Experimental Hydrocephalus in Suckling Hamster Induced by Myxovirus Infection

I. Pathogenesis of Hydrocephalus Caused by Mumps Virus

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ABSTRACT This study was undertaken to elucidate the pathogenesis of the hydrocephalus and aqueductal stenosis induced by intracerebral mumps virus inoculation in suckling hamsters.

Mild ventricular dilatation became apparent after 5 days of inoculation. Focal denuding of the ependymal layer and subsequent aqueductal stenosis were observed by 14 days after inoculation. The virus antigen was detected not only in the ependymal cells and choroid plexus, but also in some neurons in the cerebral cortex, hippocampus, midbrain and cerebellum. In the cerebral aqueduct, the orderly arrangement of the ciliary clusters was destroyed on the 5th day after inoculation. After 10 days, proliferation of GFAP positive cells was noticed around the cerebral aqueduct and subsequently caused aqueductal stenosis. In the advanced state of hydrocephalus, the cerebellum was displaced downward and showed an elongated, atrophic and sleevelike structure similar to the Arnold-Chiari malformation. It was suggested that the extensive damage of the ependymal cilia may account for early ventricular dilatation, and subsequent aqueductal stenosis with glial proliferation is the main cause of the advanced hydrocephalus. It has not yet been determined whether the mumps virus can pass through the human placenta or not. If it can, however, our results strongly suggest that mumps virus infection in the human fetus will cause congenital hydrocephalus.

Key words: hydrocephalus, aqueductal stenosis, Arnold-Chiari malformation, mumps virus, myxovirus, GFAP

TORCH (Toxoplasma, Other agents, Rubella virus, Cytomegalovirus and Herpes simplex 1 and 2 viruses) is well-known as the biological pathogens of congenital hydrocephalus (Hanshaw et al., 1985). However, the definite etiology in most cases of congenital hydrocephalus accompanied by anomalies of the central nervous system, such as the Chiari malformation, Dandy-Walker syndrome and congenital aqueductal stenosis, still remains unknown, though it has been speculated that both environmental and genetic factors sometimes play roles in the pathogenesis of some types of congenital hydrocephalus (Jacobson, 1989). On the other hand, experimental studies have demonstrated that myxoviruses such as the influenza and mumps
virus have a high frequency of inducing hydrocephalus in suckling mice, rats and hamsters (Johnson and Johnson, 1969; Johnson, 1972; Hochwald, 1985). These experimental studies strongly indicate that intrauterine infection of myxovirus, a most common pathogenic organism, would be an etiological candidate for congenital hydrocephalus of unknown origin.

In experimental hydrocephalus induced by mumps virus infection, it has been emphasized that the narrowing of the aqueduct plays an important role in the development of hydrocephalus (Johnson and Johnson, 1968). However, the details with respect to its pathogenesis still remain a matter of controversy. This experiment was undertaken in an effort to elucidate the pathogenesis of the congenital hydrocephalus and aqueductal stenosis caused by mumps virus infection. Newborn Syrian hamsters were used since they are born very prematurely after 16 days of intrauterine life, when the last group of neurons in the cerebral cortex is still being produced (Shimada and Langman, 1970). Thus the developmental stage of the central nervous system of newborn hamsters may be compared to that of 20 to 25 weeks in human embryos.

**MATERIALS AND METHODS**

**Virus used in this experiment:** The mumps virus used in this experiment was a strain isolated from the saliva of a patient with parotitis. Virus infectivity was expressed as the reciprocal of the dilution causing infection in 50% of cultures (TCD50).

**Preliminary experiment:** To examine the relationship between the inoculation of different concentrations of mumps virus and the possible occurrence and incidence of hydrocephalus, 47 newborn hamsters were subject to intracerebral inoculation with 10 μl of 200, 20 or 2 TCD50 of mumps virus using a 27-gauge needle on when 2 days old. Animals injected with the same amount of MEM (minimum essential medium) in the same manner served as the control. Daily clinical observations were made on all animals after inoculation. Macroscopic examinations were performed on the removed brains after 14—20 days of inoculations, and the incidence of hydrocephalus was estimated.

**Histological study on pathogenesis of hydrocephalus:** Forty-five 2-day-old Syrian hamsters were subject to intracranial inoculation with 2 TCD50 of mumps virus using 27-gauge needle. Eighteen animals injected with the same amount of MEM in a same manner served as the control.

For routine histological examination, these animals were anesthetized by ether or pentobarbital, perfused with saline solution and then sacrificed on 2, 3, 4, 5, 6, 7, 10, 14 or 20 days after the inoculation. Brains were removed and fixed in phosphate-buffered 10% formalin and embedded in paraffin. Serial 5 μm coronal sections were stained with hematoxylin and eosin (HE).

For immunohistochemical studies, tissues were prepared by perfusing with 4% paraformaldehyde (FA), 0.3% glutaraldehyde (GA) and 0.2% picric acid (PA) in 0.1M phosphate buffer (PB). Brains were removed from the skull and fixed overnight with 4% FA and 0.2% PA in 0.1M PB at 4°C. After immersion in 15% sucrose solution for more than 2 days at 4°C, brains were cut into 20 μm thick serial coronal sections using a cryostat knife. These sections were mounted on glass slides and preincubated in 0.1M phosphate buffered 0.3% Triton X-100 at 4°C for more than 7 days. Some of these slides were then incubated in rabbit anti-mumps virus hyperimmune serum (Denkaseiken Co., Tokyo), which was diluted to 1:1200 in phosphate buffered saline (PBS), for 2 days at 4°C to identify the location of mumps virus antigen. The other slides were incubated in rabbit antiserum to the glial fibrillary acidic protein (GFAP; DAKO JAPAN Co., Japan), which was diluted to 1:1500 in PBS, for 5 days at 4°C to examine the reactive changes of
Mumps virus induced hydrocephalus

Fig. 1  Fourteen-day-old control (left) and hydrocephalic (right) hamsters. The hydrocephalic hamster had intracerebral inoculation of 2 TCD50 of mumps virus 2 days after birth. The control hamster was injected with the same amount of MEM.

the glial cells after mumps virus infection. These slides were then incubated serially with 1:2000 biotinylated anti-rabbit IgG (Vector Lab., Inc., USA) for 2 hours and avidin-biotin-peroxidase complex (Vector Lab., Inc., USA) for 2 hours at room temperature. These sections were then incubated in 0.05% diaminobenzidine solution containing 0.01% hydrogen peroxide for 5 minutes at room temperature.

Scanning electron microscopic study: Sixteen 2-day-old Syrian hamsters were used for scanning electron microscopic study. Each of two animals in both the experimental and the control groups were sacrificed under deep anesthesia by ether after 3, 5, 7 and 10 days of virus inoculation or MEM injection. All animals were perfused with 4% GA in 0.1M PB at room temperature. The brains were sectioned in the mid-sagittal plane to expose the cerebral aqueduct, and were fixed overnight with the same fixative at 4°C. After postfixation in 1% osmium for 4 hours, the specimens were dehydrated through graded solutions of ethanol, and then were dried by the critical point CO2 method. These specimens were then mounted on aluminum buttons, and were sputter-coated with gold-palladium and examined with a scanning electron microscope (HITACHI S-570).

RESULTS

Virus concentration, clinical signs and occurrence of hydrocephalus
There were no differences in the physical growth and motor function until 10 days after birth between
Fig. 2 Whole brains and their coronal sections of 18-day-old control (A) and hydrocephalic (B) hamsters. The hydrocephalic hamster brain shows atrophy of the olfactory bulb and superior and inferior colliculi. The cerebellar vermis is extended caudally through the foramen magnum. Note the symmetrical dilatation of the lateral ventricles.
Mumps virus induced hydrocephalus

Table 1. Incidence of gross hydrocephalus* 14—20 days after intracerebral mumps virus inoculation

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. of hamsters examined</th>
<th>No. (%) with hydrocephalus</th>
</tr>
</thead>
<tbody>
<tr>
<td>200TCD50</td>
<td>12</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>20TCD50</td>
<td>15</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>2TCD50</td>
<td>14</td>
<td>13 (93%)</td>
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</table>

* Hydrocephalus determined by gross evaluation of brain.

The virus inoculated groups and the control group. After 14 days of the treatment, however, more than 90% of the animals in each experimental group failed to gain weight as compared with control animals. Moreover, these experimental animals had an occipital prominence, and squating-like posture with poor motility (Fig. 1). Most of these hamsters died between 20 and 30 days after inoculation.

When the brains of 18-day-old hamsters, which had been inoculated with different concentrations of mumps virus, were examined, all of them showed moderate to severe bulging of the cerebral hemisphere and atrophy of the olfactory bulb and of the superior and inferior colliculi as compared with control brains. The cerebellar vermis was displaced downward, and thus had an elongated, atrophic and sleeve-like structure (Fig. 2B). In coronal sections, experimental brains showed symmetrical dilatation of the lateral ventricles, and the parieto-temporal cortex was paper-thin. Control brains showed no apparent abnormal findings (Fig. 2A). These preliminary experiments demonstrated that hydrocephalus developed in more than 92% of inoculated animals regardless of the dosage of mumps virus (Table 1). This was the reason why the dosage of 2TCD50 of mumps virus was used subsequently.

**Histological examination**

In the experimental group, during the first 3 days after inoculation, no pathological findings were detectable in the ependymal layer, subependymal white matter, cerebral cortex and cerebral aqueduct. Five days after inoculation, however, mild dilatation of the lateral ventricles became apparent at the rostral portion (Fig. 3A). Inflammatory infiltration of the monocytes and neutrophils was also noticed in and around the ventricular system including the cerebral aqueduct (Fig. 3B). However, there was no inflammatory reaction in the subpial and perivascular regions of the cerebral cortex. When examined on 7 or 10 days after inoculation, dilatation of the lateral ventricles was clearly identified and extended to the middle and caudal portion. In spite of the considerable compression of the cerebral mantle caused by enlargement of the lateral ventricles, degenerative changes of the neurons were not evident. After 14 days, the lateral ventricles showed symmetrical dilatation with remarkable enlargement of the foramen of Monro (Fig. 3C). The denuding of some ependymal layer was observed in the dorsomedial portion and ventral angle of the lateral ventricles. Large areas of aqueductal surfaces were devoid of ependyma with narrowing of the aqueduct, although inflammatory change was diminished (Fig. 3D). On the 20th day after inoculation, spongy degeneration was present in the subependymal white matter especially at the dorsomedial portion of the enlarged lateral ventricles (Fig. 3E). The cerebral aqueduct lost the ependymal cells and became stenotic. No aqueductules nor small rosettes of ependymal cells were found around the stenotic aqueduct (Fig. 3F).

In the control group there were no apparent pathological findings such as inflammatory infiltration, ventricular dilatation or aqueductal stenosis in any animals.
Fig. 3  Frontal sections through the foramen of Monro (A, C and E) and coronal sections of the cerebral aqueduct (B, D and F) in hydrocephalic hamster brains. HE stain. A and B: Five days after inoculation. Mild dilatation of the lateral ventricles is recognized (A). Note the remarkable inflammatory infiltration around the cerebral aqueduct (B). C and D: Fourteen days after inoculation. The foramen of Monro is dilated (C) and the cerebral aqueduct is stenotic with focal denuding of ependymal layer (D). E and F: Twenty days after inoculation. Severe symmetrical dilatation of the lateral ventricles with subependymal edema (arrows) is noticed (E). Note the obliterated cerebral aqueduct with marked denuding of ependymal layer (F). A, C and E: 7 x; B, D and F: 150 x.
Mumps virus induced hydrocephalus

Fig. 4  Immunohistochemical demonstration of mumps virus antigen in the lateral ventricles and cerebral cortex. A and B: Two days after inoculation. Mumps virus immunoreactive cells are located only in a part of the choroid plexus and ependymal layer (arrows in A). B: Higher magnification of infected ependymal cells and ependymal fibers. C and D: Six days after inoculation. All of the ependymal cells surrounding the lateral ventricles and some neurons in the cerebral cortex have become immunoreactive (C). In some pyramidal neurons, cell soma and apical dendrites have become immunoreactive (D). E and F: Ten days after inoculation. Mumps virus immunoreactive cells have decreased in number in the ependymal layer. No immunoreactive neurons are noticed in the cerebral cortex (E). A: 70 ×; B and F: 500 ×; C and E: 30 ×; D: 400 ×.
Fig. 5  Immunohistochemical demonstration of mumps virus antigen in the cerebral aqueduct. A: Two days after inoculation. Mumps virus immunoreactive elements are recognized in some ependymal cells of the cerebral aqueduct. B: Six days after inoculation. Note marked mumps virus immunoreactivity in all of the ependymal cells and the dorsal portion of the cerebral aqueduct. C: Ten days after inoculation. A few mumps virus immunoreactive elements remain in some ependymal cells of the cerebral aqueduct. 300x.

Table 2. Distribution of mumps virus antigen in the brain after intracerebral inoculation

<table>
<thead>
<tr>
<th>Days after mumps virus inoculation</th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td></td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ependyma</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Choroid plexus</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Neurons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebral cortex</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Hippocampus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Thalamus/Hypothalamus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Midbrain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Cerebellum</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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Epithelium: -, none; +, < half; ++, > half; or ++++, all of the epithelium infected.
Neurons: -, none; +, < 20; ++, > 20–100; and ++++, > 100 infected neurons per section as a mean of the hamsters in each group.
Fig. 6 Immunohistochemical demonstration of GFAP in the cerebral cortex (A, C and E) and cerebral aqueduct (B, D and F). A and B: Ten days after inoculation in normal control. GFAP immunoreactive elements are found in subependymal white matter and hippocampal fimbria (A), and are restricted to the subependymal region and dorsal portion of the cerebral aqueduct (B). C and D: Five days after inoculation in the hydrocephalic brain. The GFAP positive cells are distributed throughout the entire white matter and the deep part of the gray matter (C). Mild proliferation of GFAP positive cells is found in the periaqueductal gray matter (D). E and F: Ten days after inoculation in the hydrocephalic brain. Note the wide spreading of GFAP positive cells from the subependymal layer to the molecular layer (E). Accompanied by remarkable periaqueductal proliferation of GFAP positive cells, the aqueduct has now become stenotic (F). A, C and E: 30 ×; B, D and F: 200 ×.
Distribution of mumps virus antigen

Mumps virus antigen became detectable in some ependymal cells of the ventricular system and epithelial cells of the choroid plexus 2 days after inoculation (Figs. 4A, 4B, 5A). Four days after inoculation, almost all of the ependymal cells of the ventricular system had become mumps virus antigen positive. After 6 days, mumps virus antigen had also become detectable in some pyramidal cells in the cerebral cortex in addition (Figs. 4C, 4D, 5B). Mumps virus antigen positive neurons were first identified in the pyramidal cell layer of the cerebral cortex and hippocampus, and then spread from the rostral to caudal portion of the brain, that is, from some nuclei of the thalamus and hypothalamus, midbrain and pons to a part of the cerebellum. Ten days after inoculation, however, mumps virus antigen had disappeared from most parts of the brain, with the exception of in some ependymal cells (Figs. 4E, 4F, 5C). Virus antigen was no longer detectable after 14 days (Table 2).

**GFAP immunohistochemistry**

In the control animals injected with 10μl of MEM, GFAP immunoreactivity was more pronounced in the hippocampus and dentate gyrus than in other brain regions. On the 5th day after the injection, i.e., 7 days after birth, the glia limitans on the surface of the dentate gyrus, alveus and fimbria of the hip-
pocampus was formed of GFAP positive small astrocytes and fibers. Many GFAP positive astrocytes were also present in the hippocampal fimbria and molecular and polymorphic cell layer of the dentate gyrus. In the white matter, GFAP positive astrocytes were distributed parallel to the fibers of the white matter in the middle portion of the corpus callosum, and in the cingulum and external capsule. In the cerebral cortex, GFAP positive small astrocytes and their fibers formed only the subpial glia limitans. Ten days after MEM injection, some GFAP positive small astrocytes had become apparent in the subependymal white matter of the lateral ventricles and perivascular area in the cerebral cortex (Fig. 6A). Intense GFAP immunoreactivity was observed in the dorsal portion of the aqueduct, and some GFAP positive small astrocytes were also identified in the periaqueductal gray matter both 5 and 10 days after injection (Fig. 6B).

In the experimental animals inoculated with mumps virus, subsequent GFAP immunoreactivity was observed more extensively in addition to findings obtained in the control animals. Five days after inoculation, the coronal sections of the hamster brains showed a number of GFAP positive astrocytes in the periventricular white matter and the adjacent deeper layers of the neocortex, i.e., in layers V and VI (Fig. 6C). The highest accumulation of GFAP positive astrocytes was noticed in the periaqueductal gray matter (Fig. 6D). On ten days after inoculation, the GFAP positive astrocytes were increased considerably in layers III and IV, and even in some parts of layers I and II (Fig. 6E). These GFAP positive cells resembled those of protoplasmic type with hypertrophic cell bodies and thickened cell processes. Around the aqueduct which had already become stenotic, periaqueductal proliferation of GFAP positive small astrocytes similar to those of the fibrous type was evident (Fig. 6F).

Scanning electron microscopy

When the aqueduct of 3- and 5-day-old control hamsters was examined using scanning electron microscopy, the surface was covered with crowded cilia waving toward the 4th ventricle (Figs. 7A, 7B). In experimental animals, the surface of the aqueduct was covered by the cluster of cilia similar to that of the control at 3 days after inoculation. After 5 days, however, the cilia had almost completely disappeared and microvilli had taken their place. A number of supraependymal cells with long processes was also found on the surface of the aqueduct (Figs. 7C, 7D). By 7 days after inoculation, the number of supraependymal cells had greatly increased, and finally the canal was very narrow or had been obliterated by adhesion 10 days after inoculation.

DISCUSSION

Many studies have been reported on the experimental hydrocephalus induced by viral infection. Many of them suggest that aqueductal stenosis plays an important role in the dilatation of the lateral ventricles. As for the pathogenesis of the aqueductal stenosis, however, different conclusions have been drawn, depending on the variety of virus inoculated. Johnson and Johnson (1968) produced experimental hydrocephalus by intracerebral mumps virus inoculation in the same way as us, and they observed aqueductules or small ependymal rosettes, but could not find any viral antigen, inflammatory reaction nor glial proliferation. Based on these results, they suggested that the pathogenesis of aqueductal stenosis in their experimental model would meet the criteria of primary agenesis of aqueduct. In other studies on the experimental hydrocephalus, which had been produced either by influenza virus (Johnson, 1972), Reovirus type 1 (Maggol and Kilham, 1969a) or pneumovirus (Lagace-Simard et al., 1980), glial proliferation at the aqueduct was observed. On the other hand, Masters et al. (1977) reported that the narrowing of the aqueduct was
a secondary phenomenon, subsequent to the compression of the midbrain by the enlarged cerebral hemisphere, and he also mentioned that the periaqueductal glial proliferation did not play so important a role.

In our experiment, mumps virus antigen was first detected in some ependymal cells on the cerebral aqueduct after 2 days of inoculation, and inflammatory cell infiltration became apparent after 5 days of inoculation. After 14 days, denuding of the ependymal layer and aqueductal stenosis were confirmed. Considerable numbers of GFAP positive cells had already been found in the periaqueductal region after 5 days, and there were much more by the 14th day. The aqueductules or small rosettes of the ependymal cells could not be detected even 14 days after inoculation in the stenotic aqueduct. These results suggest that the aqueductal stenosis in this experimental model may be caused by the periaqueductal glial proliferation which occurs as a healing process after severe and extensive ependymal cell damage. It can easily be conjectured that the aqueductal stenosis induced by various viral infections of other than mumps virus may be caused by periaqueductal glial proliferation, if these viruses have a selective affinity with the ependymal cells.

GFAP is known as the main marker protein for astrocytes. Using GFAP immunohistochemistry, distribution of the astrocyte has been extensively studied in normal rat and hamster brains (Valentino et al., 1983; Suarez et al., 1987; Kalman and Hajos, 1989; Hajos and Kalman, 1989). However, there have so far been no reports on the distribution of GFAP positive cells in the hydrocephalic brain caused by virus infection. Moreover, the mechanisms of the glial proliferation in the damaged brain are still quite controversial (Kitamura, 1989). In our experiment, GFAP positive cells appeared first in the subependymal white matter and then they spread over gradually toward the marginal layer of the cerebral cortex with the progress of dilatation of the lateral ventricles. The GFAP positive cells, thusly proliferated, had large cell soma and were considered to be the cytoplasmic type of astrocyte. The accumulation of these GFAP positive cells can be considered to be induced by the reactive proliferation of glial cells which is triggered by the dilatation of the lateral ventricles.

It is accepted that aqueductal stenosis is the main cause in most cases of severe hydrocephalus including that of post infectious origin. In this experiment, however, dilatation of the lateral ventricles appeared during the acute phase of virus infection prior to the appearance of aqueductal stenosis, as reported in previous experiments (Mims et al., 1973; Tardieu et al., 1982; Lagace-Simard et al., 1982). Functional and morphological disturbances of the ependymal cilia, which play a part in the flow of the intraventricular cerebral fluid (Friede, 1975), were proposed as the cause of early dilatation prior to aqueductal stenosis by Nielsen and Gauger (1974). Scanning electron microscopy in the present experiment showed that there was wide-spread tearing off of the ependymal cilia from the surface of the aqueduct in the acute phase of infection. This result indicates that the extensive damage of the ependymal cilia may account for early ventricular dilatation prior to the appearance of aqueductal stenosis.

In this experiment, Arnold-Chiali type of malformation was found in high frequency, which malformation is characterized by hydrocephalus and elongation and protrusion of cerebellar vermis through the foramen magnum into the cervical spinal canal. Aqueductal stenosis and/or obstruction of the 4th ventricle at its outlet foramina can be considered to play an important role in the pathogenesis of hydrocephalus in this malformation (Gabriel and McComb, 1985). However, details on the pathogenesis of the elongation and downward protrusion of the cerebellar vermis still remain unknown. Margolis and Kilham (1969b) also found the Arnold-Chiali malformation in the experimental hydrocephalus which was caused by reovirus type 1 infection. They reported that the increasing compression by the rapidly bulging cerebral hemisphere on the immature cerebellar cortex gave rise to the abnormal shape and dislocation of the cerebellar vermis.
Mumps virus induced hydrocephalus

The histogenesis of the cerebellar cortex is considerably later than that of the cerebral cortex especially in neurocytogenesis (Shimada and Langman, 1969, 1970). The production of granule cells, which occupy more than 85% of the neurons in the cerebellar cortex, begins some time around 3 to 5 days after birth in the hamster. In our experiment, dilatation of the lateral ventricles was noticed as early as 5 days after virus inoculation, when the production of granule cells was in the initial stage. Considering these facts, the cerebellar deformity with hypoplastic hemisphere and the elongation and downward protrusion of the vermis in this experiment may be better explained by the continuous pressure caused by increasing hydrocephalus to the rapidly growing cerebellar cortex as speculated by Margolis and Kilham (1969b).

There have so far been no apparent clinical cases in which congenital hydrocephalus was produced by intrauterine mumps virus infection. On the other hand, several clinical cases of acquired hydrocephalus accompanied with aqueductal stenosis which was caused by mumps virus infection have been reported (Spataro et al., 1976; Thompson, 1979; Rotilio et al., 1985). The Syrian hamster employed in this experiment is born very prematurely at the 16th day of gestation, when the neurons at layer II of the cerebral cortex are still being produced in the matrix layer (Shimada and Langman, 1969). In the human fetus, neurons at layer II of the cerebral cortex, the last neurons to be produced in the neocortex, are produced some time around the end of the 5th month (Dobbing and Sands, 1970; Shimada, 1976). Therefore, the 2nd day after the birth in hamsters, when mumps virus was inoculated in this experiment, may roughly be compared in terms of neurocytogenesis with the 5th month of gestation in humans. This was the reason why the newborn hamster was used by us to study the pathogenesis of mumps virus-associated congenital hydrocephalus. It has not yet been determined whether or not the mumps virus can pass through the human placenta. If it can, however, our results strongly suggest that mumps virus infection in the human fetus will cause congenital hydrocephalus.

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