Aqueductal Stenosis with High Protein Concentration in Ventricular Fluid

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Congenital hydrocephalus is caused by either overproduction of cerebrospinal fluid (CSF) or obstruction in the cerebrospinal passageways. The former may commonly result from a congenital hypertrophy of the choroid plexus and the latter is sometimes the result of abnormalities of neural development. There are several strategic sites of the obstruction in the CSF pathways such as the foramen of Monro, aqueduct of Sylvius, foramina of Luschka and Magendie.

Narrowing or closure of the Sylvian aqueduct is considered to be a common cause of obstructive hydrocephalus. Sometimes the infant with congenital hydrocephalus of this type is manifested clinically by enormously large head and intracranial hypertension, which leads to eventual death unless adequate surgical intervention is not made in the earlier stage of life.

The reported case is a congenital hydrocephalus due to aqueductal stenosis with unusually high concentration of protein in ventricular fluid. He was treated by ventriculo-atrial shunt with a special maneuver such as dilution of ventricular fluid and survived for nine months following the operation.

CASE REPORT

A 27 day-old male baby was admitted on March 10, 1966 because of abnormally large head. He had been diagnosed as congenital hydrocephalus during his intrauterine life by X-ray examination and had been delivered at a full term by Caesarean operation. Body weight at a birth had been 4750 gm., and 48.5 cm. in circumference of the head.

On admission, there was enormous enlargement of the head. Circumference of the head was measured as 54.5 cm. The scalp was tense with thin hairs and

dilatation of the veins was conspicuous over the scalp (Fig. 1). The fontanella was widely open and was felt tense when pressed by fingers. Cracked pot sound was characteristically heard on percussion of the head.

In spite of such unusual outlook of the head, his general condition was maintained well. Sucking power was vigorous and the amount of daily sucking was normal though vomiting occasionally occurred. No neurological abnormalities were found out.

Very thin skull all over the cranial vault was demonstrated by plain films. Pneumoventriculography revealed a huge ventricular cavity and extremely thin cerebral cortex (Figs. 2 & 3). Particularly along the midline in the occipital region, cerebral substance was appeared to be membraneous. Ventricular air did not enter into the fourth ventricle in "upside down" position (Fig. 3).

Ventricular tap was made with a pressure of 550 mm H_2O. Ventricular fluid was yellowish colored. Protein concentration of the ventricular fluid was as high as 468 mg/dl, sugar 48mg/dl, chloride 405 mg/dl, cell count 2/3.

Although lumbar puncture was unsuccessful, colorless fluid was found to be soaked into the cloths around the site of puncture following the tap.

Ventriculo-atrial shunt was performed on March 24, 1966 using a Pudenz-Heyer valve. Postoperatively, remarkable flattening of the head was resulted. Posterior margin of the frontal bone appeared to be sunken beneath the parietal bones owing to a rapid shrinkage of intracranial contents. Circumference of the head decreased to 52.0 cm. Vomiting ceased and the amount of sucking was gradually increased until 2 weeks later when vomiting was resumed. There was a leak of ventricular fluid from the operative wound around the flushing device at that time.

Shunt valve was removed at the 19th postoperative day. The openings at the tip of the ventricular catheter were completely plugged with white fibrinoid substances.

Following the removal of the shunt, repeated ventricular taps were carried out in order to relieve vomiting. Protein concentration of the fluid was consistently high up to 2275 mg/dl. at the time of the second shunt procedure on May 19.

Prior to the placement of a new shunt valve, such attempt was made that the protein-rich ventricular fluid was diluted with Ringer solution in order to prevent occlusion of the ventricular catheter. Two litters of Ringer solution was required until orange-colored fluid was diluted to become light yellowish color. After dilution of the ventricular fluid, protein concentration decreased to 287 mg/dl. The concentration of ventricular fluid proteins along the hospital course were followed during a period of more than 200 days and traced in Fig. 4. Paper electrophoresis of both fluids before and after the dilution apparently indicated that the albumin fraction was selectively diluted in comparison with other fractions relating globulin (Fig. 5).

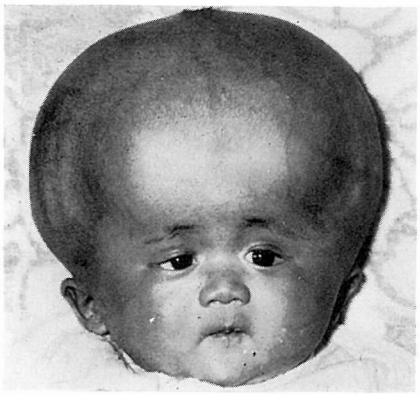

Fig. 1. Outlook of the patient's head on admission. Enormous size of the head with thin hairs and venous dilatation is seen.

Fig. 2. A brow up lateral pneumogram shows marked dilatation of the ventricular system with only less than 1 cm. thickness of the cerebral cortex anteriorly.

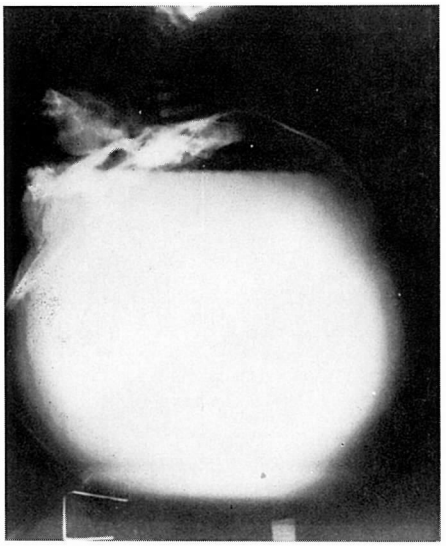

Fig. 3. Lateral ventriculogram, made with the patient inverted. The air bubble was freely traced around the cranial vault to become lodged against the tentorium cerebelli and the dorsal surface of the cerebellum.

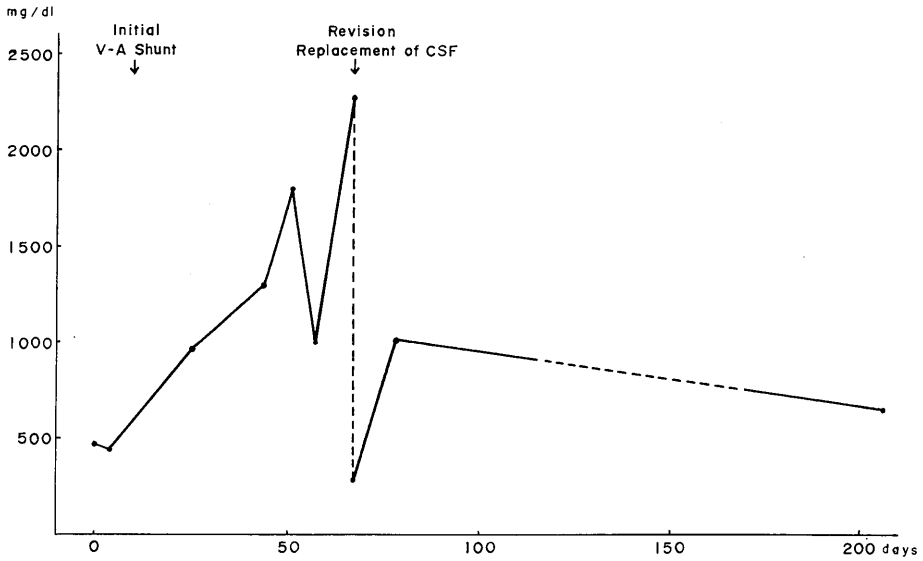

Fig. 4. Protein concentration of ventricular fluid, traced from the time of admission (0 day) to 5 months after the final operation.

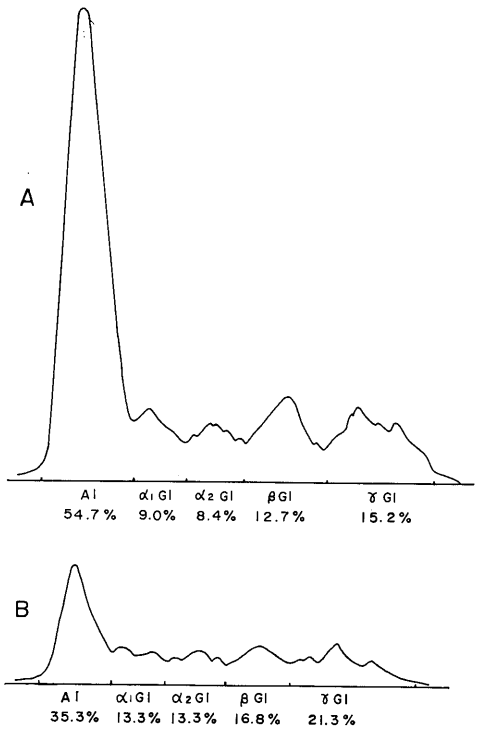

Fig. 5. Paper-electrophoresis of ventricular fluid before (A) and after (B) the dilution of the fluid at the time of revision of ventriculo-atrial shunt.

Postoperative course was uneventful and the patient regained his vitality. Circumference of the head was measured as 53 cm. at the time of discharge on June 10, 1966.

Getting out of the hospital care, he grew up normally though mental development was retarded. When he was seen at the outpatient clinic five months after the final operation, his unproportionated outlook of the head was largely improved, while the shape of his head was still abnormally flattened (Fig. 6). Instead of persistently high concentration of protein in ventricular fluid (Fig. 4), no sign of obstruction was recognized in the ventriculo-atrial shunt system.

Occasional informations were heard from his parents thereafter that he was being well and growing up normally except for mental retardation until eight months after the discharge.

He suffered from acute pneumonia with high fever and vomiting on January 31, 1967. General condition became worse rapidly and dyspnea developed. He died on the February 2, shortly after readmission to the hospital.

On autopsy, supratentorial cerebral ventricle was remarkably dilated forming a single cavity without differentiation of the lateral and third ventricles (Fig. 7). Cerebral cortex covered by thick dura mater was as thin as 1 to 3 cm. Particularly, near the midline in the occipital lobe, the cerebral cortex was extremely thined out and tightly attached to the dura mater. The choroid plexus was nowhere found even a trace over the ependymal surface of the monoventricle.

The aqueduct of Sylvius was occluded at the most caudal part. Serial section of the mesencephalic tissue showed a septum formation within the patent rostral portion of the aqueduct (Fig. 8). The fourth ventricle was found to be normal in size and shape. No obstruction of the communicating channels from the fourth ventricle to either the subarachnoid cisterns or the spinal subarachnoid spaces was found out.

Histologically, ependymal lining of the aqueduct of Sylvius was stretched (Fig. 9) in contrast to that of the fourth ventricle, where the arrangement of the ependymal cells appeared to be nearly normal (Fig. 10) and there was the normal choroid plexus. In addition, forking of the aqueduct was characteristically seen in the periaqueductal tissues (Fig. 9). In the mesencephalic tissue being more remote from the aqueduct, some glia nodules were observed suggesting an inflammatory process in the basis of this malformation (Fig. 11).

The ependymal lining of the monoventricle was completely destroyed and was covered by the network of the capillaries, while the vestige of the ependyms was fragmentally burried in the subependymal tissues (Fig. 12). Characteristic arrangement of nerve cells was seen in the cerebral cortex of the temporal lobe; grouping of the cortical nerve cells in columner blocks separated from one another by acellular strips (Fig. 13). Pia mater covering the cerebral cortex was greately hyperemic (Fig. 14).

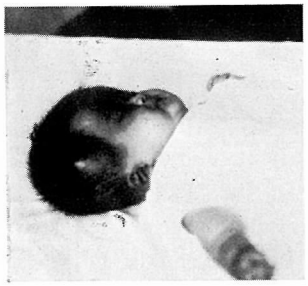

Fig. 6. Outlook of the patient's head 5 months after the final operation.

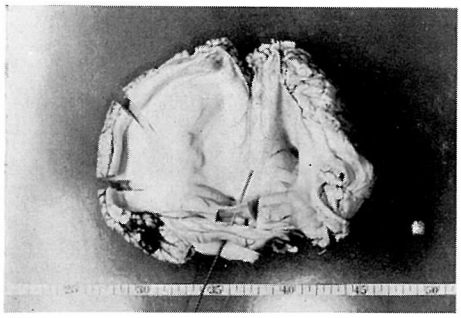

Fig. 7. Formalin fixed cerebrum. Dilated cerebral ventricle is opened at the base of the brain. The lateral and third ventricles are fused together to form a large single cavity covered with thick ependymal lining. Remarkable thinness of the cerebral cortex is noted. The choroid plexus is nowhere found out on the wall of the ventricle even a trace. The hind-brain structures and a part of the mid-brain tissue within which the aqueduct of Sylvius was obstructed were removed. A metal sound is inserted through the cephalic end of the fourth ventricle and patent rostral portion of the iter.

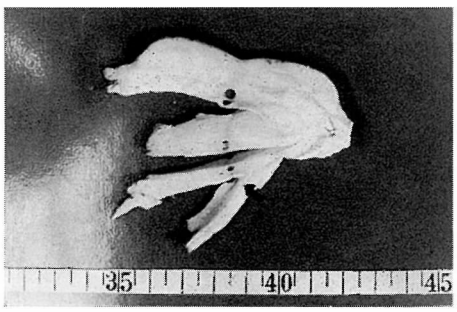

Fig. 8. Serial sections of the mid brain structure. The site of obstruction of the aqueduct is indicated with arrow in the lowest segment of the slices. Septum formation within the patent rostral part of the iter is demonstrated on the upper two slices.

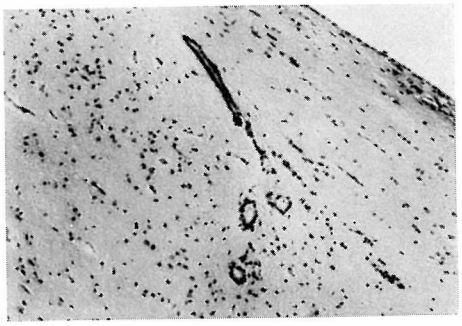

Fig. 9. Photomicrograph of the periaquedctal tissue shows flattened ependymal cells and forking of the aqueduct. H. & E. ×150

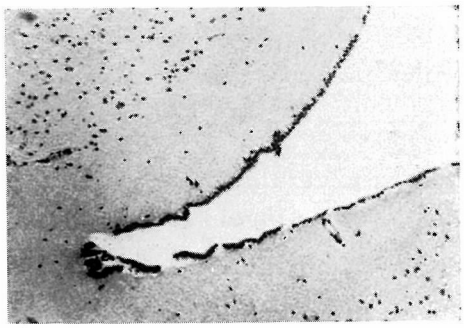

Fig. 10. Ependymal lining of the fourth ventricle shows nearly norml arrangement of ependymal cells. H. & E. ×150

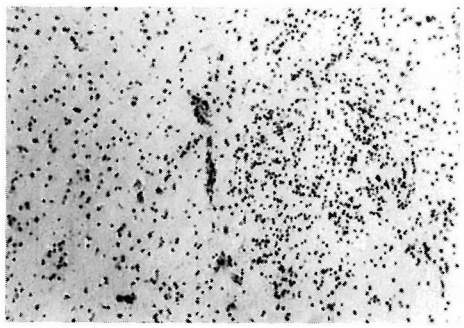

Fig. 11. Glia nodule appearing in the mesencephalic tissue. H. & E. ×150

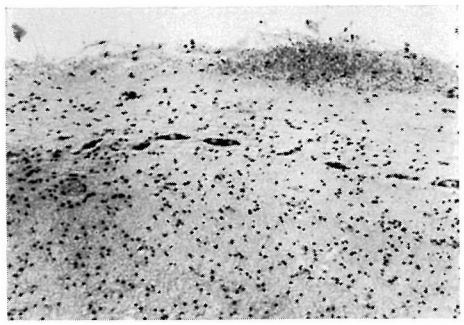

Fig. 12. Ventricular surface of the cerebrum. Ependymal lining is completely destroyed and covered by the network of the capillaries. The vestige of the ependyms is fragmentally burried in the subependymal tissue. H. & E. ×150

Fig. 13. Cerebral cortex in the temporal lobe. Characteristic arrangement of nerve cells, "columner grouping" is seen. H. & E. ×60

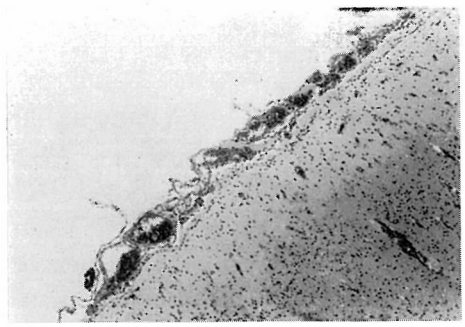

Fig. 14. Pial surface of the cerebral cortex. Pia mater is appeared to be greately hyperemic. H. & E. ×100

DISCUSSION

Four main types of aqueductal malformation have been described by Russell.[20] The first of them is "stenosis of aqueduct", which is defined as an abnormally small aqueduct without any histological abnormalities. This condition is thought to be a rare kind of aqueductal lesion.

The second category of maldevelopment is "forking of the aqueduct". This is a common cause of congenital hydrocephalus, previously described by the term "atresia". Usually two main channels of greately reduced dimensions are found in the midsagittal plain of the brain stem and separated by normal intervening tissue. These channels often branch off and some of these branches may end blindly. Even if there is a patency in some of them, narrowed lumen may be thought to be functionally inadequate.

The third entity is "septum formation". Norman[18] stated that some of these cases were associated with granular ependymitis of the ventricular system suggestive of an infection during intrauterine life.

Russell's last subspecies is "gliosis of the aqueduct". In this condition, there is an overgrowth of the subependymal neuroglia of a densely fibrillary charactor, leading to narrowing of the lumen. The pathogenesis of the gliosis is obscure.

There are two preferential sites of stenosis; the one beneath the middle of the superior corpora quadrigemina, the other at the level of the intercollicular sulcus.[18] Regarding as the septum formation, Turnbull and Drake[23] described that membrane formation might result from a small glial occlusion of the caudal end of the aqueduct.

Autopsy specimen of the present patient revealed an obliquely placed septum within the aqueduct as well as several accessory channels around the iter (forking). The former apparently was thought to be the main cause of the obliteration. Although granular ependymitis was not demonstrated, glia nodules in the mesencephalic tissue was suggestive of an inflammatory process during foetal life in the basis of this malformation.

A striking clinical feature of this patient is unusually high concentration of protein in ventricular fluid. Considering the source of this fluid, question arises as to where and how the fluid was produced with lack of the choroid plexus within the closed cavity.

It is well known that when a complete spinal block exists accumulation of protein occurs in the lumbar space distal to the block. Sweet and cowerkers,[22] employing intravenously injected RISA, have presented evidence that the increased concentration of protein below the block is secondary to a defect in absorption

or removal of protein.

The situation was reversed in our patient. Colorless fluid, with contrast to orange-colored ventricular fluid, was observed to leak following unsuccessful lumbar puncture, while no analysis of protein was made on the spinal fluid. Reasonable explanation could not made about such curious phenomenon. It is likely, however, that relative integrity in the barrier mechanism between blood and CSF in the compartment caudal to the obstructed aqueduct may serve to maintain the production of the nearly normal fluid, whereas the defective blood-CSF barrier may be responsible for colored protein-rich fluid within the cerebral ventricle.

The normal concentration of total protein in the human lumbar fluid is given as 25 to 40 mg/dl., while in the ventricles and cisterna magna the concentration are less :[6] thus Hunter and Smith[14] gave the following figures for fluid drawn from the same subjects :

Ventricle	Cistern	Lumbar
15	36	59

Although the increasing concentration of protein from the ventricle to the lumbar region has not been satisfactorily explained, Fishman et al.[9] suggested that this phenomenon was a manifestation of greater permeability of the blood-CSF barrier to protein in the lumbar region.

An increase in the protein concentration of CSF is associated with a variety of pathological processes involving the central nervous system. Cutler et al.[4] demonstrated a 8 year-old girl with diffuse subarachnoid implants of medulloblastoma whose ventricular fluid contained slightly less than 400 mg/dl. of total protein and 1845 mg/dl. of albumin in lumbar fluid. They calculated CSF albumin turnover using ^{125}I serum albumin and concluded that over 2 gm. of albumin exchanged daily between blood and lumbar CSF in this particular case implied abnormal permeability of membranes separating plasma and CSF.

Normally the protein concentration in plasma is 200 times that in CSF, while the precise information is still lacking about the mechanism preserving such concentration gradient of protein between both fluids. Recently, attention has been attracted in the exchange mechnism of albumin between plasma and CSF. Existence of a dynamic equilibrium between plasma and CSF albumin was first shown in dog by Fishman[8] and in man by Frick and Scheid-Seydel.[12] These workers demonstrated that plasma albumin is the direct precursor of CSF albumin.

In order to elucidate the source of increased protein in CSF in pathological condition, several investigations have been carried out with use of radioisotopes or technique of electrophoresis. Cutler et al,[4] as mentioned above, calculated the efflux coeffecient, denoting the fractional daily removal of CSF albumin, in 17 children and found the constancy in the efflux coefficient over a wide range of CSF albumin concentration, while the daily flux of albumin between plasma

and CSF was found to vary directly with CSF albumin. They concluded from these data that increased vascular permeability to albumin, rather than delayed removal from the CSF, was implicated in the pathogenesis of elevated spinal fluid protein.

On the other hand, Hochwald and Wallenstein[13] studied the exchange of albumin between blood, CSF, and brain in cats during steady-state ventriculocisternal perfusion using cat serum albumin-^{131}I. They suggested from their experimental results that transfer of albumin from blood to CSF was only partially dependent on bulk fluid formation; a portion of the albumin probably entered from the surrounding nervous tissue.

Kabat et al.[16] first analyzed the electrophoretic patterns of serum and CSF protein in various diseases and concluded that the major portion of CSF protein was derived from blood. They found the component X which refered to a rapidly migrating fraction moving ahead of the albumin. It has been generally considered that this fraction, later designated as "prealbumin" by Esser,[7] is absent in the plasma.[10][15] Moreover, since the prealbumin fraction is always present in brain extracts,[3] the brain is considered to be a source of that found in the CSF. In fact, according to Steger,[21] the concentration of prealbumin fraction is greater in the ventricle, less in the cisterna magna and least in the lumbar fluid.

Summarizing the difference in electrophoretic patterns between serum and CSF, the latter contains the characteristical fraction of prealbumin, an outstandingly high proportion of β-globulin and a low γ-globulin proportion by comparison with serum.

A typical patterns of protein in serum and CSF are transcribed from description by Kabat et al.[16] in comparison with the data obtained from our patient in Table 1. Undoubtedly, the protein-rich ventricular fluid of this patient has closer proportion in protein fraction to serum rather than CSF. This suggests that the origin of protein in high concentration is not through a concentrating process within the closed ventricle. Likewise, rapid recovery of its high concentration following the dilution also suggests that the ventricular fluid might have abundance of protein even at the production.

	X	Albumin	α-Globulin	β-Globulin	γ-Globulin	A/G
Serum*	—	61.0	8.5	10.8	14.1	1.6
CSF*	5.2	67.3	5.1	20.4	7.2	2.1
CSF**	—	54.7	17.4	12.7	15.2	1.2

* Cited from Kabat et al. (16) ** Data from the present patient.

Table 1. Comparison of electrophoretic protein fractions between normal serum and CSF and those of the present patient. numerals are expressed as a unit of mg/dl. except for A/G. X represents the prealbumin fraction.

Since the experimental work by Dandy and Blackfan[5] in 1914, the choroid plexus has been considered to be the source of CSF. Recent investigations, however, revealed that the ventricular ependyma also produce the fluid in a half volume of that from the choroid plexus.[19] However, Davson[6] and Bering[1] have emphasized that the exchange of substance between the plasma and CSF must be distinguished from net changes in volume. As far as protein is concerned, the choroid plexus is considered to be most likely a source of a portion of it. However, Bering[2] found that removal of the choroid plexus did not affect the entry of RISA into the isolated lateral ventricle of the dog. Thus Fishman et al.[9] stated that the choroid plexus did not appear to be essential for the entry of albumin into the CSF and there were multiple levels of CSF protein exchange along the neuraxis in accordance with Sweet et al.[22]

Retrospective of our patient, the main pathological feature was constituted by obstructive hydrocephalus with absence of the choroid plexus. Histological study revealed the completely destroyed ventricular ependyma. In such unusual condition of the ventricular linings, normal blood-CSF barrier mechanism is assumed to be no longer maintained. Therefore, the boundary membranes separating blood and CSF are thought to be endowed with more freely diffusible charactor regarding not only in CSF as a whole but any constitution in it. In other words, abnormal vascular permeability to protein may exist in such pathological condition.

As Foltz[11] has described, ventriculo-atrial shunt is apt to occlude in the presence of abnormally high concentration of protein in CSF. In such condition, when shunt maneuver is required to relieve symptoms from hydrocephalus, the dilution of ventricular fluid must be a usuful technique in order to prevent the obstruction of shunt tube.

SUMMARY

An unusual case of congenital hydrocephalus due to aqueductal stenosis is reported.

The patient was 27 day-old male baby when he was admitted in our clinic, with abnormally large head. Although he showed no neurological signs, enormously large cerebral ventricle was demonstrated by pneumoventriculography. The first attempt of ventriculo-atrial shunt was effective only a short period because of obstruction of the ventricular catheter due to unusually high concentration of protein, in fact over 2 gm/dl, in ventricular fluid.

Dilution of the ventricular fluid was attempted with successful results at the time of revision of the shunt. The patient was well growing until he died from pneumonia 8 months after discharge.

Autopsy revealed a remarkably dilated ventricle forming a single cavity without differentiation of the lateral and third ventricles, and complete absence of the choroid plexus except for in the fourth ventricle. Occlusion of the aqueduct of Sylvius by septum formation was the main cause of internal hydrocephalus. Histological study demonstrated the destroyed ependyma over the ventricular cavity.

Regarding as the origin of such a high level of protein concentration in ventricular fluid, it is likely that abnormal vascular permeability to protein may exist in the barrier mechanism.

We would emphasize that the dilution technique is an effective method when ventriculo-atrial shunt is required in existence of abnormally high concentration of protein in ventricular fluid.

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