High-energy phosphate metabolism in a neonatal model of hydrocephalus before and after shunting

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The effects of hydrocephalus on high-energy phosphate metabolism in the brain and the impact of ventriculoperitoneal (VP) shunting on these changes were studied in an experimental model of hydrocephalus. High-energy phosphate metabolism was analyzed using in vivo magnetic resonance (MR) imaging and $31^P$ MR spectroscopy. Hydrocephalus was produced in 34 1-week-old kittens by cisternal injection of 0.05 ml of a 25% kaolin solution. Sixteen litter mates were used as controls. A VP shunt with a distal slit valve was implanted in 17 of the 34 hydrocephalic animals 10 days after induction of hydrocephalus. Both MR imaging and $31^P$ MR spectroscopy were obtained 1 and 3 weeks after either kaolin or distilled water injection. Untreated hydrocephalic animals had marked dilation of the lateral ventricles and periventricular edema. Magnetic resonance spectroscopy showed a significant decrease in the energy index ratio of phosphocreatine (PCr): inorganic phosphate (Pi) and an increase in the Pi:adenosine triphosphate (ATP) ratio. There was a direct correlation between the decrease in the energy index and ventricular size. Compared with preoperative scans, shunted animals showed no periventricular edema, and the ventricles decreased in size. Also, PCR:Pi and Pi:ATP ratios were within the levels of controls. This study suggests that neonatal hydrocephalus results in a mild hypoxic/ischemic insult that is treatable by VP shunting.

Key Words • ventriculoperitoneal shunt • metabolism • hydrocephalus • magnetic resonance spectroscopy • neonate • cat

Although hydrocephalus remains one of the most common disorders treated by neurosurgeons, particularly pediatric neurosurgeons, there are still many fundamental issues regarding its pathophysiology that are unresolved. Although a reduction in cerebral blood flow (CBF) has been documented by us as well as by others, controversy still exists about whether this is a primary or secondary event. Also unresolved are questions regarding the effects of ventriculoperitoneal (VP) shunts on the prevention or alleviation of the metabolic effects of hydrocephalus.

We have used $31^P$ magnetic resonance (MR) spectroscopy, a noninvasive technique that allows measurement of high-energy phosphate metabolites in the brain, to study the evolution of changes and the effects of VP shunts on hydrocephalus in a neonatal kitten model. We selected a neonatal model because we were particularly interested in the effects of hydrocephalus in young children. Development is a crucial process in the immature brain and an adult model would not enable us to study the effects of hydrocephalus on maturation. Furthermore, since $31^P$ MR spectroscopy can also be performed noninvasively in humans, it may ultimately provide important diagnostic information for patients with hydrocephalus.

Materials and Methods

The experimental protocol for this project was approved by the Animal Care Committee of the Research Institute of The Hospital for Sick Children. Fifty-three mongrel kittens were obtained at 1 week of age from the breeding colony of the Animal Facilities at The Hospital for Sick Children. They were randomly assigned to three groups: a control group (16 kittens), an untreated group (17 kittens), or a shunted (treated) hydrocephalic group (17 kittens). Figure 1 outlines the experimental protocol for this project.

Induction of Hydrocephalus

Hydrocephalus was induced 7 to 9 days after birth. The animals were anesthetized with a mixture of 4% halothane and 50% nitrous oxide, and the occipital region and neck were shaved and prepared with 10% povidone-iodine. The animals were then placed in a flexed position so that the space between the occipital bone and the first cervical vertebra was maximized. The cisterna magna was punctured with a No. 25 butterfly needle and 0.05 ml of a sterile solution of 25% kaolin was injected. Control ani-
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Fig. 1. Outline of experimental protocol. n = number of animals included in each group; MRS = magnetic resonance spectroscopy; MRI = magnetic resonance imaging; VP = ventriculoperitoneal.

Animals were injected with 0.05 ml of sterile distilled water. The whole procedure was accomplished in 5 minutes or less, and all animals promptly recovered from anesthesia.

The kittens were examined daily to assess development. The variables noted were weight, head shape, anterior fontanelle size and skull suture displacement, timing of eye opening, and any abnormal eye deviations, gait development, or states of consciousness.

Imaging Studies

Coronal and sagittal proton MR imaging was performed in all animals 1 week and 3 weeks after the injection of kaolin or distilled water (Fig. 2). For the MR imaging and MR spectroscopy procedures, anesthesia was induced as described above for insertion of the VP shunt. Because these examinations were painless, anesthesia was maintained with lower doses of inhalatory anesthetics, namely 1% halothane and 50% nitrous oxide. The kittens were positioned supine in the coil so that the partial regions of both hemispheres were closest to the center of the coil. The skin overlying the skull was kept intact. A 2.0-tesla small-bore spectrometer was used. The probe used for MR spectroscopy and surface imaging consisted of a single-tuned circular surface coil 3.5 cm in diameter for \(^{31}\text{P} \ (34.56 \text{ MHz})\) and a butterfly-shaped surface coil of a similar size for \(^{1}\text{H} \text{NMR} \ (85.56 \text{ MHz})\). The magnet was shimmed with the \(^{1}\text{H} \text{NMR} \) signal of the fluid in the animal’s brain to an average line width of 11 Hz. The pulse sequence used for \(^{31}\text{P} \text{NMR} \) spectroscopy was a single hard pulse. Four separate spectra were obtained, each with 256 free-induction decays, sweep width of 5000 Hz, repetition time of 4 seconds, and pulse width of 150 msec.

Images were obtained with the proton surface coil immediately before every \(^{31}\text{P} \text{NMR} \) spectroscopy study to ensure good head positioning. No manipulation was necessary between examinations, so that the images produced by the proton coil established the region sampled by the phosphorus coil. We used these images to assess the regions of tissue sampled by the \(^{31}\text{P} \) coil. Twenty-five coronal images were analyzed (two control animals and seven hydrocephalic animals at 1 week; six control animals and 10 hydrocephalic animals at 3 weeks). The total sample area (assuming a semicircular area centered beneath the coil and equal to its radius) including ventricular area, as well as gray and white matter contributions, were measured and the results compared using independent Student t-tests. Due to the multiplicity of comparisons, a p value equal to or less than 0.03 was considered significant.

The \(^{31}\text{P} \text{NMR} \) spectroscopy studies were performed 1 and 3 weeks after the induction of hydrocephalus for control and hydrocephalic animals. Kittens assigned to the shunted group underwent \(^{31}\text{P} \text{MRMR} \) spectroscopy 3 weeks after kaolin injection only; spectroscopy was not performed 1 week after kaolin injection for this group because of technical constraints. However, the shunted animals were comparable to untreated hydrocephalic animals in all clinical aspects at 1 week postinjection and thus should also have presented comparable phosphorus spectra.

Ventriculoperitoneal Shunting

A VP shunt was inserted 10 days after induction of hydrocephalus for the 17 animals in the shunted group. The system implanted consisted of a ventricular catheter and an abdominal catheter with a distal slit valve joined by a plastic straight or right-angle connector (Fig. 3). The animals were anesthetized as described above, and anesthesia was maintained with 1.5%
Fig. 3. Radiograph demonstrating ventriculoperitoneal shunt system in situ. A distal slit valve was used in this system.

halothane and 50% nitrous oxide. The occipital area, neck, and right side of the back and abdomen were shaved. The kittens were positioned on the operating table supine, head slightly elevated and turned to the left, with the right frontal limb secured over and above the left shoulder. The abdominal catheter was passed subcutaneously from an occipital to an abdominal incision through the back. The ventricular catheter was introduced into the right lateral ventricle through a small right occipital craniectomy. Once adequate positioning was confirmed by free flow of cerebrospinal fluid (CSF), the two catheters were joined with a plastic connector. The tip of the abdominal catheter was then inserted into the peritoneal cavity. Both incisions were closed in two layers and the anesthetics discontinued. The surgical procedure lasted approximately 1 hour, and the animals were returned to their cages 2 to 3 hours afterwards.

**Spectral Analysis**

For the spectral analysis, the four separate spectra were added and processed in the following manner. Before Fourier transformation was performed on the data, the baseline was corrected and the data zero-filled to 2000 data points. The first three data points were deleted to eliminate the broad background component of the spectra. Residual baseline distortion was removed with a correction procedure. An exponential 3-Hz filter was applied. The data were then Fourier transformed and the spectra manually phased until all peaks were symmetrical with first- and second-order phase corrections. The spectra were analyzed with a nonlinear line-fitting deconvolution routine using a Lorentzian line-shaped model. Seven distinct peaks could be identified: β-, α-, and γ-adenosine triphosphate (ATP); phosphocreatine (PCR); phosphodiester; inorganic phosphate (Pi); and phosphomonooester (MONO) (Fig. 4). The chemical shift position for each of the seven peaks was assigned in relation to the PCR peak. Intracellular pH was determined from measurement of the chemical shift of the Pi peak.18

The height at the center of each peak and the width at mid-height were calculated by computer with the fitted spectra. The area under each curve was defined as the product of height and width; this area correlates with the concentration of the compounds represented by each peak. The ratios of the areas under the various peaks for each spectrum were calculated using the β-ATP peak as the internal standard (PCR:ATP and Pi:ATP). The PCR:Pi ratio was also calculated and can be considered an energy index since it compares the relative concentration of ATP reserves (that is, PCR) and ATP breakdown products (that is, Pi).

Differences in sample composition could induce changes in the analysis results of these ratios. To account for this possibility, we analyzed the correlation between PCR:Pi, Pi:ATP, and the size of the lateral ventricles in the surface coil images.

**Statistical Analysis**

Independent two-tailed Student’s t-tests were used to analyze the differences between hydrocephalic and control animals at 1 and 3 weeks. Since more than one measurement was taken for the same animal, repeated measures of analysis of variance were used to analyze the effects of time and the presence of hydrocephalus. Linear regression analysis with the least-squares method was used to study the correlation between anatomical and MR variables. Because of the multiplicity of comparisons being tested, a p value less than or equal to 0.03 was considered significant.

**Results**

Three animals had to be excluded from the study, one because of problems with anesthesia and the other two because of failure of hydrocephalus induction. Every litter was represented in all groups so that normal variation between different litters was controlled.

**Clinical Examination**

Body weight was used to assess the animals’ nutritional status and general health. On the day of kaolin or distilled water injection, hydrocephalic and control kittens were similar in weight: the untreated hydrocephalic group averaged 224.4 ± 38.2 gm (± standard deviation); the shunted group weighed 208.5 ± 21.4 gm; and the control group weighed 227 ± 24.2 gm (p = 0.09). However, by 48 hours after injection, the body weight of the hydrocephalic kittens was significantly lower than that of the controls (p = 0.0001). By approximately Day 6 after injection, the weight of the hydrocephalic kittens was again within the range of the control group. After that, the weight gain curves for the three groups were similar, even though body weight tended to be lower in the hydrocephalic animals. The insertion of the VP shunt did not affect the weight gain curve of the animals.

The timing of eye opening was not statistically different among the groups (p = 0.057). Control animals opened their eyes on average 9.0 days after birth; untreated hydrocephalic animals, 9.4 days after birth; and shunted animals, 9.0 days after birth.

The anterior fontanelle and sutures were closed in control animals at a mean of 11.7 days of age. On the other hand, 12 (71%) of 17 untreated hydrocephalic animals still had an open anterior fontanelle at the time of the last spectroscopy at 25 to 30 days of age. All shunted animals had an open anterior fontanelle at the time of surgery. For all but one kitten, the anterior fontanelle was closed by Day 3 after insertion of the VP shunt.

**Proton MR Imaging Measurements**

Total brain (parenchyma plus ventricles) and ventricular cross-sectional areas were measured with coronal MR imaging at the level of the third ventricle in eight hydrocephalic and two control animals at 1 week and in nine hydrocephalic and two control animals 3 weeks after the injection of kaolin or distilled water (Fig. 2). One week after the injection of kaolin, the total brain area of hydrocephalic kittens was 130% of the
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controls (p = 0.06). Lateral ventricles comprised 23% of the total brain area in hydrocephalic animals compared with 0.4% for controls. Three weeks after injection, the cross-sectional area of the brain seen on coronal MR imaging was 148% of the size of age-matched control litter mates (p < 0.01). Lateral ventricles comprised 26% of the total brain area for hydrocephalic animals compared with 1% for controls. Also, hydrocephalic animals had varying degrees of periventricular edema. Those hydrocephalic animals that were later shunted also had an increased (120%) cross-sectional area of the brain on coronal MR images at the level of the third ventricle 1 week after the induction of hydrocephalus, when compared with controls. Lateral ventricles comprised 17% of the total brain area for these animals.

Ventriculoperitoneal shunting promptly alleviated the hydrocephalus. Magnetic resonance imaging demonstrated a significant decrease in ventricular size for the majority of animals 10 days after insertion of the VP shunt (p = 0.005; Fig. 2). Furthermore, no animal from this experimental group had periventricular edema compared to hydrocephalic animals that were not shunted. However, ventricular reduction varied considerably within shunted animals, with total brain area remaining essentially unchanged from preshunt levels. Data from MR imaging before and after shunting indicated that 10 of 13 animals for which images were available had a decrease in ventricular size. The lateral ventricles remained unchanged in one animal and in two others were slightly larger after VP shunting.

Phosphorus-31 MR Spectroscopy

No significant change in intracellular pH was demonstrated either at 1 week or at 3 weeks after injection of kaolin or distilled water.
One week after the induction of hydrocephalus, no significant change in PCR:ATP or PI:ATP ratios was demonstrated in hydrocephalic animals compared with control animals (p = 0.4 and p = 0.4, respectively). As a consequence, PCR:PI ratios were not significantly different for the two 1-week measurements (p = 0.8).

Three weeks after kaolin or distilled water injection, the PCR:ATP concentration ratio was similar for control, untreated hydrocephalic, and shunted animals (Fig. 5). However, the PI:ATP ratio for untreated hydrocephalic kittens was significantly increased compared with that of the controls (p = 0.002). Shunted kittens had a PI:ATP ratio comparable to that of control animals (p = 0.97) and significantly different from that of untreated hydrocephalic kittens (p = 0.03; Fig. 6). As a result, the PCR:PI ratio was lower for untreated hydrocephalic kittens than for controls (p = 0.0004), but PCR:PI ratios for shunted animals were not different from controls (p = 0.83; Fig. 7).

Development also influenced high-energy phosphate metabolism. The PCR:ATP ratio increased with age but was unaffected by hydrocephalus (p = 0.0005). The PI:ATP ratio decreased with age in control animals and increased in the hydrocephalic kittens when analyzed for independent effects. Both age and hydrocephalus significantly affected the PCR:PI ratio (p = 0.0001 and p = 0.02, respectively).

To assess the effect of the severity of hydrocephalus on changes in high-energy phosphate metabolism, we analyzed the relationship between ventricular size and the ratios previously described for untreated hydrocephalic and shunted animals. Data were available for seven hydrocephalic and 16 shunted kittens at 3 weeks after injection of kaolin. There was a significant correlation between PCR:PI and ventricular size on MRI imaging for untreated hydrocephalic animals (p = 0.02; r² = 0.65); increases in ventricular size led to decreases in the ratio. No correlation was demonstrated between PCR:PI and ventricular size for shunted animals (p = 0.68; r² = 0.01), suggesting a relationship between severity of ventriculomegaly and the degree of energy impairment before treatment.

Discussion

Animal Model

The feline model of hydrocephalus used in this experiment is well suited to the study of neonatal hydrocephalus.10,16 The animals develop rapidly increasing head size as well as split sutures, sun setting of the eyes, and in most cases progressive neurological deterioration. The use of standard shunt equipment results in rapid resolution of the hydrocephalus. In terms of the brain's maturational stages, there is not exact correspondence of developmental stages between humans and cats but an approximate comparison is feasible, especially for motor development. Both kittens and humans are born fairly immature and both are dependent on others for survival. One-week-old kittens are comparable to newborn humans in that they have very limited myelination of the brain and their responses to the environment are mostly reflex. Cats develop at a faster pace, however, and by 2 weeks of age are able to stand and walk, although unsteadily. By 4 weeks of age (the time of the second MR spectroscopy study in our experiment) kittens are active and playful, and able to perform more complex motor tasks. At the histological level, the internal capsule is fully myelinated. Their motor development can be compared to that of a human toddler, although at this point differences in develop-
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![Graph showing ATP/PI ratios for control, hydrocephalic, and stunted animals at 1 week and 3 weeks after injection.]

**Time of experiment**

1 week

3 weeks

**Effects of Experimental Variables**

**Anesthesia.** The experiments performed required that the animals be anesthetized before the spectra were obtained. General anesthetics are known to induce changes in CBF and cerebral metabolism, as well as in the cardiovascular and respiratory systems. It is therefore important to identify the potential effects of the anesthetics used on the variables studied.

Halothane and nitrous oxide were used for this experiment. Nitrous oxide does not exert toxic effects on the central nervous system or change the CBF response to CO₂ or autoregulation. Experimental studies have shown that there are no significant differences in the levels of ATP or PCR in animals exposed to air compared to an anesthetic mixture of nitrous oxide and oxygen.

On the other hand, halothane may lead to dose-dependent arterial hypotension and ventilatory depression. Cerebral vessels dilate during halothane anesthesia, and CBF and CSF pressures increase. The cerebral metabolic rate of oxygen consumption is reduced. There is no evidence that halothane anesthesia interferes with energy metabolism in the brain in general or with high-energy phosphate metabolism in particular, unless excessive doses are used. Under these circumstances, hypotension and hypoxia become apparent and ATP and PCR levels fall.

Since obtaining the spectra was a painless process and anesthesia was used mostly to ensure good positioning and immobilization, only a small concentration of the anesthetic gases was used. Also, the extent of time the animals were under anesthesia was carefully monitored and did not exceed 2 hours. Consequently, the anesthesia used for our experiments was not expected to affect the concentration of the compounds involved in high-energy phosphate metabolism for either control or hydrocephalic animals.

**Localization With a Surface Coil.** Surface coils are very useful, versatile probes for localizing and studying compounds that are close to the surface of a sample. However, because of the probe characteristics, not all regions in a sample contribute equally to the signal. Under normal circumstances, the signal detected by a surface coil comes from a hemispheric region below the coil with a radius approximately equal to the radius of the coil. Regions located nearer to the coil center produce a stronger signal than those at the periphery.

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within this hemispheric region. Regions outside the hemispheric volume produce weak signals and are not significantly represented in the spectra. For this experiment, the circular surface coil had a radius of 1.75 cm and was positioned over the parietal regions. The region of the brain sampled, the parietal cortex, was constant throughout the experiment. Even for hydrocephalic animals, only a small portion of the ventricles was represented in the total sample volume.

Homogeneity of Samples. Sample homogeneity is another important consideration for MR spectroscopy. The spectra obtained are a reflection of the concentrations of the compounds in the entire volume sampled. Differentiation between regions within a given sample is not possible. For this project, the brain volume studied was composed of gray and white matter, plus part of the lateral ventricles for some hydrocephalic animals. Both white and gray matter have a high PCR content. White matter’s high PCR content is due to its population of glial cells,17,21,35 and neurons have a high level of PCR that accounts for the elevated levels in gray matter.12 Despite the changes in brain morphology produced by hydrocephalus, the relative amounts of gray and white matter sampled by the surface coil were similar for all groups. The relative position of gray matter surrounding central white matter was also maintained.

Other Studies. Evidence from other experiments in this neonatal model allows analysis of the probable localization of the site of changes observable by 31P MR spectroscopy. Cerebral blood flow measurements performed with quantitative autoradiographic techniques in the same animal model demonstrated a significant decrease in the regional blood flow of periventricular white matter in hydrocephalic kittens and no change in that of the gray matter, compared with age-matched controls 3 weeks after induction of hydrocephalus (MC da Silva, unpublished data). Similarly, local glucose use, also measured by quantitative autoradiographic techniques, showed that hydrocephalic animals had patchy areas of increased and decreased glucose use in the white matter that likely represents an increase in the anaerobic metabolism of those areas. Gray matter showed no significant changes from age-matched controls.11 Lastly, histological examination of the brains of hydrocephalic kittens failed to demonstrate any significant injury to the cerebral cortex. Periventricular white matter, though, showed evidence of axonal injury and severe interstitial edema and, in a few animals at later stages, evidence of infarction. Myelination was delayed histologically in all hydrocephalic animals studied. Hence, the changes observed in 31P MR spectroscopy in the brains of hydrocephalic kittens would appear to reflect changes predominantly if not solely in the white matter.

Normal Developmental Changes in the Brain

Since the control animals in this experiment were normal kittens, the changes observed in the spectra reflect changes in high-energy phosphate metabolism of the developing brain. As expected, the relative concentration of PCR and the PCR:PI ratio increased significantly with age. These changes reflect the maturation of energy metabolism pathways during development of the brain.1,6,9,16,37 Phosphorus-31 MR spectroscopy has been used by many to study these changes. Developmental changes similar to the ones presented here have been reported in the literature for various species.5,20,30,42,40,41,51 In all species studied, the pattern of developmental increases in the relative concentration of PCR compared to ATP and in the PCR:PI ratio is repeated, although the timing of the changes may vary from one animal species to another depending on the maturity of the brain at birth. For example, newborn guinea pigs, which are born more fully developed than rat pups, have higher ratios (that is, are more adult-like). The sharp increase in PCR relative concentration tends to accompany the sharp increase in brain activity that occurs with development. An interesting finding in our experiment was a decrease in the relative concentration of PI with age in control animals. Such a change has not been previously reported. We believe that this decrease in the relative concentration of PI is related to an improvement in the efficiency of energy metabolism that is also observed with age.

Hydrocephalic Changes in the Brain

High-energy phosphate metabolism in hydrocephalus has been incompletely studied with 31P MR spectroscopy. In a study of experimental hydrocephalus in adult dogs,29 a moderate decrease in the PCR:PI ratio in the acute (10 days) and subacute (15 days) stages of the disease was demonstrated. No changes in ATP were seen. This study had a small number of experimental subjects and only one control animal for comparison. Another study30 used 35 rats 20 to 30 days old with congenital hydrocephalus. (Note: the weaning age for rats is 21 days.) The animals showed a significant decrease in PCR:PI ratios, to 56% of control levels for mild hydrocephalus. The study also demonstrated that this ratio had prognostic value for survival. Because both these studies used older animals, the effects of hydrocephalus on normal brain development may not have been fully appreciated. The results from our experimental neonatal model, however, confirm the findings of these studies: the effects of hydrocephalus on high-energy phosphate metabolism is similar in both adult and immature brains. We also saw an increase in the relative concentration of PI that was not reported in previous studies. Whether the increased PI concentration represents a change peculiar to young subjects is not known.

The changes observed in the spectra of hydrocephalic animals can be explained by several mechanisms related to ischemia. The effects of hypoxic or ischemic injuries of the brain have been extensively studied with 31P MR spectroscopy.2,8,10,15,19,23-25,37,29,45 Studies using 31P MR spectroscopy during acute severe ischemia or hypoxia have demonstrated sharp decreases in PCR and ATP levels, generally to the nondetectable range and associated with large increases in PI. As a rule, PCR levels fall before ATP levels are altered. These changes
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in the spectra are generally followed by morphological evidence of severe energy metabolism failure, namely histological infarcts. Moreover, in children with severe anoxia, very low levels of PCR have been consistently associated with death or severe developmental delay. Low-grade hypoxia or ischemia, on the other hand, typically does not lead to such dramatic changes. In most cases PCR concentration decreases but is still detectable, whereas PI concentration increases but does not become the predominant peak. Periods of mild ischemia or hypoxia are usually not associated with changes in ATP levels. Thus, changes seen in the present hydrocephalic animals are consistent with a condition of mild ischemia. Decreases of CBF in the white matter of hydrocephalic animals at the same age have been observed by us, and reductions in CBF during hydrocephalus have been reported by others.

Another explanation for the changes observed on 31P MR spectroscopy is that incorporated in the sample volume were focal areas of severe involvement that were significantly masked by surrounding normal areas. These normal areas could be gray matter and/or white matter. This highlights one of the limitations of MR spectroscopy in terms of the requirement of a large sample volume in order to get a reasonable signal-to-noise ratio. More localized regions could be studied at a higher magnetic field without requiring inordinate anesthesia duration. In this study, the region of probable abnormality, namely the parietal gray matter, was in the most sensitive region of the coil, alleviating the heterogeneity problem to some degree.

The changes seen on 31P MR spectroscopy in this study are also consistent with postsischemic injury. In some cases of severe ischemia or hypoxia, PCR and ATP metabolism are permanently damaged, so that despite restoration of flow, decreased PCR concentration persists and may be accompanied by decreased ATP levels. It has been speculated that this metabolic scar reflects permanent damage to the mitochondrial energy production mechanisms: reducing equivalents are oxidized, but ATP is not formed. Severe head injury in humans, in whom a secondary ischemic or hypoxic injury plays an important role, can lead to such energy metabolism sequelae. A decrease in ATP concentration has also been demonstrated in chronic cerebral infarctions. This alternative explanation for the changes in high-energy phosphates appears unlikely, considering the fact that in one of our series of hydrocephalic animals only a few presented with areas of infarction and only at later stages of the disease (MR Del Bigio, unpublished data).

Another important factor in the pathophysiology of ischemia in hydrocephalus is the stage of development of the brain. By interfering with the normal maturation of the brain's energy metabolism in the face of increasing energy demands, hydrocephalus may delay or restrict other important maturational processes. We have observed decreased myelin formation in hydrocephalic animals. Oligodendrocytes are known to have a high level of creatine phosphokinase activity that is thought to be linked to their role in myelin formation. A decrease in the availability of energy may be the pathogenetic mechanism for this finding.

Alleviation of Hydrocephalus by VP Shunting

The main goals of hydrocephalus treatment are to prevent further damage caused by the progression of the disease and, if possible, to reverse the injury already inflicted on the brain. In clinical and experimental settings, VP shunts have been shown to alleviate intracranial pressure, reduce ventricular size, and grossly reconstitute the distorted anatomy. The associated clinical symptoms are also usually reversed. In this experiment, inserting a shunt 10 days after the onset of hydrocephalus (at which time there were no changes on 31P MR spectroscopy in the hydrocephalic animals) prevented the reduction in the PCR:PI ratio seen at 3 weeks. The questions of the exact timing of the onset of the changes seen on 31P MR spectroscopy and the extent to which they could be reversed have not been answered in this study. Suda, et al., have shown that delayed shunting in a rat model of congenital hydrocephalus does lead to irreversible changes in dendritic morphology and behavior. Therefore, timing is a factor of crucial importance when treating hydrocephalus.

Conclusions

Hydrocephalus of 3 weeks' duration leads to a significant change in high-energy phosphate metabolism in this experimental model and is characterized by a decreased PCR:PI ratio and increased PI:ATP ratio. The changes observed are consistent with a mild hypoxic or ischemic insult. Ventriculoperitoneal shunting at 10 days after the onset of hydrocephalus reduced the ventriculomegaly and prevented changes in high-energy phosphate metabolism. Phosphorus-31 MR spectroscopy of the brain may ultimately provide diagnostic and prognostic information for children with hydrocephalus.

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