Effects of hydrocephalus and ventriculoperitoneal shunt therapy on afferent and efferent connections in the feline sensorimotor cortex

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Object. The authors of previous studies have suggested that connectivity within the cerebral cortex may be irreversibly altered by hydrocephalus. To examine connectivity-related changes directly, the authors conducted a study in which they used an axonal tracer in an animal model of infantile hydrocephalus.

Methods. In five hydrocephalic kittens low-pressure ventriculoperitoneal (VP) shunts were placed 10 to 14 days after induction of hydrocephalus by intracisternal kaolin injections. Wheat germ agglutinin-conjugated horseradish peroxidase was injected laterally into the motor cortex in hydrocephalic animals 9 to 15 days after kaolin injection, and 1, 2, and 4 weeks after VP shunt insertion in shunt-treated animals, and in age-matched controls.

Reduction of antero- and retrograde labeling was most profound within the contralateral cortex and portions of the midbrain. Thalamic nuclei exhibited reductions in anterograde and retrograde labeling. Labeling within cell bodies of the ventral tegmental area decreased greatly in animals with untreated hydrocephalus, in which retrograde labeling was reduced in the locus coeruleus but did not affect the raphe nucleus. Shunt treatment increased both antero- and retrograde labeling of contralateral motor cortex to near-normal levels. Thalamic relay nuclei recovered antero- and retrograde labeling, although not to levels exhibited in controls. Shunt therapy restored cellular labeling within the ventral tegmental area and locus coeruleus. Recovery of labeling occurred as early as 7 days after shunt insertion.

Conclusions. Collectively, analysis of these data indicates the following. 1) Cortical connectivity involving both afferent and efferent pathways was impaired in untreated hydrocephalic animals. 2) Shunt therapy improved both cortical afferent and efferent connectivity. 3) Complete reestablishment of the cortical efferent pathways, however, did not occur. Cortical pathway dysfunction, if permanent, could cause many of the motor and cognitive deficits seen clinically in children with hydrocephalus.

KEY WORDS • hydrocephalus • axonal transport • connectivity • sensorimotor cortex • shunt • cat

HYDROCEPHALUS has long been regarded as a so-called white matter disease. In fact, on magnetic resonance images periventricular lucency and white matter edema are characteristic findings in hydrocephalus and are believed to be predictive of outcome in children with hydrocephalus. Histopathological studies have confirmed many types of damage, including delayed maturation of subcortical white matter, deafferentation, demyelination, neuronal and glial death, reactive astrogliosis, microgliosis, axotomy, synaptic and dendritic degeneration, metabolic changes, and neurotransmitter perturbations. Indirect evidence indicative of disruption of cortical connectivity includes loss of synapses and dendritic deterioration, altered levels of neurotransmitters, and decreased conduction velocity. In general, the cytoarchitecture of the cortical laminae is dramatically altered, which most likely disturbs both the intrinsic connections between cortical laminae and the extrinsic afferent and efferent connections of the neocortex.

Unfortunately, there is little direct evidence regarding the integrity of axonal pathways and entire connectivity systems in hydrocephalus. Shirai and Ishii directly evaluated corticospinal pathways by injecting the cervical spinal cord of hydrocephalic rats with the neuronal tracer HRP. They postulated that the gradual disappearance of retro-
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graded labeled corticospinal projections was due to destruction of Layer V pyramidal neurons. The experimental design of that study, however, did not allow comprehensive mapping of all corticofugal and -petal projections. Furthermore, there was no opportunity for functional restoration of HRP-injected neurons by ventricular shunting.

We have conducted a more comprehensive study that includes a simultaneous evaluation of axonal projections to and from the motor cortex in animals with infantile hydrocephalus. We also included a shunt-treated group to broaden our understanding of which pathways can be selectively rescued and to establish the time course for their recovery.

Materials and Methods

Animal Preparation and Surgery

Fifteen cats were divided into three groups of five animals each: control, untreated hydrocephalus, and shunt-treated hydrocephalus (Fig. 1). Obstructive hydrocephalus was induced at 9 to 11 days of age by intracisternal injection of 25% kaolin as described previously.52 Five of the hydrocephalic animals received VP shunts at 10 to 14 days after kaolin injection; we used a preestablished technique in a neonatal feline model.76,103 Briefly, neonatal ventricular access catheters (Medtronic PS Medical, Goleta, GA) were implanted 1 to 2 cm below the skull into the frontal horn of the lateral ventricle, connected to a distal catheter with low-pressure slit valves (Medtronic PS Medical), and tunneled subcutaneously into the peritoneal cavity. Age-matched normal intact littersmates served as controls; previous gross morphological and cytoarchitectural results indicated that these animals were comparable to those receiving intracisternal saline injections. Hydrocephalic and shunt-treated animals were examined daily for changes in weight, anterior fontanelle size, general behavior, and neurological performance. Additionally, ultrasonography was performed periodically to assess gross morphological alterations in situ and to obtain quantitative measurements of ventricular size. All procedures were reviewed and approved by the institutional animal care committee at the Temple University School of Medicine, where these experiments were performed.

Tracer Injections

A bidirectional neuronal tracer, wheat germ agglutinin-conjugated HRP (Sigma Chemical Co., St. Louis, MO) was injected unilaterally into sensorimotor Brodmann Areas 3, 4, and 6 of the neocortex (Fig. 2). Hydrocephalic animals received HRP injections between 9 and 15 days after kaolin-induced hydrocephalus. The shunt-treated animals received HRP injections at 1, 2, and 4 weeks after shunt insertion. Control animals received HRP injections at 10 days of age and at subsequent dates corresponding to injections in shunt-treated and hydrocephalic animals. Animals were anesthetized (1 mg/kg Nembutal) intraperitoneally and placed in a stereotactic head frame. Using sterile technique, standard neurosurgical procedures were undertaken to produce a craniotomy over the pericruciate region. Five 1-μl injections of 1% HRP solution were made laterally around the cruciate sulcus into the pre- and postcruciate gyrus 1.5 to 2 mm beneath the pial surface (Fig. 2). The dura mater was then repositioned, and small pieces of Gelfoam (Pharmacia & Upjohn, Kalamazoo, MI) pre-soaked in sterile saline solution, were placed over the dura. The bone flap was replaced and a small piece of Surgicel (Johnson & Johnson, New Brunswick, NJ) was placed over the flap for additional protection. After thoroughly irrigating the wound with sterile saline, the skin flap was closed using stainless steel staples. The animal was removed from the stereotactic device and placed on a heating pad to recover. The kitten was monitored closely until it regained consciousness and was then returned to the litter.

Tissue Collection and Histochemical Analysis

Two days after HRP injections, all animals received a lethal dose of Nembutal for anesthesia and were killed by transcardiac perfusion of saline and a subsequent mixture of 2% paraformaldehyde and 2% glutaraldehyde in phosphate buffer (pH 7.4). The brains were removed immediately and placed in a 20% sucrose solution for 20 hours. The whole brains were frozen and serially cut into 50-μm-thick coronal sections (Fig. 3). At intervals of 500 μm, sections were selected for histological examination. One set of sections was processed using the tetramethylbenzidine HRP procedure87 and mounted on glass slides. Other sets were processed for HRP and counterstained with neutral red or stained with cresyl violet.

Tissue Analysis

Sections were examined using bright- and dark-field light microscopy, and photomicrographs obtained from representative cortical and subcortical structures. Additionally, serial plots of camera lucida drawings were made for each animal by a single trained observer (J.S.W.) to confirm the location and relative density of retro-

FIG. 1. Chronological timeline of surgical procedures and survival periods for each group of animals. Control animals received HRP injections at time points corresponding to HRP injections in untreated hydrocephalic and shunt-managed groups. All hydrocephalic animals received HRP injections 9 to 15 days after kaolin-induced hydrocephalus, whereas shunt-treated animals received HRP injections at 1, 2, and 4 weeks after shunts were placed. All animals were killed 2 days after injection of HRP.

FIG. 2. Photograph of a normal gross kitten brain demonstrating the HRP injection sites within the sensorimotor cortex. Five injections were made near the cruciate sulcus (Cru) into regions that represented Brodmann Areas 3, 4, and 6. Each injection was aimed at a depth of 2 mm to center the delivery of HRP tracer to Layer IV of the sensorimotor cortex.
Results

Animal Population

Detailed histories of each animal are summarized in Table 1. The untreated hydrocephalus group (mild, moderate, and severe hydrocephalus in one, one, and three animals, respectively) proved to provide an accurate representation status prior to shunt treatment. The duration of ventriculomegaly in both untreated hydrocephalic and shunt-treated groups varied between 10 and 17 days. Survival after shunt insertion ranged from 9 to 30 days. In accordance with previous studies, VP shunt therapy reversed all behavioral abnormalities, including spastic movements, extensor rigidity, and lethargy.

Gross Morphological Findings

Similar to findings in our earlier reports, untreated hydrocephalic animals exhibited proportional enlargement in all portions of the cerebral ventricles (Fig. 4). When hydrocephalus went untreated for longer than 10 days extensive thinning of neocortical regions occurred medial, dorsal, and lateral to the body of the lateral ventricles, and frontal brain areas were displaced anteriorly. The postcruciate gyrus was thinned and stretched, occupying a more dorsal position compared with that in controls. Varied degrees of subcortical structural distortion and damage were observed, depending on the extent of hydrocephalus. The septal region was severely compressed and the septum pellucidum was obliterated, allowing open communication between the lateral ventricles. The hippocampus was compressed medially with a thin remnant of the fornix stretched over the dorsum of the diencephalon. The loss of subcortical white matter correlated with the extent of hydrocephalus, as indicated by a severely attenuated corpus

TABLE 1  
Summary of treatment-related data in the three groups of animals

<table>
<thead>
<tr>
<th>Group &amp; Case No.</th>
<th>Duration of Hydrocephalus (days)</th>
<th>Postop Survival (days)</th>
<th>Anterior Fontanelle Diameter (mm)*</th>
<th>Weight At Death (g)</th>
<th>Gain (+) or Loss (−)</th>
<th>Age at Death (days)</th>
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<tbody>
<tr>
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* The sizes of the fontanelle before shunt surgery reflected various degrees of hydrocephalic severity; after placement of the shunt, hydrocephalus resolved. Scores: 0, no measurable hydrocephalus; 0 to 2, mild hydrocephalus; 2 to 7, moderate hydrocephalus; greater than 7, severe hydrocephalus.

† Measurements were obtained 9 to 15 days after induction of hydrocephalus in both untreated hydrocephalic and shunt-managed animals.

‡ The value is relative to weight at time of kaolin-induced hydrocephalus.
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![Image of brain sections](image)

**Injection Site**

The HRP injections filled the lateral part of the precuneate gyrus (Area 6), most of the postcruciate gyrus (Area 4), and extended medially into the white matter of the lateral gyrus and ventrally into the coronal gyrus. (Figs. 2 and 3)
5). Extending from each injection site, HRP filled all layers of the cortex and the underlying white matter. Although the same amount of enzyme was injected into all animals, larger injection sites were observed in hydrocephalic brains because of the expanded motor cortex. Nevertheless, the cortical areas filled with tracer were comparable in all experimental groups.

Frontal Cortex and Basal Forebrain Connectivity

In control animals, HRP labeling was exhibited in cortical neurons and axons contralateral to HRP injection sites (Fig. 5). Most of the contralateral retrograde labeling was found in two regions of the postcruciate gyrus: in the lateral half of Area 4 adjacent to the cruciate sulcus or along the dorsal surface of the hemisphere. Within the precruciate gyrus, labeled neurons were concentrated near the lateral tip of the cruciate sulcus. A few retrogradely labeled neurons were also found ipsilaterally outside of the injection site in the coronal and prepiriform gyri (data not shown). Anterograde labeling in control animals was concentrated in the white matter immediately lateral to the cruciate sulcus in the pre- and postcruciate gyri. Labeled ipsilateral axons from the internal capsule passed through the mediodorsal head of the caudate nucleus and laterally into the external capsule. Various subcortical structures of the ventral forebrain were also labeled, including the septum, medial cortex anterior to the septum, olfactory tubercle, ventral part of the putamen/globus pallidus, claustrum, and substantia innominata.

The most striking effect of hydrocephalus on the forebrain was the absence of interhemispheric cortical connections. In cases of severe hydrocephalus in which the corpus callosum was obliterated there was no retro- or anterograde labeling in the contralateral cortex as well as a complete loss of retrograde labeling in the anteromedial cortex. In contrast, contralateral labeling was present in moderately hydrocephalic cases in which the corpus callosum was severely attenuated, with most neuronal somata located in Layers II and III. In cases of moderate hydrocephalus, attenuated retrograde labeling of the ventral forebrain was also demonstrated.

Shunt therapy restored the level of retrograde labeling in the forebrain to that in controls. Anterograde labeling, however, was only restored within the white matter of the ventral and medial frontal lobes, but axonal labeling did not return to normal in the area lateral to the cruciate sulcus.

Thalamic Connectivity

In control animals, dense retro- and anterograde labeling was seen in the ventral anterior nucleus and VLN of the thalamus (Fig. 6). The ventral anterior nucleus was not uniformly labeled, with more HRP-positive neurons located in ventral regions. In contrast, the VLN was more uniformly labeled. The entire area of the VLN was heavily labeled with axons and axon terminals. The central medial nucleus, PCN, CLN, intralaminar CMN, and parafascicularis nucleus all contained many labeled cell bodies (Figs. 7 and 8). Some anterograde and dense patches of retrograde labeling appeared in the ventral posterolateral nucleus of the VBC, but it was sparse compared with that in the VLN (Fig. 7). The midline nuclei reuniens and rhomboideus contained some heavily labeled large-to-medium-sized somata.

Among the intralaminar thalamic nuclei, anterograde labeling was conspicuous only in the CLN.

In the untreated hydrocephalic animals, the most prominent deviation from controls was a reduction in the amount of preterminal and terminal anterograde axonal labeling. In
the principal relay nuclei of the thalamus, the intensity of anterograde labeling was decreased but the overall location of label within each nucleus was remarkably similar. In the VLN, labeling of the corticothalamic terminal field was confined to small clusters interspersed in ventrolateral portions of the nucleus (Figs. 6 and 8). Reduced retrograde labeling was notable in the VLN, and the somata of HRP-positive neurons were more round with less conspicuous proximal dendrites (Fig. 6). Within the intralaminar nuclei (CLN, PCN, and CMN), there was a slight reduction in the number of labeled cells in animals with either moderate or severe hydrocephalus (Figs. 7 and 8). Specifically within the CLN, labeled somata appeared more dispersed compared with those in controls (Fig. 7); this cytoarchitectural change could have been caused by gross distortion and stretching. In caudal regions of the posterior thalamus, retro- and anterograde labeling was reduced in animals with moderate hydrocephalus. Similarly in VBC, anterograde labeling was diminished in quantity and density compared with that in controls (Fig. 7).

In all VP shunt-treated animals, retrograde labeling of the thalamic relay nuclei returned to near-control levels after variable post–shunt therapy recovery periods. In particular, this improvement occurred as early as 9 days after shunt placement in one animal (Case 14) with severe hydrocephalus (anterior fontanelle 10 mm in diameter) at the time of shunt insertion. In the VLN, labeled neurons exhibited oblong or fusiform somata with prominent proximal dendrites, and they occupied positions similar to the patterns observed in controls (Figs. 6 and 8). Retrograde labeling returned to control levels in the CMN and PCN as well as in the hypothalamus; however, retrogradely labeled neurons of the intralaminar CLN remained diminished and/or dispersed (Fig. 7). Overall, shunt-treated animals exhibited anterograde labeling within ipsilateral thalamic nuclei that was increased relative to untreated hydrocephalic animals but remained lower than levels observed in controls (Figs. 6–8). For example, in the VLN the density of terminal labeling appeared normal but was confined to a smaller area in the central core of this relay nucleus. In addition, a few separate clusters of anterograde label remained in regions peripheral to the central terminal field in the VLN, but these clusters were less numerous than those found in control animals. Within the CLN there was no recovery of anterograde terminal labeling at any point after shunt placement.
FIG. 7. Photomicrographs obtained from the centrolateral (left column) and ventrobasal thalamic (middle brightfield and right darkfield columns) nuclei showing representative labeling patterns in control (A–C), untreated hydrocephalic (D–F), and VP shunt–treated (G–I) animals. In general, the most conspicuous change was a decrease in anterograde labeling within these nuclei, with a return to near-normal levels after placement of a shunt. Tetramethylbenzadine method for HRP, counterstained with neutral red.

FIG. 8. Camera lucida drawings of the midthalamic level demonstrating the absence of change in control animals (A) compared with the changes in connectivity that occurred in untreated hydrocephalic (B) and shunt-treated (C) animals. In VLN (VL) and intralaminar thalamic nuclei (CLN [CL], CMN [CM], and PCN [PC]), both retro- and anterograde labeling was markedly decreased, whereas axonal labeling in the internal capsule (IC) was not changed in animals with untreated hydrocephalus. In shunt-treated animals retrograde labeling in the VLN and in all intralaminar nuclei except CLN recovered to near-normal levels. In contrast, anterograde labeling in the VLN and CLN increased somewhat after shunt placement but was not fully restored within the 7- to 30-day recovery period. Note also that some ventriculomegaly remained in shunt-treated animals, as evidenced by an enlarged third ventricle (3V) and compressed diencephalon. Am = amygdala; CC = corpus callosum; Hy = hypothalamus; LG = lateral geniculate nucleus; LP/LD = lateral posterior/lateral dorsal nuclei; MD = mediodorsal nucleus; OT = optic tract; P = pulvinar; R = reticular nucleus; VPm = ventral posteromedial nucleus.
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Connectivity in the Midbrain and Pons

In untreated animals with hydrocephalus, retrograde labeling of the ventral tegmental area, periaqueductal gray matter, and reticular formation was diminished markedly. In contrast, no appreciable decrease in anterograde labeling within the crus cerebri was observed. Shunt therapy restored retrograde labeling of the ventral tegmental area to normal levels, but recovery of labeled neurons was not demonstrated in the periaqueductal gray matter or the re-

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The locus coeruleus exhibited a moderate loss of retrograde labeling in untreated hydrocephalic animals, and VP shunt therapy restored cellular labeling completely (Fig. 10). Retrograde labeling within the nucleus of the raphe was unchanged in the three experimental groups. These results are summarized in Table 2.

**Discussion**

This study is the first of its kind to evaluate connectivity changes in both afferent and efferent pathways of the sensorimotor cortex in experimental hydrocephalus. As summarized schematically in Tables 2 and 3, kittens with untreated hydrocephalus exhibited marked reductions in retrograde (neuronal somata) HRP labeling in the contralateral motor cortex, ipsilateral thalamic relay and intralaminar nuclei, midbrain raphe, and the ventral tegmental area. Anterograde (axonal and synaptic) labeling in these animals was dramatically reduced in the contralateral motor cortex and ipsilateral thalamus. Shunting returned anterograde labeling within the locus coeruleus and VBC to near-normal levels. Shunt therapy increased both somatic and axonal labeling considerably in all areas that showed decreases in untreated hydrocephalus. In particular, anterograde labeling of the contralateral motor cortex returned to normal, whereas ipsilateral thalamic labeling remained lower than that in age-matched controls regardless of the survival period after shunt placement. Because the improvement in retro- and anterograde labeling after shunt insertion occurred as early as 7 days later, it is likely that recovery of axonal transport mechanisms, rather than regeneration of new connections, plays an important role in the repair of these pathways.

**Pathophysiology of Hydrocephalus**

Although the causes of hydrocephalus appear to exert a strong influence on neurological outcome, the mechanisms underlying its pathogenesis are poorly characterized, in part because of the multifactorial nature of the disorder. The multitude of overlapping mechanisms includes axonal degeneration, cell death (neurons and glia), demyelination, ischemia, hypoxia, neurapraxia, and inflammation/gliosis. Furthermore, the ventriculomegaly, which defines the hydrocephalic condition, compresses the corti-
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**TABLE 2**

<table>
<thead>
<tr>
<th>Structure</th>
<th>HRP Label in Hydrocephalic Groups</th>
<th>Preop</th>
<th>7–30 Days Postop</th>
</tr>
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<tbody>
<tr>
<td>periaqueductal gray matter</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
<td></td>
</tr>
<tr>
<td>ventral terminal area</td>
<td>↓↓↓↓↓</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>reticular formation</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
<td></td>
</tr>
<tr>
<td>locus coeruleus</td>
<td>↓↓↓↓↓</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>crus cerebri</td>
<td>no change</td>
<td>normal</td>
<td></td>
</tr>
</tbody>
</table>

* Label intensity ranges from ↓↓↓↓↓ (complete loss of label) to ↓ (minimal loss of label). Preop = before shunt placement; postop = after shunt placement.

**TABLE 3**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>HRP Label in Hydrocephalic Groups</th>
<th>Preop</th>
<th>7–30 Days Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>contralateral motor cortex</td>
<td>↓↓↓↓↓</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>afferents</td>
<td>↓↓↓↓↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>thalamocortical</td>
<td>↓↓↓↓↓</td>
<td>↓</td>
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<tr>
<td>corticohypothalamic</td>
<td>↓↓↓↓↓</td>
<td>↓</td>
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<tr>
<td>corticospinal</td>
<td>normal</td>
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<tr>
<td>ventral terminal area–cortex</td>
<td>normal</td>
<td>normal</td>
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* Corticospinal tracts were unaffected by hydrocephalus, whereas labeling of afferent and efferent pathways of the contralateral cortex and ipsilateral thalamic relay nuclei were severely attenuated. Shunt therapy restored retro- and anterograde labeling and, in some cases, completely reversed the effects of hydrocephalus.

Neuronal cell death in hydrocephalus can result from various mechanisms, including the retrograde effects of axotomy, deafferentation, depletion of neurotransmitters and -modulators, metabolic dysfunction, ischemia, breakdown of the blood–brain barrier, toxicity following stasis of cerebrospinal fluid and interstitial fluid flow, and inflammation secondary to injury (see reviews by McAllister and Chovan, Del Bigio and McAllister, Del Bigio and Bigio). Regardless of the cause, neuronal cell death provides one of the more straightforward explanations for the decreased labeling of motor cortex pathways in hydrocephalus. These findings correlate well with our previous descriptions of dark neurons and decreased density of normal neurons in this model. These alterations occurred primarily in Layers V and VI of the neocortex and thus could be responsible for the diminished anterograde HRP labeling in corticohypothalamic projections. In contrast, relatively few degenerating neurons have been observed in Layers II and III, indicating that the loss of anterograde labeling in the contralateral motor cortex may not be due to neuronal death. Likewise, no studies (including our own unpublished observations) have provided evidence of
hydrocephalus-induced neuronal death in the relay and intralaminar nuclei of the thalamus, the ventral tectal area, and the locus coeruleus. In particular, our preliminary examination of the glial response to hydrocephalus throughout the brain has revealed many reactive microglia among Nissl-stained neurons of the lateral geniculate nucleus that appear completely normal. Therefore, it seems likely that neuronal dysfunction, as well as cell death, contributes to the lack of HRP labeling in motor cortex pathways.

Neurapraxia. In the present study, the placement of a ventricular shunt restored or improved both antero- and retrograde labeling in all neocortical motor pathways. Collectively, examination of these data indicates a third, transient mechanism underlying the connectivity changes caused by hydrocephalus. Neurapraxia, which is a temporary loss of neuronal function, may in fact be the predominant mechanism underlying the changes we have observed. A key observation involving this hypothesis is that both antero- and retrograde HRP labeling increased within 7 days after shunt therapy. Such rapid restoration of labeling does not support mechanisms that cause permanent cellular damage such as axotomy, necrosis, or cell death. Structural repair or physical remodeling of corticofugal and corticopetal connections is unlikely within this short period of time. Instead, we propose a functional impairment of axoplasmic transport in the neurons affected by hydrocephalus, also referred to as a so-called functional injury by Tashiro, et al. This type of lesion can be reversible, depending on the time at which compression is relieved.

It is important to recognize that the tract-tracing techniques used in this study rely on normal axoplasmic flow for both retro- and anterograde labeling. The injected HRP label is either translocated anterogradely by intracellular transport from the soma to synaptic terminals, or it is uptaken by pinocytosis at the axon termini and transported retrogradely to the cell body. Any impairment in these mechanisms could reduce the transport of HRP, especially in the 2-day postinjection period we used. It is conceivable that longer postinjection survival periods may have produced labeling distributions in hydrocephalic animals similar to those seen in controls.

Impaired axonal function in lieu of axotomy or complete axonal degeneration should have electrophysiologic consequences, and studies in hydrocephalic rats have demonstrated that electrical conduction is impaired during hydrocephalus. Furthermore, findings in feline studies indicate that these changes may depend primarily on intracranial pressure because increased latencies were not observed until late stages of hydrocephalus when intraventricular pressure was 75 to 100 mm Hg. Although direct evidence for functional impairments of motor cortical pathways has not been reported, Yamamura has shown that somatosensory conduction velocity decreases in H-Tx rats with untreated hydrocephalus and significantly improves after shunt placement. Diminished neuronal activity and responsiveness have also been reported at the cellular level where neocortical neurons exhibit decreased RNA expression and immunoreactivity for the immediate early gene c-fos.

The onset and reversibility of these functional changes appear to be correlated with CBF. Significant decreases in cortical perfusion have been shown in adult and infant patients as well as in experimental animals. Furthermore, in a feline model identical to that used in this study, one group of authors has shown that small focal regions of periventricular white matter exhibited an increase in glucose utilization, indicative of anaerobic glycolysis. Another key finding reported by these investigators was that local CBF was significantly and chronically decreased only in the periventricular white matter of the cortical mantle. This reduction occurred as early as 7 days after the onset of hydrocephalus and was accompanied by similar blood flow reductions in the posterior thalamus, hippocampus, and periaqueductal gray matter. Furthermore, local CBF returned to normal in animals in which shunts were inserted 7 days after induction of hydrocephalus, which was approximately 1 week prior to the time our shunts were placed. Taken together, these findings indicate that ischemia plays a prominent role in the transient HRP labeling patterns we have observed in most of the motor cortex pathways. The propensity for white matter ischemia to occur in untreated hydrocephalus makes it one of the most common threats to neuronal function and one of the primary mechanisms leading to neurapraxia.

Clinical Relevance

Although our current findings and the numerous observations of hydrocephalus-related axonal damage indicate that connectivity impairments play a prominent role in the pathogenesis of this disorder, the clinical consequences of these alterations are more difficult to define. Nevertheless, the relatively high incidence of learning disabilities, visual impairments, and seizure activity in shunt-dependent children with hydrocephalus implies that cortical circuits may not have developed properly. In this regard, two examples of developmental alterations are worth noting. First, in some of our initial attempts to evaluate cortical connectivity indirectly, we observed dramatic reductions in norepinephrine throughout the neocortex 9,75 and these deficits had not recovered 30 days after shunt placement. These neurotransmitter deficits could have obvious relevance to cortical afferent systems because norepinephrine can only be delivered to the neocortex via the pathway from the locus coeruleus. Additionally, and perhaps more importantly, the lack of norepinephrine (but perhaps not other monoamines such as serotonin) during development could have significant cellular consequences because dendritic differentiation depends on this molecule as a trophic factor. Likewise, Zhang and Del Bigio have recently reported increases in growth associated protein-43 in periventricular axons during hydrocephalus in juvenile animals. This molecule plays a prominent role in axonal growth, synaptogenesis, synaptic plasticity, and long-term potentiation. Its increase in the periventricular white matter during hydrocephalus could be caused by impaired axonal transport, which if not reversed in time could have
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long-term effects on the establishment and remodeling of cortical afferents.

Thus, the connectivity alterations observed in this study could profoundly affect both neuronal communication and neuronal maturation. Nevertheless, the relatively rapid reversal of axonal impairments, and the apparent preservation of the structural integrity of these pathways, indicates that early decompression may promote optimal neurological recovery in children with hydrocephalus.

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