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Learning deficits in congenitally hydrocephalic rats and prevention by early shunt treatment

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Abstract Shunt surgery is the usual treatment for infantile hydrocephalus; however, the extent to which it avoids subsequent neurological deficits is uncertain. The effect of early-onset hydrocephalus was tested in H-Tx rats using the Morris water maze. Spatial learning was assessed at 21 days after birth in control ($n=18$), hydrocephalic ($n=18$) and hydrocephalic rats shunt-treated at 4–5 ($n=7$) or at 10–12 days of life ($n=13$). The time taken to find a hidden platform was measured in five trials on 2 consecutive days and the data analyzed by one- and two-way ANOVA and *t*-tests. The latencies of the control rats decreased significantly between the first and second trial on the 1st day, and learning was retained until the 2nd day. The hydrocephalic group had longer latencies than controls on both days, with no significant decrease between any trials. Performance was not significantly different between the two shunt groups. Overall, the shunted rats had latencies which were not significantly different from controls but were significantly lower than hydrocephalics. Despite this, the shunted rats did not perform as well as the controls. It is concluded that, although shunt treatment improved learning, some effects of early-onset hydrocephalus may not be reversible and/or a longer recovery time is required.

Key words Rat congenital hydrocephalus · Shunt treatment · Spatial learning · Water maze

Introduction

Infantile hydrocephalus is a relatively common condition which can arise for a number of different reasons, and ventricular shunts are usually placed promptly to prevent further brain damage and improve the long-term prognosis. The outlook for infants with long-standing prenatal hydrocephalus treated postnatally is often poor and may be related to the timing of the prenatal onset and its effect on brain development [6, 20]. Taken as a whole group, a significant proportion of shunt-treated infants have a lower than normal IQ, with the verbal IQ performance better than the nonverbal [4, 10]. Furthermore, hydrocephalic children with an IQ in the normal range have reduced verbal IQ, memory, and fine motor skills compared to controls, and there are often associated abnormalities in ocular motility and acuity [29]. The effect of shunt treatment on IQ and subsequent neurological deficits may be related to the thickness of the cortical mantle after shunting [6, 28].

The H-Tx rat has inherited congenital hydrocephalus due to aqueduct obstruction in late gestation [11]. This early-onset hydrocephalus has severe effects on the gray matter of the cerebral cortex and on subcortical structures [12] and, unless shunt-treated, the rats die at 4–7 weeks after birth. We have shown that early shunt treatment in the first 2 postnatal weeks prevents further ventricular expansion but does not completely normalize the ventricle volume or the thickness of the cerebral cortex [9, 13]. The total dentritic length of the layer V pyramidal cells in the auditory cortex of H-Tx rats is decreased by around 50% in hydrocephalics at 21 days of age, and shunt treatment par-

tially restores the dendrites to within 10–20% of controls [8]. Another study on hydrocephalic H-Tx rats found reduced dendritic spine density in layer VI cortical neurons at 14 days [18]. This same study also showed that when shunt treatment was carried out at 4 weeks of age, rats did not perform as well as control rats in a Y-maze test when tested at 12 weeks, whereas H-Tx rats shunt treated at 7 days performed as well as control rats by the time they reached 12 weeks [18, 24].

The present investigation was initiated to determine the extent to which the hydrocephalic rats exhibit learning deficiencies and the effect of early shunt treatment for reversal of any observed deficits. The water maze was selected because it is a test of spatial learning and memory [19]. It can be used on rats of weaning age (21 days) since it does not require withholding of food prior to testing and swimming ability is already well established by this age [1].

Materials and methods

Animals

The H-Tx is a mutant strain of rats which originated from albino rats of unknown origin. Male and female H-Tx rats weighing 25–59 g were used in this study. Litters were inspected soon after birth, and pups affected by hydrocephalus were determined by external observation of the head. Some of these underwent shunt surgery (see below). All rats were tested on 2 consecutive days. The mean age on the day of the first test for the control group was 21 days ($n=18$), for the hydrocephalics it was 22 days ($n=18$), for the first shunt group it was 20 days ($n=7$), and for the second shunt group it was 21 days ($n=13$).

Shunt surgery

Rats were shunted at 4–5 days or at 10–12 days after birth. These ages were selected because they correspond to mid to late gestation and the early neonatal stage in the human. Shunts were made from Teflon tubing (0.3 mm internal diameter and 0.76 mm external diameter) shaped into a 90° angle for insertion into the ventricle and attached distally to a piece of silicon tubing. Using a sterile technique and halothane anesthesia (1–2% in N_2O:O_2 2:1 mixture), a shunt was inserted into the right lateral ventricle, sealed in place with cyanoacrylate glue, and anchored to the thin skull with dental cement. The distal end was left open and placed subcutaneously at the neck. Shunted rats were weighed daily to monitor general health and the ventricles were measured close to the first day of the maze test using magnetic resonance (MR) imaging or from fixed brain slices prepared immediately after the maze testing. For imaging, contiguous multislice proton MR images were obtained on a 4.7-T Oxford Magnet using a T_1-weighted inversion-recovery sequence. As has been found previously [13], shunt treatment resulted in a decrease in the size of the lateral ventricles, although control-sized ventricles were not achieved (Fig. 1).

Water maze tests

A round galvanized tank 81 cm in diameter and 61 cm deep, filled with tap water (25 ± 1 °C) to a depth of 18 cm, was used as the pool. It was arbitrarily divided into four equal quadrants by placing markers on the outside of the rim. The walls of the tank were painted dull yellow with a metal primer and the water was made opaque by the addition of white, nontoxic, liquid tempera, which ensured concealment of the platform. The platform was a white plastic bottle, 8.9 cm in diameter and 17 cm tall, filled with stones and water. This was placed in the center of one quadrant with the top 1 cm beneath the water level. To reduce extra-maze stimuli a semiopaque black curtain, attached from the ceiling, was hung around the pool. A proximal visible cue, formed from white tape, 5 cm long and 2 cm wide, was placed on the side of the tank 1–2 cm above the water and adjacent to the platform. A video camera, connected to a monitor for observation and timing, was installed 1.55 m above the water level and a light was placed close to the camera. Rats were swum on 2 consecutive days (D 1 and D 2), each day with five trials (T 1–T 5) and the cue was removed for the fifth trial on each day. Groups of litter mates, consisting of 2–6 rats each, were tested in the same order, one after another, for each trial. The intertrial time was 3–18 min. The rat was placed in the water, facing the wall, in one of the three quadrants not containing the platform. The starting quadrant was changed for each trial, rotating anticlockwise around the tank. Rats that found the platform in less than 100 s were left on it for 10 s before being removed, at which time they were dried with a paper towel and placed back into the cage. Rats that failed to find the platform within 100 s were manually lifted out of the water, placed on the platform for 10 s, and given a score of 100 s. The rats were timed using a stopwatch and the latencies were recorded into a laptop computer.

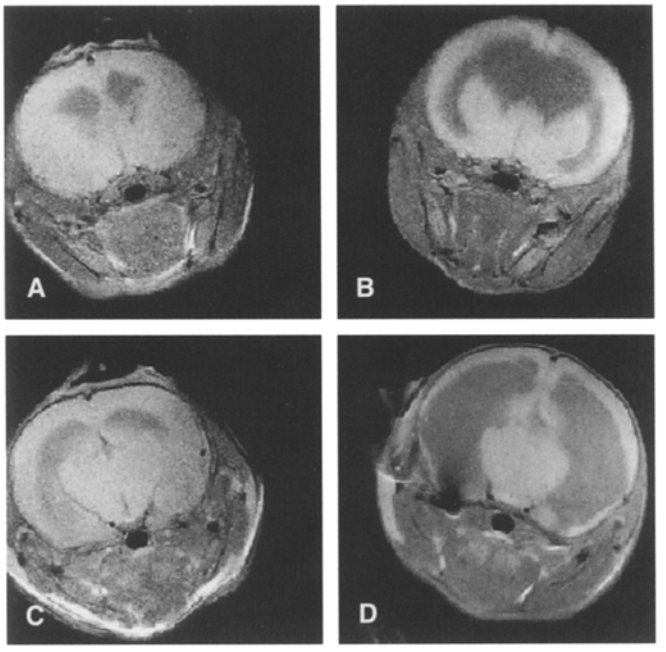

Fig. 1 Magnetic resonance images of a 21-day-old hydrocephalic rat shunted at 4 days after birth (**A**, **C**) and a 21-day-old untreated hydrocephalic rat (**B**, **D**), **A**, **B** at the level of the sensor-motor cortex and **C**, **D** at the level of the auditory cortex. These coronal images show the reduction in size of the lateral ventricles typically seen after shunt treatment and the extreme ventriculomegaly seen in hydrocephalic rats

Statistical analysis

All data are represented as means ± SEM. Two-way ANOVA was used to test for overall significant differences between rat groups and

for differences between days and trials within groups. One-way ANOVA was used to test between trials within groups for each day. *t*-Tests were used to test for differences between individual trials between groups. *t*-Tests were also used to compare individual trials on different days within groups, and to test for differences between total trial times. Regression analysis was used to test for correlation between age and latency.

Results

As expected, the rats showed a natural swimming ability when placed in the tank. This is consistent with previous developmental studies (e.g., [1]). Three exceptions were rats which were very severely hydrocephalic and had to be excluded from the study. Another severely hydrocephalic rat swam asymmetrically but was not excluded. There was no significant effect of age at the day of testing on trial times (regression analysis) or of sex on mean total trial time (*t*-test) for any group. There was no significant difference between T 4 and T 5 (no cue) on either day, and this was true for all groups. Hence, the latencies for T 5 were analyzed in the same way as T 1–T 4 throughout.

Control and hydrocephalic rats

The mean total latency for control rats for all trials on D 2 was significantly lower than on D 1 (179.9 ± 15.62 s and 224.8 ± 13.94 s, respectively; *t*-test; $P<0.05$; Fig. 2). On D 1, the control rats had a mean latency of 79.1 ± 7.72 s for the first trial (T 1), which decreased significantly for the subsequent trials to 32.8 ± 7.85 s for T 5 (Fig. 3). There were significant differences between the latency for T 1 and T 2, T 1 and T 3, T 1 and T 4, T 1 and T 5 (one-way ANOVA, $P<0.01$, or $P<0.001$), with the largest decrease occurring between T 1 and T 2. On D 2, the mean latency for T 1 was 43.6 ± 6.76 s, which was not significantly different from D 1–T 5, indicating that learning was retained from D 1 to D 2. No further significant decrease in latency occurred on D 2. Overall, because of the rapid learning on D 1, there was no significant difference between D 1 and D 2, but there was a significant difference between trials (two-way ANOVA, days × trials; $P<0.001$).

Unlike the controls, the hydrocephalic rats had a mean total latency for all five trials which was not significantly lower on D 2 than on D 1 (298.9 ± 29.31 s and 343.8 ± 23.90 s, respectively; Fig. 2). On D 1, the latency for the hydrocephalic group was 78.9 ± 6.90 s for T 1 and 70.2 ± 8.28 s for T 4, with a decrease to 52.1 ± 8.28 s for T 5 (Fig. 3), but there was no significant difference between any of the trials (one-way ANOVA). Although the largest decrease, between T 4 and T 5, was not statistically significant, it suggests that some delayed learning may have occurred in this group. On D 2, there was also no significant difference between the trials, indicating that no learning occurred on D 2. Furthermore, there was no overall difference between D 1 and D 2, nor between trials (two-way ANOVA, days × trials).

On D 1, the mean total latency of all five trials for the controls was significantly lower than for the hydrocephalics, and this was also true on D 2 ($P<0.001$ and $P<0.01$, respectively; Fig. 2). The latencies for the control group were significantly lower than for the hydrocephalic group over all ten trials (two-way ANOVA, group × trials, $P<0.001$). On D 1, the latencies for the hydrocephalics were significantly longer for T 2, T 3, and T 4 (*t*-test, $P<0.01$; Fig. 3). On D 2 there was a significant difference between the groups for T 3 ($P<0.001$) and for T 5 ($P<0.05$).

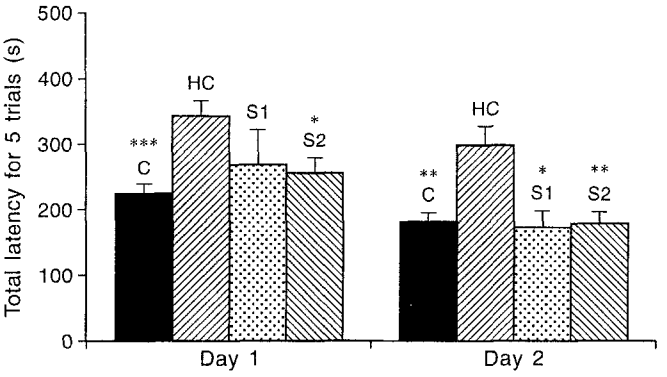

Fig. 2 The total water maze escape latencies for groups of control rats (*C*, $n=18$), hydrocephalic rats (*HC*, $n=18$), rats shunted at 4–5 days (*S1*, $n=7$), and rats shunted 10–12 days (*S2*, $n=13$) for five successive water maze trials on 2 consecutive days. Data are means ± SEM; *, **, *** indicate significantly differences from hydrocephalic rats ($P<0.05$, 0.01, 0.001, respectively)

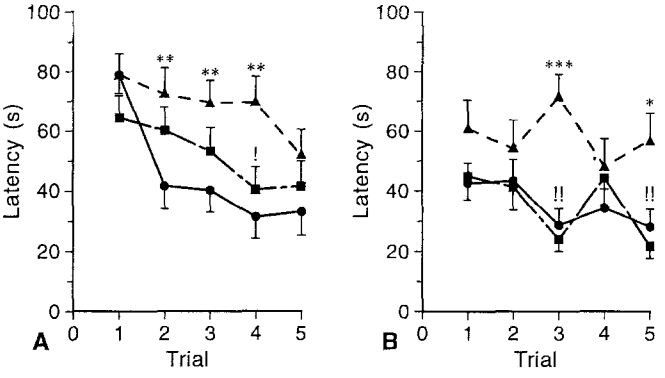

Fig. 3A, B The water maze escape latencies over five trials for **A** day 1 and **B** day 2 in groups of control rats (●, $n=18$), hydrocephalic rats (▲, $n=18$), and shunt-treated rats (■, $n=20$). Data are means ± SEM; *, **, *** indicate significant differences between control and hydrocephalic groups ($P<0.05$, 0.01, 0.001, respectively). !, !! indicate significant differences between the hydrocephalic and shunted rats ($P<0.05$, $P<0.01$, respectively)

Shunt-treated rats

In the rats shunted at 4–5 days the mean latency for D 1–T 1 was 64.86 ± 10.54 s, decreasing to 41.43 ± 14.55 s by T 5. On D 2 the trial times were more variable, with 37.9 ± 7.88 s at T 1 and 20.0 ± 3.94 s at T 5. Overall, the latencies for D 2 were significantly lower than for D 1, although there was no significant difference between trials (two-way ANOVA, days × trials, $P < 0.05$). In the rats shunted at 10–12 days the mean latency for D 1–T 1 was 63.9 ± 9.68 s, decreasing to 46.6 ± 10.25 s for T 5. On D 2 the latencies were also somewhat variable, but decreased from 52.8 ± 11.85 s for T 1 to 25.6 ± 5.83 s for T 5. However, overall D 2 latencies were significantly lower than on D 1, with no significant difference between trials (two-way ANOVA, days × trials, $P < 0.05$). There was no significant difference in the mean total latency between the controls and either shunt group, either on D 1 or on D 2 (*t*-test, Fig. 2). However, the mean total time for each shunt group was significantly lower than that for the hydrocephalics ($P < 0.05$, or $P < 0.01$) except on D 1 for the rats shunted at 4–5 days.

Overall, there were no significant differences between rats shunted at 4–5 days and those shunted at 10–12 days (two-way ANOVA, groups × trials); therefore, the data from both shunt groups were combined for further comparisons (Fig. 3). For this combined group, there was a significant difference between D 1 and D 2, and between trials (two-way ANOVA, days × trials, $P < 0.01$, $P < 0.05$, respectively), which was in contrast to the hydrocephalics. The latencies of the combined shunt group were not significantly different from the controls, but they were significantly different from the hydrocephalic group (two-way ANOVA, groups × trials, $P < 0.001$). On both days, there were no significant differences between the combined shunt group and the controls for individual trials (*t*-test). However, latencies in shunted rats were significantly different from those in hydrocephalics for D 1–T 4, D 2–T 3, and D 2–T 5 (*t*-test, $P < 0.01$).

Discussion

Control rats

The significant reduction in latency on D 1 between T 1 and T 2 indicates that the control rats rapidly learned to find the platform and escape from the water. The latencies achieved by these young rats (30 s) were not as low as has been reported for older rats (e.g., [19]), although they are comparable to latencies achieved by the 20-, 22-, and 24-day-old Sprague-Dawley rats used by Tonkiss et al. [25]. Previous studies have shown that place navigation improves with age, and adult-like learning ability is not achieved until after 28 days in Long-Evans hooded rats [23]. Furthermore, 20- to 25-day-old albino Sprague-Dawley rats do not perform as well as pigmented Long-Evans hooded rats – a difference which appears to be related to a strain difference in spatial learning ability [25]. Another possible reason for failure to achieve latencies lower than 30 s may have been due to the use of curtains around the pool, which minimized distal cues. However, since learning did take place, we conclude that sufficient cues, such as uneven lighting from a nearby window which was partly visible through the curtains, provided the rats with navigational aids. The white tape strip placed inside the tank wall was intended to provide a proximal cue for navigation. However, since there was no increase in latency when it was removed for T 5, we conclude that the rats did not use this to guide their escape. This is consistent with an age-related study on young rats which showed that for rats of this age distal cues are more important than proximal ones [22]. It is also possible that, since we did not place the cue directly on the platform, it was not sufficiently prominent to be useful.

Hydrocephalic rats

The performance of the hydrocephalic rats was clearly different from the control rats. They did not achieve latencies lower than 50 s and they did not improve with trial number on either day. Although there was a decrease between T 4 and T 5 on D 1, this was not statistically significant, and in five out of the ten trials the latencies were significantly higher than the control group. The question arises as to whether this is due to a deficiency in learning ability, in motor skills, or in visual acuity. A previous study has shown that motor activity is not impaired in hydrocephalic H-Tx rats until around 28 days after birth [17], and apart from in the severely hydrocephalic animals that were eliminated from this study and one other mentioned above, swimming ability appeared to be intact. However, since in H-Tx rats the posterior cortex is more severely affected than the anterior cortex [12], the possibility exists of a deficiency in visual processing in the hydrocephalic group. In a simple light-darkness discrimination test performed at 21 days of age, both control and hydrocephalic rats showed similar preferences for the dark box (H. C. Jones, N. G. Harris, Y. Y. Cason, unpublished observations). The assessment of visual acuity, however, may require a more sophisticated test which will be planned in future experiments.

Shunt-treated rats

Rats shunted at 4–5 days performed as well as those shunted at 10–12 days, indicating that both procedures were equally effective in preventing the effects of hydrocephalus. The latencies of both shunt groups were significantly lower than those of the hydrocephalics on both days.

There were no significant differences in individual trials or in total latencies between the combined shunt group and the controls on either day, although more subtle differences were observed. For example, on D 1 the shunt-treated rats did not achieve a mean latency of less than 40 s, compared with 30 s for the controls, although on D 2 they were much closer to the controls. Also, on D 1 the controls showed a significant decrease between T 1 and T 2 with no subsequent decrease, whereas the shunt-treated rats had a more gradual decrease in latency with the largest decrease occurring after T 3. This suggests that although the shunted rats had a superior performance when compared to the hydrocephalic rats, learning potential may not be completely normalized by shunt placement.

One possible reason for these differences is that irreversible brain damage may have occurred before shunts were inserted. The ventricles are already dilated at birth and dilatation progresses rapidly after birth [7, 11]. Histological studies have shown that hydrocephalic H-Tx rats at 7–10 days show cortical thinning and disruption of the laminar structures, particularly in the deeper layers V and VI of the posterior cortex [12, 26]. Furthermore, cystic cavitations of the brain lateral to the basal ganglia, together with ependymal cell changes, are already present by 7 days after birth [27], and by 14 days reductions in dendritic spine density are evident in layer-VI neurons [18]. The extent to which these changes are reversible, however, are uncertain. In adult rabbits with induced hydrocephalus, although the ventricles returned to normal size after shunting, the pathological changes in the periventricular tissue were not completely reversed [3]. In the H-Tx rat, shunt treatment did not completely normalize ventricular size [13]. Furthermore, in kittens with induced neonatal hydrocephalus, partial ventriculomegaly remained after shunt-placement as well as compression of the cortical mantle, disorientation of neurons with altered dendrites, and edema in the periventricular white matter [5, 15, 16].

Another possibility for the differences seen between the shunt-treated rats and the control group is that changes existing at the time of shunting are reversible, but that a longer interval between surgery and behavioral testing may be required for complete normalization of brain function. We found in an earlier study that shunt treatment in the first 2 postnatal weeks in H-Tx rats only partially restored the normal histological appearance of the cerebral cortex when examined at 21 days [9]. Electron microscopic examination of H-Tx rats at 21 days has shown that in cortical layers V and VI the pyramidal cells are severely abnormal in hydrocephalics, with edematous cytoplasm and swollen neurites. Tissue from rats shunted at the same ages as studied here contained neurons which were apparently more active than in control rats, with increases in Golgi complexes, centrioles, mitochondria, and ribosomes, suggesting that fast regeneration may be taking place [2, 14]. There were also remaining deficiencies in synaptic contacts. Also, as mentioned earlier, shunt treatment only partially restores the dendritic fields of the cortical pyramidal cells when examined at 21 days [8]. On the other hand, another study which delayed examination until sexual maturity found that shunts inserted at 7 days in H-Tx rats prevented the reduction in dendritic spine density seen in pyramidal cells from layers II and III of the frontoparietal cortex, and that learning ability in a Y-maze test was no longer impaired [24]. Together, these studies indicate that the potential may exist for full functional restoration after early-onset hydrocephalus, but that recovery may be delayed beyond the 3-week stage used here.

This may have implications for early-onset hydrocephalus in humans and is consistent with a number of studies which indicate that children with shunt-treated infantile hydrocephalus have neuropsychological and intelligence deficits which continue into childhood and adolescence [4, 21]. A longitudinal study with assessments separated by 1 year, carried out in children with shunt-treated communicating hydrocephalus aged 4–11 years, showed that some impairments remained stable with time (e.g., verbal IQ), some improved (e.g., verbal memory), and some worsened (performance IQ and speed of information processing), the general pattern being that although the hydrocephalic children made progress, they failed to keep up with the control group [29]. How long these deficits continue to persist is not known.

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