time between injection of kaolin and sacrifice. Any enlargement of the plexectomized side was most pronounced at the region of the foramen of Monro, where, in 1 animal, it approached symmetrical enlargement. However, in spite of this local enlargement, the remainder of the ventricle was smaller than the opposite side both anteriorly and posteriorly. There was a shift of mid-line structures toward the plexectomized side which seemed to be related to the degree of enlargement of the ventricle with the choroid plexus intact.

One of these animals also had a ventriculotomy on the side opposite the choroid plexectomy. This procedure did not alter the results and asymmetrical hydrocephalus developed with shift of structures toward the side of the plexectomy in spite of transventricular scars which occurred in the region of the ventriculotomy on the side with the choroid plexus (Fig. 3).

The 4th ventricles of all these animals were enlarged to the expected degree.

The 6 hydrocephalic animals that had a unilateral choroid plexectomy without blocking the foramen of Monro were sacrificed at intervals of 2 to 13 weeks after operation. All but 1 animal showed a progressive collapse of the ventricle from which the choroid plexus was removed, and, concomitantly, a continued enlargement of the opposite ventricle with shift of mid-line structures toward the side of the plexectomy. The 4th ventricle was always enlarged the expected amount (Fig. 4).

In 1 animal sacrificed 5 weeks after plexectomy, the ventricles remained almost equal in size. This animal had no septum pel- lucidum and the ventricles were united as one large cavity (Fig. 5).

Unilateral Choroid Plexectomy With Occlusion of the Foramen of Monro. Unilateral choroid plexectomy with occlusion of the foramen of Monro on the same side was carried out in 14 hydrocephalic dogs with satisfactory survival in 10 animals. These animals, sacrificed at intervals of 1 week to 4 months after operation, showed a decrease in the size of the plexectomized ventricle, and a steady increase in the size of the opposite ventricle with a concomitant shift of the mid-line structures toward the side of the plexectomy. The 4th ventricle enlarged in the
whether the foramen of Monro was open or closed.

Bilateral Choroid Plexectomy. Bilateral choroid plexectomy was done in 3 normal dogs which were sacrificed 8 and 16 weeks later. These animals showed some transventricular adhesions and some slight enlargement which was about the same as that seen with ventriculotomy in normal dogs.

Bilateral choroid plexectomy with subsequent intracisternal kaolin was done in 4 dogs with sacrifice 2 to 16 weeks after injection of kaolin. The lateral cerebral ventricles of these animals were only slightly larger than in the animals that did not receive kaolin. The development of transventricular adhesions did not cause shift or distortion of mid-line structures. The enlargement of the 4th ventricle was equal to that of the controls and proceeded at the expected rate.

Bilateral choroid plexectomy was carried out on 9 hydrocephalic dogs which subsequently were sacrificed after 5 days to 5 months. Such animals showed a decrease in ventricular size following plexectomy, but never a return to normal size. The greatest amount of collapse occurred in the body of the ventricle in the region of the incisions, but it remained open. The 4th ventricle was of expected size at the time of sacrifice.

DISCUSSION

These experiments confirm the work of other investigators but in addition they provided a new and very important observation. This was that symmetrical hydrocephalus did not develop nor was it maintained in an animal subjected to a unilateral choroid plexectomy with the foramen of Monro open.

Hassin et al. suggested that the ventricular collapse and the mid-line distortion that follow unilateral choroid plexectomy were the result of transventricular adhesions and formation of scar at the site of the cortical incision. The ventriculotomy experiments reported here show that transventricular adhesions do not prevent ventricular enlargement in developing hydrocephalus, cause collapse in established hydrocephalus, or cause a mid-line shift (Figs. 1 and 3). The
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Fig. 4. Four coronal sections from brains of hydrocephalic dogs which had unilateral choroid plexectomies with the foramina of Monro left open showing progressive collapse of the ventricle without the choroid plexus.

(A) N-145-54, right ventriculotomy, 12 wks. before
(B) N-42-54, right choroid plexectomy, 5 wks. before
(C) N-1-54, right choroid plexectomy, 6 wks. before
(D) N-162-54, right choroid plexectomy, 13 wks. before

Scarring that occurred after plexectomy sometimes seemed to be greater than after ventriculotomy, and it might be argued that the interposition of the tissue of the choroid plexus between the walls of the ventricle might prevent sufficient scarring to keep the ventricle from expanding. However, this would not explain the small size of the frontal and temporal horns, the failure of the ventricle to collapse when the septum pel- lucidum was absent, or the gradual decrease in ventricular size after unilateral choroid plexectomy in established hydrocephalus.

The conclusions from this are that formation of scars and adhesions can not account for the results observed, and that the distortion of the mid-line structures does not keep the ventricle without a choroid plexus from enlarging but that a ventricle without a choroid plexus remains small or collapses because of the absence of any positive force expanding it.

Hydrocephalus was produced in these animals by blocking the outlets of cerebrospinal fluid of the 4th ventricle and any back pres-

Fig. 5. Coronal section of brain of hydrocephalic dog which had right unilateral choroid plexectomy 6 weeks before sacrifice, showing symmetrical ventricular enlargement and absence of septum pellucidum.
sure from retention of fluid was directed into all of the cerebral ventricles. This should have resulted in a symmetrical enlargement of the entire ventricular system if the pressure from retention of fluid alone was responsible for the enlargement regardless of the site of formation of fluid. A decrease in production of fluid might have decreased the rate of ventricular enlargement in developing hydrocephalus, or caused a temporary decrease in the ventricular size in already established hydrocephalus, but the net result from an increase in pressure caused by retention of fluid should have been a symmetrical ventricular system. The fact that this did not occur leads to the conclusion that the pressure produced by retention of fluid was not the major force causing ventricular enlargement, and that some other local force must have been responsible for the marked variation in ventricular size.

Ventricular enlargement will occur only if there is a difference in pressure between the cerebrospinal fluid and the brain, which these experiments showed was not created by back pressure of blocked flow of cerebrospinal fluid. They did indicate that the presence of the choroid plexus was important to the development of ventricular enlargement or for the prevention of collapse, and, therefore, it must provide some local force to do this. The choroid plexuses do generate an adequate local force through the pressure wave that they transmit to the cerebrospinal fluid as they fill with blood with each pulse. This compression wave normally is absorbed in part by the brain, in part by pumping cerebrospinal fluid out of the ventricular system, and finally by the venous system over the cerebral hemispheres. If either or both the pathway of cerebrospinal fluid and the flow of venous blood out of the cranial vault is blocked this compression wave will not be damped, the pulse pressure will increase and the brain will have to absorb the entire force. The result of this is ventricular enlargement.

This hypothesis can explain all of the experimental results without any assumptions. A compression wave such as the one generated by the choroid plexus travels away from its source in a straight line and does not turn a corner unless reflected. In a lateral cerebral ventricle the choroid plexus is elongated and produces a pressure wave which is directed toward the ventricular walls around it, and
only reflected waves would reach the opposite ventricle through the foramina of Monro. The fact that there is not reflection of the pulse wave from one ventricle to another (Fig. 7) indicates that it is absorbed by the ventricular walls which yield to this pressure with eventual ventricular enlargement.

The almost symmetrical enlargement of both ventricles sometimes seen at the level of the foramina of Monro (Fig. 2) was the result of the pulse wave from the choroid plexus on one side as it goes through the foramen of Monro and enters the 3rd ventricle passing in a straight line through the other foramen of Monro to hit the lateral wall of the opposite ventricle. Because it was not reflected anteriorly or posteriorly there was little or no effect on the anterior and posterior horns. When the septum pellucidum was absent, there was no barrier to this pressure wave passing into both ventricles, and it is seen that symmetrical enlargement of the ventricular body results under these conditions (Fig. 4). In those animals in which the plexectomy was incomplete the wave was small, local, and caused only a slight local enlargement.

The distortion of the mid-line structures, which developed gradually when one choroid plexus was removed, also can be explained by the pulse wave. With each pulsation the mid line was subjected to a compression wave on one side unopposed on the other (Fig. 7), an unequal strain which caused the wall gradually to give way and the ventricle enlarged to the unsupported side, distorting the mid-line structures. It is important to point out again that this was not the thing that kept the ventricle on the opposite side from enlarging, but rather it was the absence of any positive force within the collapsed ventricle expanding it.

The arterial pulse wave is transmitted by the cerebrospinal fluid to the venous system and can be recorded in the cerebral veins, the dural sinuses and the upper part of the internal jugular vein (Fig. 8). The venous pressure in the dural sinuses is nearly that of the cerebrospinal fluid, but as soon as the blood leaves the skull the venous pressure drops quickly and the arterial pulse wave fades out. Block of the cerebral venous outflow from the skull will prevent the final dissipation of this pulse wave, the intracranial pulse will rise, and the extra energy will be absorbed in the ventricles by the brain. It has been demonstrated experimentally that hydrocephalus will develop following chronic increase in the cephalic venous pressure. In these experiments on

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**Fig. 7.** Intraventricular pulse measured simultaneously from ventricles of a dog with unilateral choroid plexectomy on the right and both foramina of Monro open.

**Fig. 8.** Recording of venous pressure from a 1-year-old infant showing disappearance of arterial pressure wave and drop in pressure as blood leaves the skull. (S) Recording from sigmoid sinus intracranially. (C1) Recording from internal jugular vein at level of 1st cervical vertebra. (C3) Recording from internal jugular vein at level of 3rd cervical vertebra.
normal animals, their brains untouched and formation and flow of cerebrospinal fluid unaltered, hydrocephalus developed when the cephalic venous pressure was increased by occluding the venous drainage in the neck and spine. The increase in venous pressure by distending the cerebral venous system blocked its damping effect. The pulse of cerebrospinal fluid was increased 20–30 mm. H₂O in the animals in which hydrocephalus developed, and when it was not increased hydrocephalus did not occur. The degree of hydrocephalus was related to the increase in the pulse of cerebrospinal fluid, with the larger pulse causing the greater degree of ventricular enlargement.

The experiments recorded here give very little information about the bulk formation of cerebrospinal fluid, but the problem must be considered. It was mentioned in the introduction that Dandy assumed in the interpretation of his experiments on the formation of cerebrospinal fluid that if the choroid plexus of one lateral ventricle was removed, the foramen of Monro left open and then the animal made hydrocephalic, symmetrical hydrocephalus would result. This assumption has been shown to be wrong, and therefore, Dandy’s experiments cannot be considered as proof that the choroid plexuses are the major source of cerebrospinal fluid. Cerebrospinal fluid has been shown to come from both the choroid plexuses and from the ventricular wall, but the proportion from each site remains to be demonstrated. The experiments reported here give no information as to the site of formation but suggest that the cerebrospinal fluid is formed passively to fill any available space and the force of production of cerebrospinal fluid is small in relation to the force of the pulsation of the choroid plexus.

From the evidence and experiments cited it can be inferred that if the choroid plexuses supply the pumping force of the circulation of cerebrospinal fluid and if the pressure of formation is relatively small, the removal of the plexuses should cause a drop in pressure of cerebrospinal fluid to a level near the venous pressure of the sagittal sinus, which is the controlling hydrostatic pressure of outflow of cerebrospinal fluid. This has been found by experiment to be the case. The pressure of cerebrospinal fluid of normal dogs was found to be 99 (±2.4) mm. H₂O, and after bilateral choroid plexectomy it fell to 72 (±4.2) mm. H₂O. This was clearly a significant drop in pressure and the final pressure was very nearly that in the sagittal sinus.

SUMMARY

1. Symmetrical hydrocephalus did not occur in dogs when the choroid plexus was removed from one lateral cerebral ventricle, the foramen of Monro left open and the animal made hydrocephalic. The ventricle without the choroid plexus remained small or did not enlarge. If a unilateral choroid plexectomy was done in established hydrocephalus that ventricle collapsed while the opposite one continued to enlarge.

2. It was concluded that the back pressure of blocked flow of cerebrospinal fluid was not the force causing ventricular enlargement, but rather it was caused by a special local force produced by the choroid plexus.

3. The cerebrospinal fluid is circulated actively by the choroid plexuses which generate their pumping force as they fill with blood with each arterial pulse. This creates a compression wave in the cerebral ventricle which normally is absorbed in part by the brain, in part by pumping of the cerebrospinal fluid out of the ventricles and finally by the veins over the surface of the brain. When either or both pathways of cerebrospinal fluid or venous drainage of the cranial vault are blocked, the intraventricular pulse is increased correspondingly and this entire force must be absorbed by the brain. The ventricular walls yield to this pressure wave rather than reflect it, and ventricular enlargement results.

4. These experiments give little or no information about the site of formation of cerebrospinal fluid. They do demonstrate that the basic assumption Dandy used in the interpretation of his experiments was
and his work does not prove that the choroid plexuses are the major site of formation of cerebrospinal fluid. This may be so but it remains to be proven.

REFERENCES